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The significance of bioelectricity on all levels of organization of an organism. Part 1: From the subcellular level to cells

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ABSTRACT

Bioelectricity plays an essential role in the structural and functional organization of biological organisms. In this first article of our three-part series, we summarize the importance of bioelectricity for the basic structural level of biological organization, i.e. from the subcellular level (charges, ion channels, molecules and cell organelles) to cells.

1. Introduction

Significant new findings about the role of *bioelectricity* to understand biological functions have been made in the last couple of years (Funk et al., 2009; Harris 2021; Levin 2007; Levin et al. 2017, 2019, 2021; Levin and Martyniuk 2018; Levin and Djamgoz 2022; Mathews and Levin 2018; McCaig et al., 2005; Schofield et al., 2020; Tseng and Levin 2013; Tyler 2017; Whited and Levin 2019; Levin, 2020). The field of bioelectricity is growing, and more fundamental discoveries are just around the corner due the increasing interest as well as the novel and refined methods now available, from microscopy to novel tools in cell and molecular biology, to high precision biosignal measurements and computational modelling. It is not an exaggeration to state that we are currently witnessing the beginning of a "bioelectricity revolution" (Adams et al., 2019), aiming, for example, to crack the "bioelectric code" (Levin et al., 2017) (as an analogy to the genetic code) and to research the "electrome" (the sum all electrical aspects) (De Loof, 2016) of organisms.

As a continuation and update of previous reviews by us (Fels et al., 2015; Funk et al., 2009; Funk 2012, 2015, 2018, 2019; Scholkmann 2015), we want to use the present review to summarize the current knowledge and our take on how bioelectricity plays an important role for biological function on all levels of organization of an organism. In our summary, we focus on multicellular organisms.

Due to the enormous amount of information now available on bioelectrical issues in organisms, we are dividing our review into three parts, which will be published gradually. The first part is about bioelectricity at the first levels of structural organization, i.e. the subcellular level up to cells.

Biological organisms comprise functional units on different levels of organization. In general, the following hierarchy (or holarchy, for a more precise term (Koestler 1967)) is valid for higher multicellular biological organisms: electrical charges and atoms (level 1), molecules and macromolecules (level 2), cell organelles (level 3), cells (level 4), tissue (level 5), organs (level 6), organ systems (level 7) and organism (level 8). It is obvious that on each level of organization, bioelectricity plays a significant role. In our multi-part review, we used this classification of levels to organize our material.

Our review corresponds to a narrative review and is characterized by our subjective selection of the facts and phenomena presented due to the abundance of available data. We ask for the readers' understanding that we can only present a relatively small selection herewith due to the wealth of information available. We summarize aspects that are most relevant in our opinion. At the same time, we also attempt to present a good general overview about this interesting research topic, and made great efforts to visualize the main information in informative, easy-to-understand and appealing graphics. Our review is especially intended for all interested persons who have not yet dealt with the subject of

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bioelectricity in depth and/or are looking for an overview of the various bioelectrical phenomena.

2. Bioelectricity at the level of electrical charges, atoms and molecules

2.1. Electrical charges and atoms

Electrical charges in forms of electrons (negative) and protons (positive) are present everywhere in biological systems. Furthermore, positively (cations) and negatively (anions) charged atoms (i.e. ions) of different charge strength are also omnipresent in organisms, including calcium (Ca^{2+}), potassium (K^{+}), sodium (Na^{+}) and iron (Fe^{2+} and Fe^{3+}). These types of electrically charged matter can flow in form of electrical currents and produce electrical fields (when at rest), magnetic fields (when moving with constant velocity) and electromagnetic fields (when moving with varying velocity). In biological systems, the flow of current is happening along various structures and with different mechanisms (Alfinito et al., 2011; Delaney and Barton 2003; Regan et al., 1993; Schlag et al., 2007; Williams 1989; Y. Zhang et al., 2014), including charge transport in the conduction band in biomolecules (forming semiconductors) as electron holes (i.e. a lack of an electron in an atom or a lattice, forming a positive charge) (Pethig 2009; Rosenberg 1962; Rosenberg and Postow 1969; Sosorev 2021), as proposed already in the 1940s by Szent-Györgi (Szent–Gyorgyi 1941). Also quantum tunneling between biomolecules take place, e.g. in the respiratory complex I where electron tunneling happens which is synchronized with conformation-mediated proton pumping enabling efficient energy conversion (de Vries et al., 2015). Quantum tunneling plays also a role for proton transfer reactions in enzymes (Bothma et al., 2010).

The great variety of different types of charges with different signs and strengths create a complex landscape of diverse electrical phenomena and processes already at the basic level of biological organization, including charge transports, near- and long range electrical

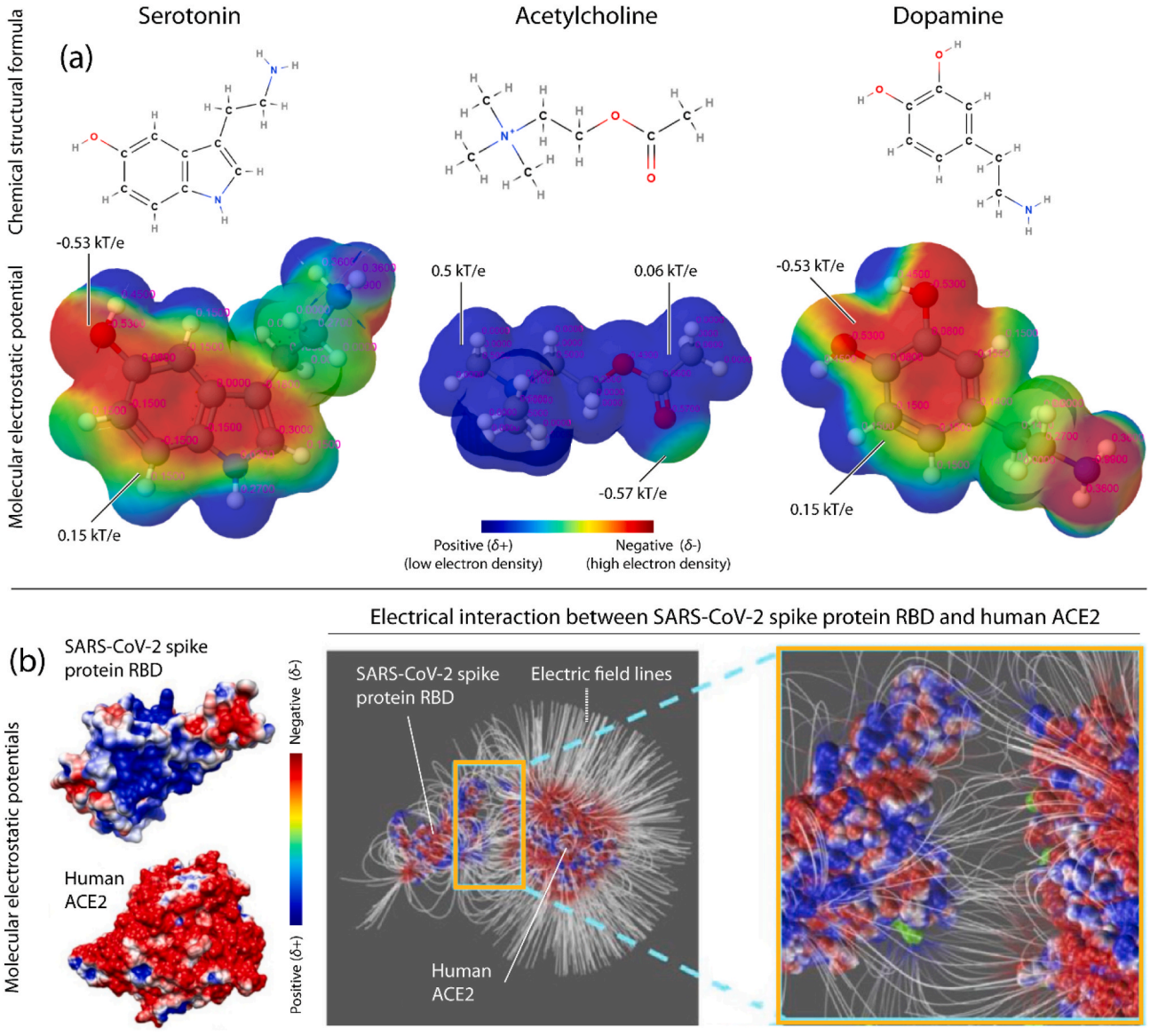

Fig. 1. Electrostatics in the molecular domain. **(a)** Molecular electrostatic potential (MEP) maps of three neurotransmitters (calculated and visualized via the online simulation software molview.org). **(b)** MEP of SARS-CoV-2 spike protein binding receptor domain (BRD) and the human angiotensin-converting enzyme 2 (ACE2) receptor as well as the electrostatic interaction between both. Reprinted and modified from Xie et al. (Xie et al., 2020), with permission from the publisher. The white lines covering ACE2 like spikes represent the vectors of the electrical field caused by the charge distribution. In the zoomed-in image, the field lines (white lines) connect both macromolecules, visualizing the electrostatic interaction between both.

interactions, electrical force fields and electromagnetic radiation.

Life is characterized by processes causing charge-separation, leading to a complex nested organization of compartments at different structural levels. These different compartments are generally characterized by different ionic compositions. For example, the cytosolic ion composition is different to the extracellular milieu. In the cytosol, the concentration of K^+ is about ten times greater than the concentration of Na^+, and the opposite is true for the extracellular space (Hodgkin 1951; Steinbach 1952).

2.2. Molecules and macromolecules

In biological organisms, specific molecules function as charge carriers and are involved in redox reactions, e.g. nicotinamide adenine dinucleotide (NAD^+/NADH) and flavin adenine dinucleotide (FAD/$FADH_2$).

Molecules and macromolecules have a specific charge distribution, i.e. the molecular electrostatic potential (MEP). The electrical potential is thereby generally not homogenously distributed over the molecule giving rise to an electric dipole moment. For example, proteins from the tubulin family have a high charge (−22 e^- on average) and a very large electric dipole moment (2166 Debye on average) (Marracino et al., 2019), causing a strong electrical field around them and making them exceptionally sensitive to external electrical influences. The MEP plays a key role for the interaction between molecules due to location-dependent electrostatic attraction and repulsion. Fig. 1(a) shows exemplarily the MEP of some neurotransmitters (note for example the MEP difference between serotonin and acetylcholine). Fig. 1(b) visualizes exemplarily the MEP of the SARS-CoV-2 spike receptor binding domain and the human angiotensin-converting enzyme 2 receptor, as well as the electrostatic interaction between these macromolecules.

Electrical charges flow along different biomolecules and structures inside the cell, like proteins (Amit et al., 2014; Kharkyanen et al., 1978; Malvankar et al., 2014), nucleic acids (Boon and Barton 2002; Genereux and Barton 2010; Giese et al., 1999; Slinker et al., 2011) and lipids in membranes (Jeuken et al., 2007; Ketterer et al., 1971; Nath 2021).

Inside the cell, the cytoskeleton (comprising actin filaments, intermediate filaments and microtubules) can be regarded as a structural network facilitating electrical charge and signal transmission (Friesen et al., 2014).

It is not surprising that microtubules, which are cylindrical protein polymers comprising tubulin dimers, draw specific attention due to their specific electrical properties. Microtubules, serving as structural elements of the cytoskeleton, have been identified to possess special electrical properties, i.e. behaving as sub-cellular memristors (Tuszynski et al., 2020) (i.e. a nonlinear electrical component that combines a persistent memory with electrical resistance) and memory-switching elements (Sahu et al., 2013a). Furthermore, a MT has a better electrical conductivity than the single tubulin molecules that constitute it (Sahu et al., 2013b). Fig. 2 visualizes the various electrical aspects of

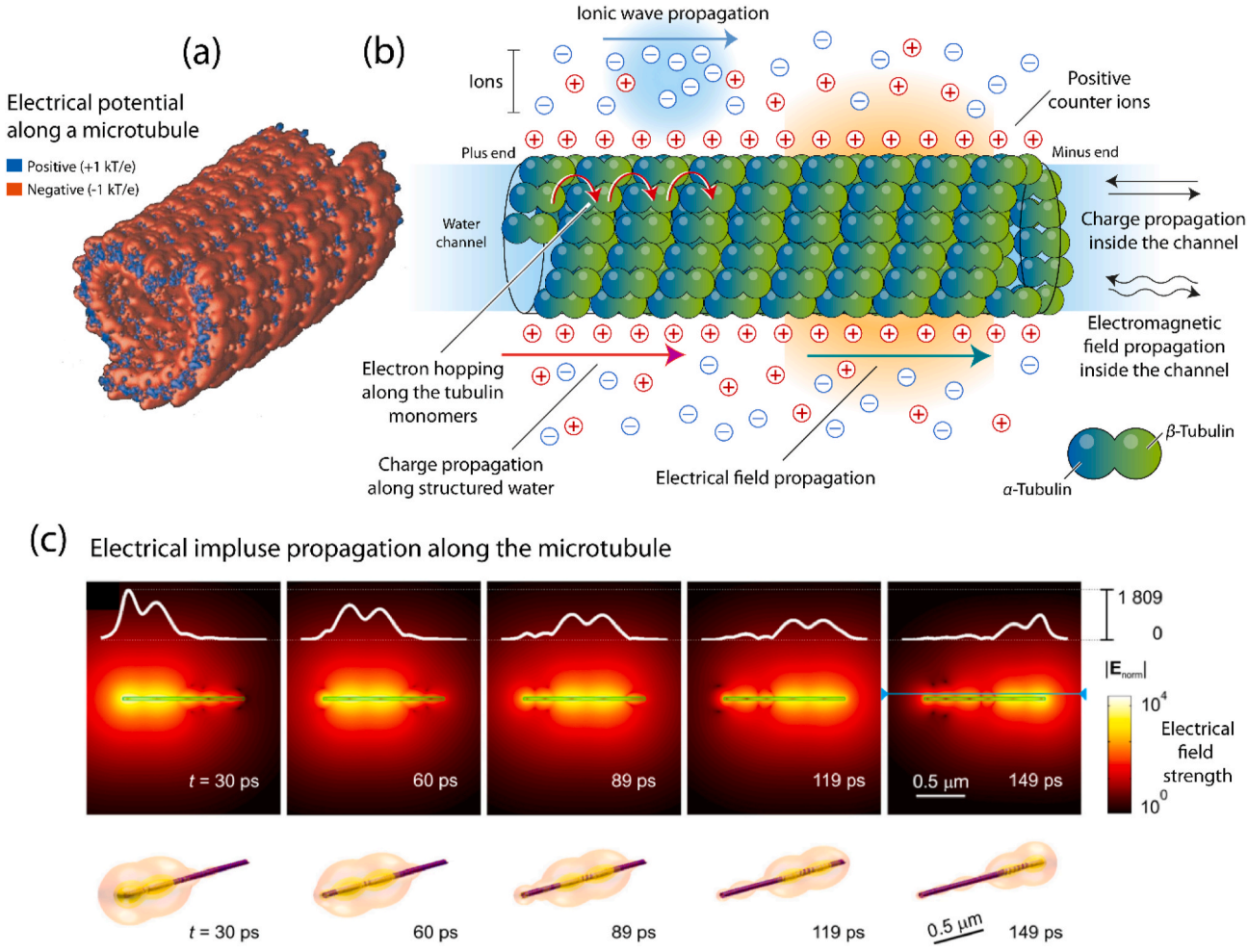

Fig. 2. Electrical aspects of microtubule. **(a)** Electrical surface potential of a microtubule according to a simulation by Baker et al. (Baker et al., 2001). Potential isocontours are shown at −1 kT/e and +1 kT/e. Reprinted and modified from Baker et al. (Baker et al., 2001), with permission from the publisher. **(b)** Possible electrical charge and electrical field propagation mechanisms along and inside microtubules according to Friesen et al. (Friesen et al., 2015). **(c)** Simulation of an electrical pulse propagation along a microtubule. Reprinted and modified from Havelka et al. (Havelka et al., 2014), with permission from the publisher.

microtubules, including the electrical potential along the microtubule, the many different ways of electric charge and field propagation inside and outside the microtubule (i.e. ionic wave propagation, electron hopping along the tubulin monomers, charge propagation along structured water, electrical field propagation outside the tubule as well as electromagnetic field and charge propagation inside the tubule). Simulations of electrical impulse propagation along a microtubule are shown in Fig. 2(c), highlighting the possibility of action potential like electrical signalling along microtubules. It can be speculated that this kind of phenomenon is used for intracellular and intercellular electrical signalling, for example inside axons where the microtubule network inside may facilitate an (so far undiscovered) additional electrical signalling pathway between brain cells (Craddock et al., 2010). It was hypothesized that the "dendritic cytoskeleton, including both microtubules and actin filaments plays an active role in computations affecting neuronal function" (Priel et al., 2006). The cytoskeleton in brain cells may enable subcellular bioelectric information processing, underlying certain types of learning and memory (Priel et al., 2009).

Apart from microtubules, actin has specific bioelectric properties too. Similar to microtubules, F-actin has a relatively high surface charge, is net negatively charged and has a heterogenous charge distribution with a highly charged subdomain 1s (Angelini et al., 2006) (Fig. 3(a and b)). The highly charged nature of F-actin and the specific heterogeneous charge distribution cause "collective dynamics of counterions that mediate like-charge attraction between F-actin filaments" as observed in aqueous solutions with high-resolution inelastic x-ray scattering (Angelini et al., 2006). Actin filaments (F-actin) have cable-like properties that allow charge transmission along the fibres (Lin and Cantiello 1993). F-actin can be regarded as a nonlinear electric transmission line (Sataric et al., 2012), enabling for example the propagation of ionic Ca^{2+} ion waves (Tuszynski et al., 2018) and electrical impulses in form of solitons (Hunley et al., 2018) (Fig. 3(c)). Actin can be also considered to be a "nano-capacitor" due to its ability to store and transport Ca^{2+} ions (Tuszynski et al., 2018). Already in the 1990s, it was concluded that "the ability of actin filaments to conduct electrical signals may have important implications in the coupling of intracellular signals" (Lin and Cantiello 1993). Since F-actin fibres are inside axons, there is a possibility of an (largely unexplored) electrical signalling between brain cells via F-actin based ion waves and electrical impulses, in addition to the electrical signalling via microtubules, i.e., the whole cytoskeleton could serve as an electrical network for information exchange and processing. The possibility of the cytoskeleton as an electrical signalling system between the cell membrane and the nucleus has been also pointed out already (Frieden and Gatenby 2019). The role of nonlinear Ca^{2+} ion wave propagation along actin filaments has been also discussed (Gartzke and Lange 2002; Tuszynski et al., 2018).

The significance of the flow of electrical charge carriers for biological functioning in the subcellular domain is most obvious in the electron transport chain (ECT) within the mitochondria. Through the ECT, protein complexes in the mitochondrial membrane enable a coupled electron and proton transfer with help of electron donors and acceptors, generating an electrochemical proton gradient enabling the synthesis of adenosine triphosphate (ATP) (Guo et al., 2018). The membrane potential is also necessary for this function (Dimroth et al., 2000).

Also, the nucleic acid molecules have particular electrical properties. Fig. 4 shows the MEP of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) molecules, as well as the MPE of DNA's four bases, the nucleosome and the surface charge density of a DNA sample in an aqueous solution. The surface charge density of the DNA varies with its conformation (higher charge density in the B conformation compared to the Z conformation) (Kominami et al., 2019). The electrical properties are relevant for the structural stability and conformation of DNA/RNA (Gebala et al., 2019; Gebala and Herschlag 2019), define interactions with molecules (e.g. DNA−DNA chiral electrostatic interactions; (Cherstvy 2008)), and there is a charge transfer happening along these molecules; the base pair stack within double helical DNA facilitates an efficient charge transport (Boon and Barton 2002). Chromosome motion during mitosis is also governed by electrical forces (Gagliardi 2002, 2005; Gagliardi and Shain 2014; John Gagliardi and Shain 2016).

Electrical forces due to the intrinsic MEPs of the interacting biomolecules govern many molecular interactions including protein-protein, enzyme-substrate, protein-nucleic acid, or protein-lipid interactions (Bergers et al., 1993; Honig and Nicholls 1995; Sankaram and Marsh 1993; Swasthi and Mukhopadhyay 2017; Zhou and Pang 2018) (Fig. 5(a)).

Electrical potentials and forces play also an important role in protein synthesis in the ribosomes (Fig. 5(b)). The ribosome has a highly negative MEP (Ban et al., 2000; Trylska et al., 2004) and the so-called ribosomal exit tunnel seems to have a particular electrical function. Proteins assembled by the ribosome have to pass through the ribosomal

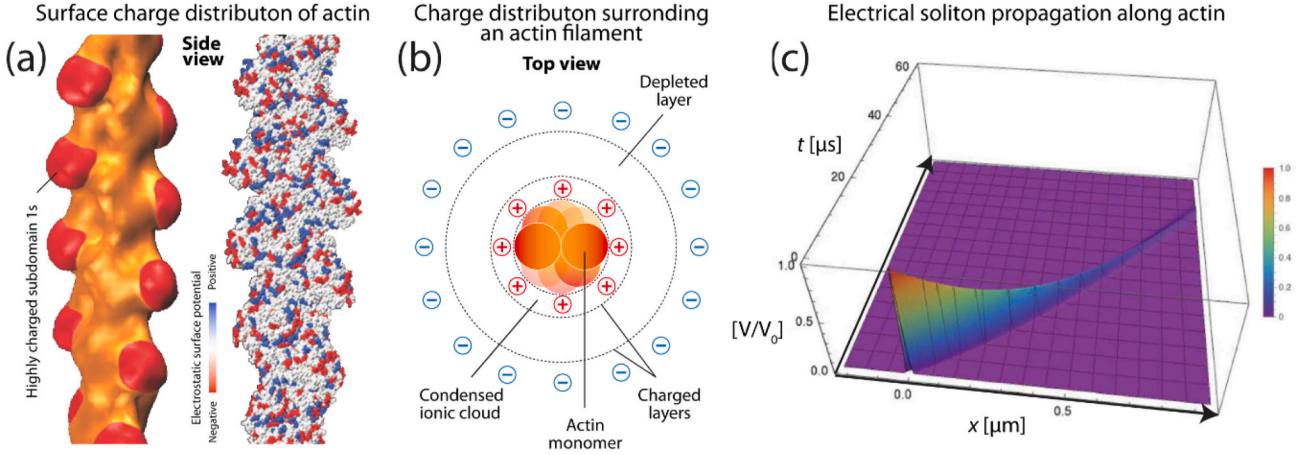

Fig. 3. Electrical aspects of actin. **(a)** Heterogenous charge distribution on the surface of F-actin (left: low-resolution density map, right: high-resolution density map). The heterogenous charge distribution causes an inhomogeneous electrical field around the fibre and modulate the surrounding counterion distribution. Reprinted and modified from Angelini et al. (Angelini et al., 2006), with permission from the publisher. **(b)** Counterion charge distribution around F-actin. Under physiological conditions, positively charge Ca^{2+} ions surround the actin filament due to attractive Coulomb forces, forming a cylindrical ionic cloud. Surrounding the positively charged ion layer, a layer depleted of ions exists, surrounded by a layer of negative ions. Reprinted and modified from Tuszysnki et al. (Tuszynski et al., 2018), with permission from the publisher. **(c)** Simulation of an electrical impulse (soliton) triggered by a 0.15 V input voltage peak traveling along F-actin in intracellular conditions. The soliton travels about 1 μm. For comparison, F-actin has a diameter of about 6 nm, a microtubule one of about 25 nm. Reprinted and modified from Hunley et al. (Hunley et al., 2018), with permission from the publisher.

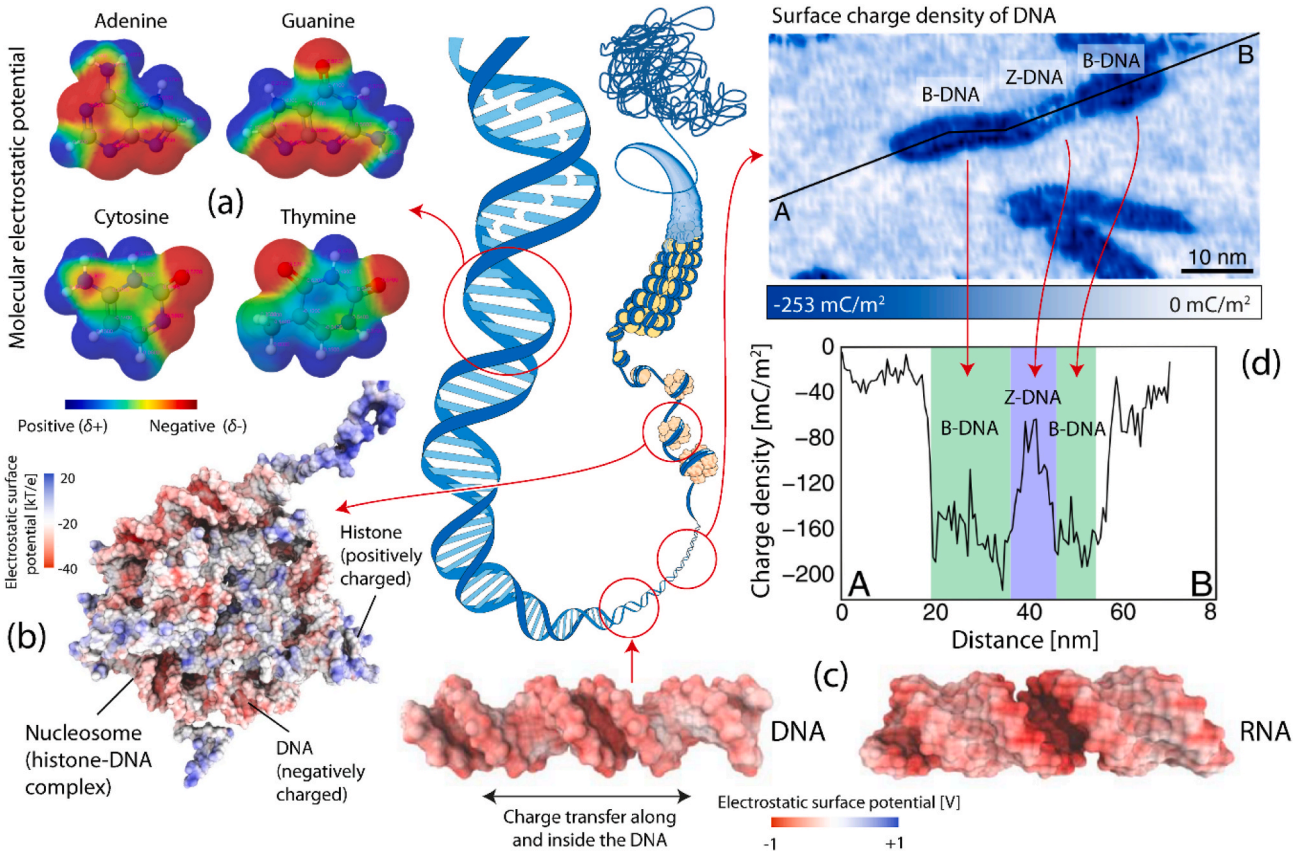

Fig. 4. Electrostatic properties of DNA. **(a)** Molecular electrostatic potential (MEP) maps of DNA's four bases (calculated and visualized via the online simulation software molview.org). **(b)** MEP of the nucleosome. Reprinted and modified from Gebala et al. (Gebala et al., 2019), with permission from the publisher. **(c)** MEP of DNA and RNA. Reprinted and modified from Gebala and Herschlag (Gebala and Herschlag 2019), with permission from the publisher. **(d)** Surface charge density of a DNA sample in an aqueous solution. Reprinted and modified from Kominami et al. (Kominami et al., 2019), with permission from the publisher.

exit tunnel (Mankin 2006). The tunnel is 0.1–0.2 nm wide (Ban et al., 2000; Beckmann et al., 2001), contains water (Voss et al., 2006), is negatively charged (Lu et al., 2007) and has an electrical potential on the inner surface that varies along the length (from −8 mV to −22 mV) (Lu et al., 2007) (Fig. 5(c)). The nascent peptides interact with the tunnel electrically, affecting the functions of the ribosome and the peptide, causing redistribution of charges of the peptide, modulation of translation rates, chaperone interactions or peptide folding (Lu et al., 2007). The charge distribution of nascent proteins emerging out of the ribosomal exit tunnel is bimodal (either negatively or positively charged; Fig. 5(d)) and they interact electrically with the end of the ribosomal exit tunnel, modulating the dynamical properties of the proteins (Knight et al., 2013).

Also, protein-ribosome recognition is governed by electrostatic effects. For example, ribotoxins (cytotoxic ribonucleases that inactivate ribosomes and kill cells; secreted by certain fungi) are positively charged which promotes cellular uptake (Futami et al., 2002; Vives et al., 2003) and exploit the MEP of the ribosome to find the ribosome (electrostatic attraction via the electrical fields of the protein and the ribosome) and achieve binding specifity (Korennykh et al., 2006).

While in nature the majority of proteins have a moderately net charge, some proteins are highly charged ("supercharged proteins"; defined as having more than one net charge per kilodalton of molecular weight) (Ma et al., 2020) (Fig. 5(f)). The charge of proteins depends on the pH of the surrounding solution (Losdorfer Bozic and Podgornik 2017). The net charge of proteins can be positive or negative, while the charge is normally not uniformly distributed due to the cationic (lysine, arginine, histidine) and anionic (glutamate, aspartate) amino acid residues (Gitlin et al., 2006; Isom et al., 2010). About a third of the amino acids on the protein-water interface of a typical proteins are charged, and charged functional groups can be found also in the interior of proteins (Gitlin et al., 2006). Supercharged proteins are available in folded and unfolded (i.e., intrinsically disordered proteins, IDPs) forms. Plotting the net charge per residue and hydrophobicity per residue of proteins in a scatter plot shows that there is significant relationship between charge, hydrophobicity and the folding state of proteins (Uversky et al., 2000; Yaeger-Weiss et al., 2020) (Fig. 5(g)). The conformational ensembles of IDPs is modulated by the net charge per residue (Mao et al., 2010).

An example for the significance of the electrical properties of proteins is protein aggregation as exemplarily happening in Alzheimer's disease with the accumulation of β-amyloid plaques. Assarsson et al., (2014) could show that charge variants of two hydrophilic proteins retard amyloid formation of Aβ40 in a manner highly dependent on their net charge. The proteins displayed interactions with Aβ40 monomers, small aggregates, or both. Electrostatics therefore play a part in nucleation. Another example is alpha-synuclein aggregation, happening in for example Parkinson's disease (Lucking and Brice 2000), where the major role of anions is modulation by protein-water interactions. Electrostatic effects must be considered in this process since fibrillation of alpha-synuclein in the presence of anions is caused by the loss of the uncompensated charge and by an increase in the preferential hydration. These effects trigger partial folding and aggregation via strengthening of hydrophobic interactions (Munishkina et al., 2004).

There is also charge transport happening in proteins with the short- and long-range hopping motion of the mobile charges depending on the physical state of the protein-bound water (Gascoyne et al., 1981). Furthermore, in α-helical proteins, energy released in the hydrolysis of

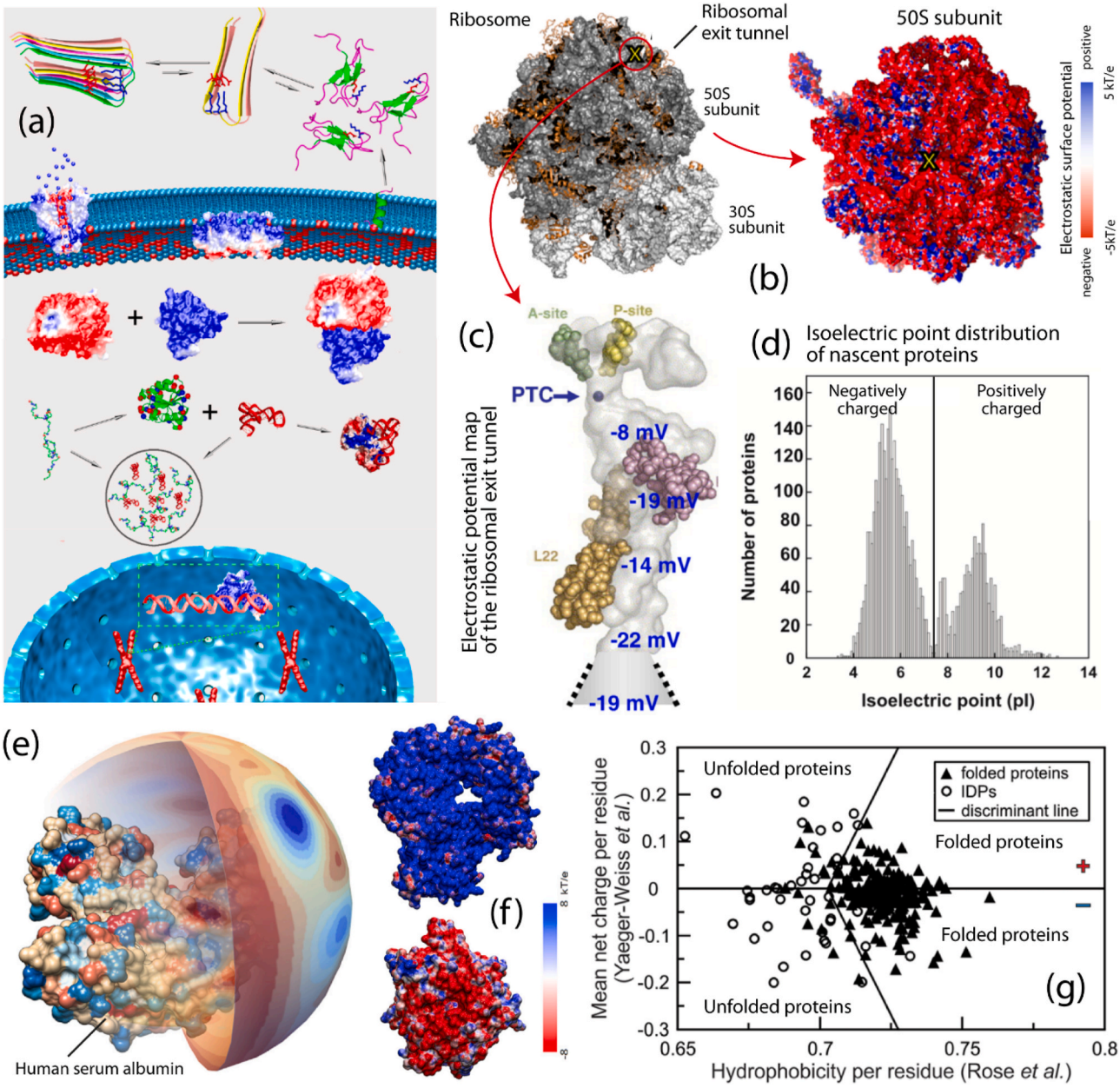

Fig. 5. Electrostatic properties of proteins and the ribosome. **(a)** Visualization of different biochemical processes inside and outside the cell involving electrostatic interactions of proteins, involving protein folding, protein condensations (fibrillation and droplet formation) and binding to other proteins, cell membrane and nucleic acids. Reprinted and modified from Zhou & Pang (Zhou and Pang 2018), with permission from the publisher. **(b)** MEP of the *E. coli* ribosome and the *E. coli* ribosome 50S subunit in proximity of the exit tunnel. Ribosomal proteins are shown in brown and rRNA is shown in grey. The location of the ribosomal exit tunnel is denoted by a yellow x in a red circle. Reprinted and modified from Knight et al. (Knight et al., 2013), with permission from the publisher. **(c)** The specific electrostatic properties of the ribosomal exit tunnel. PTC: peptidyl transferase center. Reprinted and modified from Lu et al. (Lu et al., 2007), with permission from the publisher. **(d)** Distribution of net charge (isoelectric point) for all nascent *E. coli* proteins emerging out of the ribosomal exit tunnel. The distribution is bimodal, i.e. nascent proteins are either positively or negatively charged. This is also true for full-length proteins. Reprinted and modified from Knight et al. (Knight et al., 2013), with permission from the publisher. **(e)** MEP of human serum albumin. The surface charge distribution is shown superimposed onto a circular sphere with projected multipole expansion. Amino acid charges at 7 pH are shown in red (positive charge) or blue (negative charge). Reprinted and modified from Božič and Podgornik (Božič and Podgornik, 2017), with permission from the publisher. **(f)** MEP of two proteins: a strongly positively charged one (telomerase reserve transcriptase; top) and a strongly negatively charged one (nucleosome-remodeling factor subunit RbAp48; below). Reprinted and modified from de Graff et al. (de Graff et al., 2016), with permission from the publisher. **(g)** Net charge nonpolar (NECNOP) plot showing the net charge per residue and hydrophobicity per residue of single-domain globular folded proteins and unfolded (i.e., intrinsically disordered proteins, IDPs). The plot highlights the significant relationship between charge, hydrophobicity, and the folding state of proteins. The visualization can be regarded as an extension of the classical charge-hydropathy plots by Uversky et al. (Uversky et al., 2000). Reprinted and modified from Yaeger-Weiss et al. (Yaeger-Weiss et al., 2020), with permission from the publisher.

ATP is transferred in the form of vibration solitons (Davydov solitons) (Davydov 1977).

While short-range electrostatic interactions play an important role in binding of proteins (Sheinerman 2000), long-range electric-field effects also happen between proteins (Ganguly et al., 2013; Shashikala et al., 2019). The net charge of a protein is influenced by a neighbouring protein when both approach each other below the Debye length, possibly affecting the function of the protein(s) (Dashnaw et al., 2021). As shown recently, long-range charge reorganization acts as an allosteric control signal in proteins ("charge-reorganization allostery") which seems to be an important mechanism for protein interactions (e.g. antibody–antigen binding) (Banerjee-Ghosh et al., 2020).

3. Bioelectricity at the level of cell organelles and cells

3.1. Cell organelles and the intracellular space

All cell organelles have a specific membrane potential (and pH value) (Fig. 6(a)) (Bagkos et al., 2014; Koivusalo et al., 2011; Steinberg et al., 2007; Tyner et al., 2007), giving rise to a complex intracellular environment with respect to bioelectric currents and forces.

While ion channels are key factors in regulating the membrane potential, the source of the cellular resting membrane potential is still debated with important works challenging the current standard explanatory model (relying primarily on active pumping of ions through the membrane) and pointing out the significant role of water adsorption and desertion on proteins for the generation (Bagatolli et al., 2020; Jaeken 2017; Ling 1975, 1982; Matveev 2019; Tamagawa and Ikeda 2018). According to a recent work (Lee 2020), "the neural resting/action potential is essentially a protonic/cationic membrane capacitor behaviour", but this claim was also contested (Silverstein 2022). Concerning the membrane potential of mitochondria, electron flow through electron transport chain complexes I–IV seems to be the main source for it (Bagkos et al., 2014).

The bioelectric aspects of mitochondria are of particular relevance (Figs. 7 and 8(a)). Mitochondria not only stand out because of their high membrane potential but also since they can form mitochondrial networks that can be electrically coupled. Mitochondria can be regarded as electrical transmission fibres (Amchenkova et al., 1988; Skulachev 2001). According to Skulachev (2001) at least three charge transmission

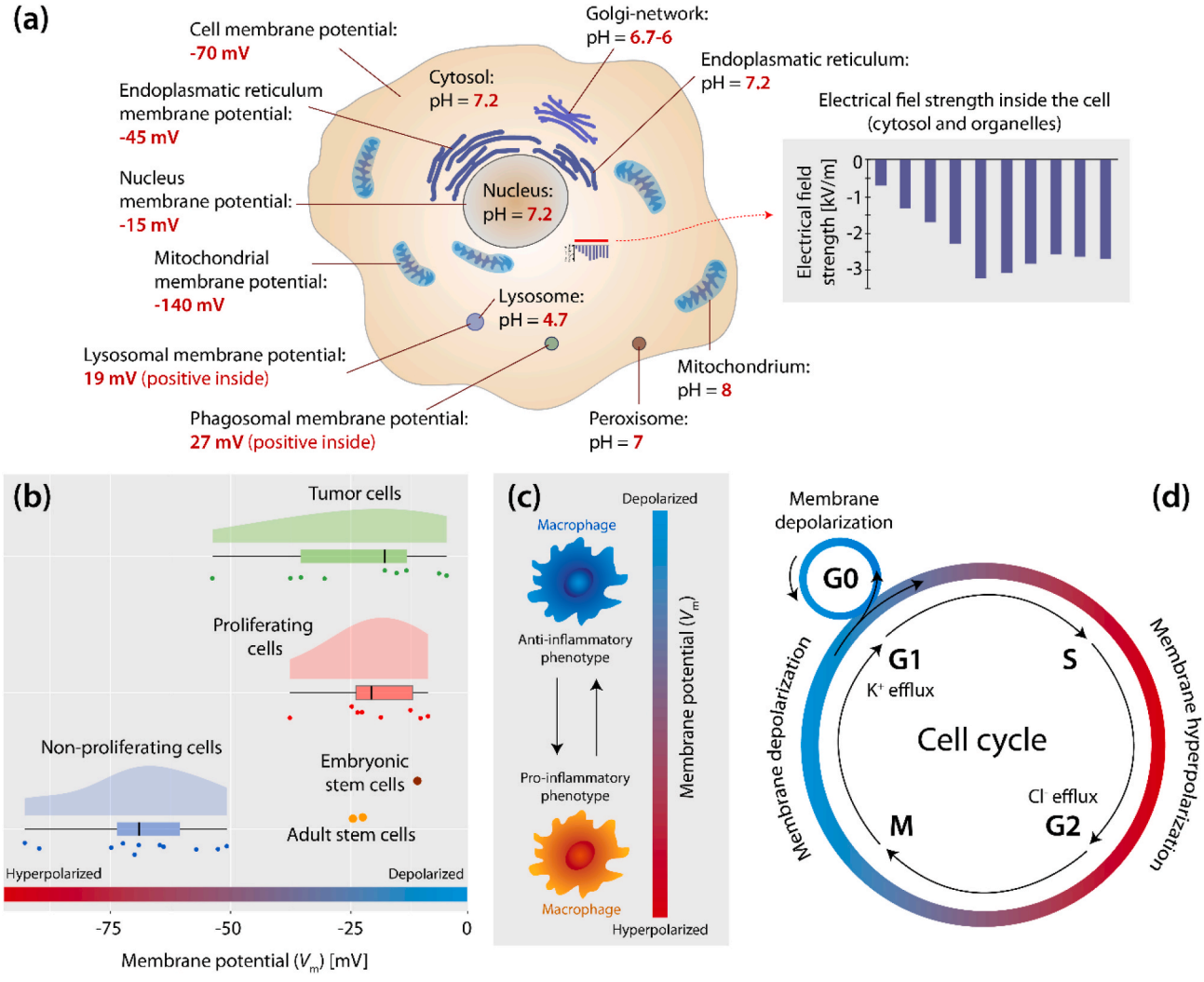

Fig. 6. Visualizations of the importance of the membrane potential (V_m) for cellular function. **(a)** Membrane potentials and pH values of subcellular structured of a cell (values according to (Audi et al., 2020; Bagkos et al., 2014; Koivusalo et al., 2011; Steinberg et al., 2007)). The values represent typical values measured). The insert shows measured electrical field strength values (with a fluorescence probe) from a section inside the cell (covering cytosol and cell organelles) according to Tyner et al. (Tyner et al., 2007). The different pH values of cell organelles and molecules form pH gradients inside the cell (Martin et al., 2011; Slavík 1983). **(b)** Cell types can be grouped according to their V_m (according to data from Levin et al. (Levin and Stevenson 2012),). **(c)** The phenotype of macrophages depends on Vm. Modified after Erndt-Marino and Hahn (Joshua and Mariah, 2016). (c) V_m during the cell cycle with hyperpolarization during the S and G2 phase and depolarization during the M G1 phase as well as at G0. Modified after Yang and Brackenburry (Yang and Brackenbury 2013).

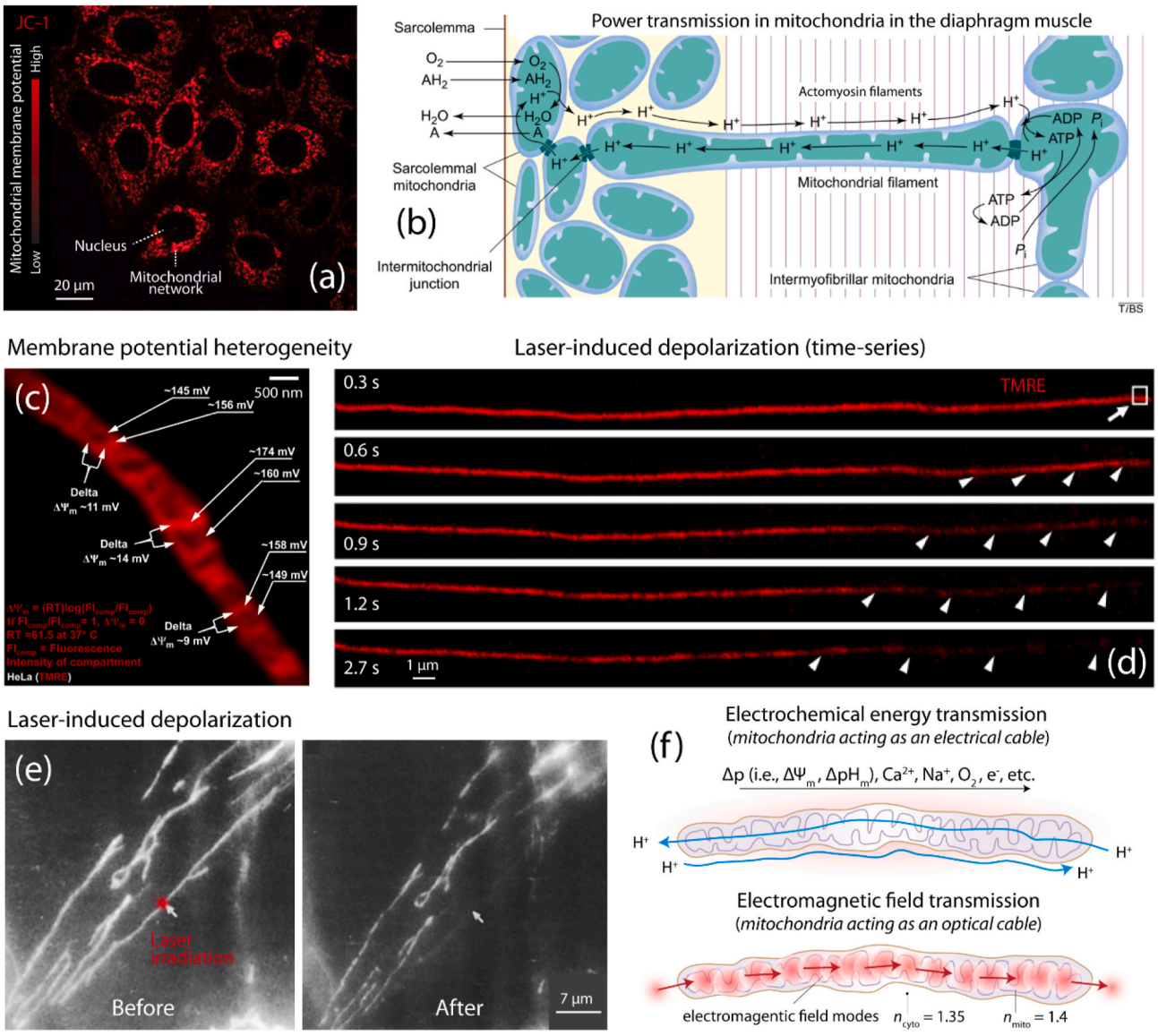

Fig. 7. Electrical properties of mitochondria. **(a)** Fluorescent images of living and dead HepG 2 cells showing the membrane potential of mitochondrial networks. Stained with the fluorescence probe MR-1. Reprinted and modified from Tian et al. (Tian et al., 2019), with permission from the publisher. **(b)** Possible mechanism of power transmission in mitochondria in the diaphragm muscle. A proton (H^+) current flows from subsarcolemmal mitochondria along a mitochondrial filament to an intermyofibrillar mitochondrion. During ATP synthesis, H^+ ions move to the matrix and diffuse back to the subsarcolemmal mitochondrion inside the matrix of the mitochondrial filament. Reprinted and modified from Skulachev (Skulachev 2001), with permission from the publisher. **(c)** Live-cell Airyscan image of a mitochondrion in a HeLa cell, showing the heterogeneity of the membrane potential. (d) Live-cell Airyscan images of laser-induced mitochondrial membrane depolarization in living human skin fibroblasts. A gradual, wave-like, loss of the membrane potential along the inner mitochondrial membrane (arrowheads) was observed. Staining with TMRE. **(c)** and **(d)** reprinted and modified from Wolf et al. (Wolf et al., 2019), with permission from the publisher. **(e)** Laser-induced depolarization of the membrane potential of a 40 µm long mitochondrial filament (as part of a mitochondrial network) in a human fibroblast by a focused laser beam (spot size ≤0.5 µm). Staining with ethylenediamine. Reprinted and modified from Amchenkova et al. (Amchenkova et al., 1988), with permission from the publisher. **(f)** Possible physical energy transmission mechanisms in mitochondria: electrical/electrochemical and optical. Reprinted and modified from Scholkmann, 2016, with permission from the publisher.

processes could take place on and in mitochondria: (i) transmission of electrochemical transmembrane H^+ potential difference Δp (i.e. membrane potential and pH) in form of diffusion of mobile ions (e.g., K^+, Cl^-, Na^+), (ii) lateral movement of H^+ along the mitochondrial membrane surface (i.e. a proton current) "via membrane-bound water molecules forming ice-like structure" and H^+ movement inside the mitochondria, and (iii) by lateral and intermembrane electron (e^-) transport (i.e. an electrical current), as summarized in a recent publication of one of the present authors (Scholkmann (2016)).

The proton current along the mitochondrial membrane surface would enable a high charge transmission rate since higher in structured water, i.e., ice or bound water around the mitochondrion.

Mitochondria near the nucleus (i.e., in the perinuclear region) have generally a lower membrane potential than in the periphery of the cell (Collins et al., 2002; Pletjushkina et al., 2006). There is a great heterogeneity with respect to morphology and the metabolic state (indicated by the membrane potential) of mitochondria in cells (Collins et al., 2002; Kuznetsov and Margreiter 2009). The mitochondrial membrane potential is not constant but shows continuous spontaneous variations ("mitochondrial potential fluctuations" or "mitochondrial flickers" (Loew et al., 1993; O'Reilly et al., 2003; Teodoro et al., 2018; Vergun et al., 2003) with periods in the order of seconds or minutes and a

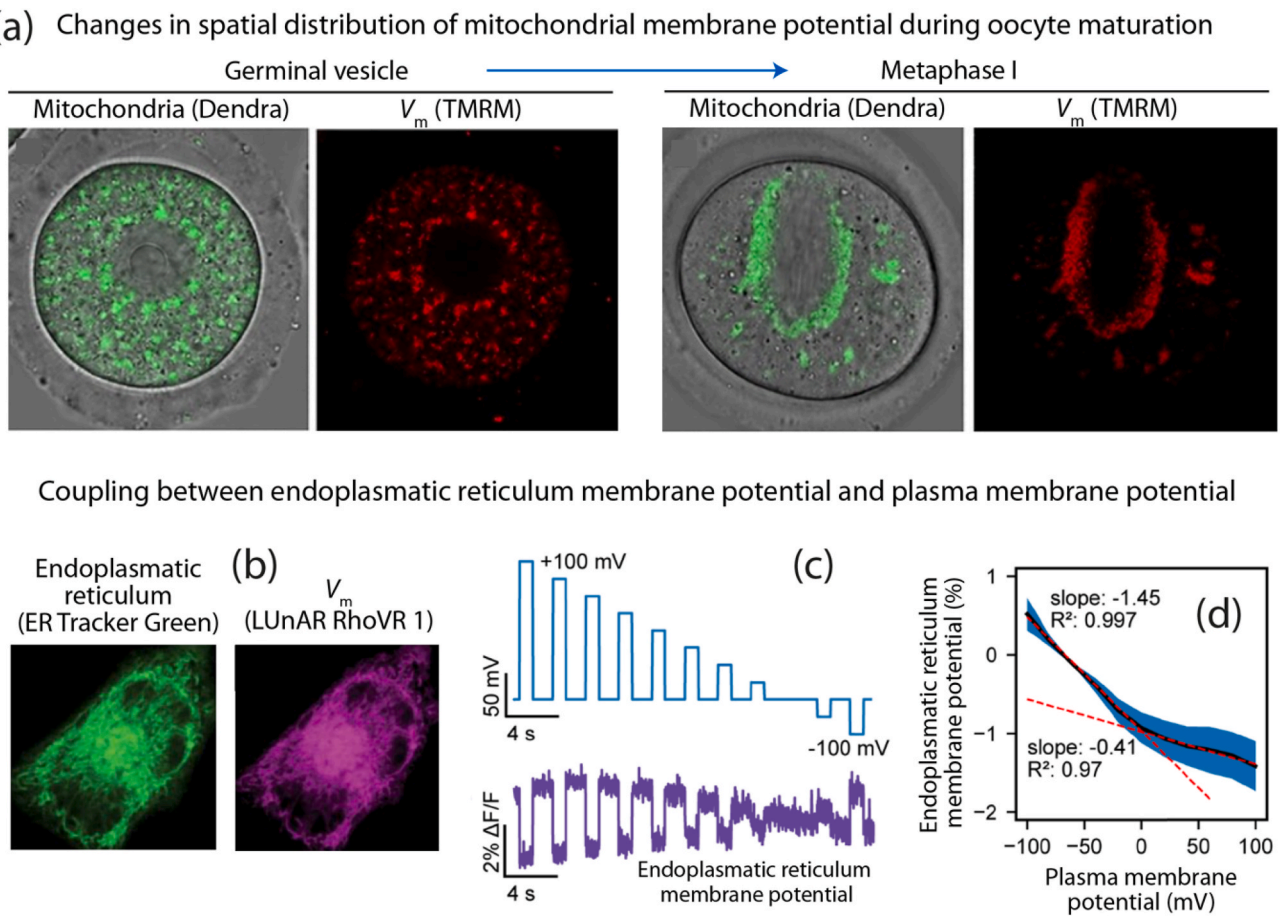

Fig. 8. Membrane potential of mitochondria and the endoplasmic reticulum. **(a)** Spatio-temporal dynamics of mitochondrial membrane potential were observed during oocyte maturation (Al-Zubaidi et al., 2019). The images show the result of staining the oocytes for mitochondria (Dendra; green) and mitochondrial membrane potential (TMRM; red) at two different time-points (germinal vesicle, metaphase I). It is clearly visible that mitochondria around the germinal vesicle have higher membrane potential than the mitochondria not surrounding it. Reprinted and modified from Al-Zubaibi et al. (Al-Zubaidi et al., 2019), with permission from the publisher. **(b–d)** Features of the endoplasmic reticulum membrane potential (Klier et al., 2022). HeLa cells stained for endoplasmic reticulum (ER Tracker Green; green) and endoplasmic reticulum membrane potential (LUnAR RhoVR 1; magenta). **(c, d)** Electrical coupling between the endoplasmic reticulum and the plasma membrane of HeLa cells. Shown are time-series of the patch-clamped HeLa cells and the fluorescence associated with the endoplasmic reticulum membrane potential. The relationship between the two electrical membrane potentials follow a non-linear relationship. It sees that the endoplasmic reticulum "rectifies, or opposes, plasma membrane potential commands at values more positive than 0 mV" (Klier et al., 2022). Reprinted and modified from Klier et al. (Klier et al., 2022), with permission from the publisher.

significant amplitude, e.g. 17.6 ± 1.0 mV (range: 6–130 mV) based on the analysis of a large sample of mitochondria (O'Reilly et al., 2003). The fluctuations are linked to the metabolic state of the mitochondria (Teodoro et al., 2018). As shown in muscle mitochondrial networks, mitochondria are linked by intermitochondrial junctions to form dynamic subnetworks that exclude dysfunctional mitochondria so that they are no longer electrically coupled to the network (Glancy et al., 2017). High-resolution fluorescence microscopy also showed recently that the inner mitochondrial membrane (which consists of cristae and inner boundary membranes) does not have a uniform electrical potential (as traditionally believed) but is divided into segments with distinct membrane potentials (Wolf et al., 2019). The membrane potential of cristae was higher compared to the inner boundary membranes of the mitochondria. There is therefore an intramitochondrial heterogeneity of the mitochondrial membrane potential.

Laser-induced depolarization of the mitochondrial membrane potential affects electrically connected parts of the mitochondrial network (Amchenkova et al., 1988), whereas the decline in membrane potential is gradually and spreads in a wave-like manner with inhomogeneous changes of the membrane potential inside the mitochondrion (Wolf et al., 2019), indicating that mitochondria cannot be compared to simple electrical cables but complex charge transmission cables with independent bioenergetics units inside.

Mitochondria are also the source of radiating high-frequency electromagnetic fields in the optical spectral region, i.e. spontaneous (low-level) chemiluminescence or ultra-weak photon emission (Hideg et al., 1991; Radi et al., 1993; Stauff and Ostrowski 1967), most likely as a result of redox reactions due to reactive oxygen species (ROS) of the mitochondria constantly released by mitochondria (0.1–0.4% O_2 consumed) (Murphy 2009). The emissions in the ultra-violet spectral region were assigned to tryptophan in particular (Konev 1967).

There is a spatio-temporal change of the membrane potential of mitochondria and mitochondrial networks. For example, characteristic spatio-temporal dynamics of mitochondrial membrane potential were observed during oocyte maturation (Fig. 8(a)) (Al-Zubaidi et al., 2019). In this study, the authors found that the mitochondrial membrane potential increases through the time course of oocyte maturation and that an increased membrane potential was detected in mitochondria in the vicinity of the first meiotic spindle.

The membrane potential can be measured using electrode-based recording techniques and optical recording techniques (Lazzari-Dean et al., 2021). There is much progress currently in developing genetically-encoded voltage indicators (GEVI) that are able to measure the membrane potential of cell organelles. Recently, a GEVI specific for

the endoplasmic reticulum membrane potential was developed (Klier et al., 2022). Application of the GEVI showed that there is a functional coupling between the endoplasmic reticulum membrane potential and the plasma membrane potential (Fig. 8(b) (Klier et al., 2022)). It is foreseeable that in the near future GEVIs for each cellular organelle will be developed and the electrical functional coupling between the organelles as well as the organelles and the whole cell (i.e. plasma membrane potential) will be explored in detail. Recently, however, it was shown that one has to be careful when using fluorescence dyes for the quantification of the membrane potential, as chemical modifications of the fluorescence markers also occur, which have so far received too little attention (Zorova et al., 2022).

In the cytoplasm, lipid droplets are present that have important biological functions, including the maintenance of cellular homeostasis (Gao and Goodman 2015). Interestingly, there is a strong electrical field (in the order of 10^7 V/cm) at the water-oil interface of water microdroplets in oil (Xiong et al., 2020). This strong field might be also present in lipid droplets in the cytoplasm, having an effect on the droplet's interaction with the surrounding molecules and cell organelles.

The cytoplasm is heavily crowded with ions, (macro)molecules, cell organelles and vesicles. According to Spitzer and Poolmann (Spitzer and Poolman 2005) "charged cytoplasmic macromolecules are stabilized electrostatically by their ionic atmospheres" and the "high cytoplasmic crowding (25–50% of cell volume) shapes the remaining cell volume (50–75%) into transient networks of electrolyte pathways and pools." Powered by variable electrochemical gradients inside the cell, 'semi--conductive' electrolyte pathways are predicted to exist inside cells that "guides the flow of biochemical ions throughout the cytoplasm." (Spitzer and Poolman 2005). Electrical gradients within the cytoplasm are seemingly involved in intracellular structural and functional organization. Thus, a cell can be considered as a "miniaturized electrophoresis chamber" (De Loof 1986). As Flegr highlighted (Flegr 2009), assuming that only diffusion is moving the proteins inside a cell leads to the conclusion that it would require about 26 min for a typical protein to move across the interior of a HeLa cell (Wheatley 1985). This is in conflict with *in vivo* measurements that show that such a movement across the whole cell takes place in seconds (Stacey and Allfrey 1977). That the distribution of proteins (RAF and pRAF) in the cell does not follow diffusion but electrical gradient was shown with computer simulations and *in vitro* experiments; the concentration gradients of these proteins observed *in vivo* could well explained by electrostatic forces acting on them but not by diffusion (Cunningham et al., 2012) (Fig. 9 (a)). While the classical view is that the electrical field produced by a charged surface (membrane) decay rapidly (Debye length: 1 nm), the modern view it that this does not apply to the situation in the cell where the charged surfaces are not impermeable but ion transporters, pores and ion channels exist on the membranes. As Cunningham et al. explain for the case of the nuclear membrane, "the flux of ions through the pores prevent them from screening the nuclear membrane charge and creates a counter-current as ions flow from the nucleus into the endoplasmatic reticulum where membrane pumps return them to the cytoplasm" (Cunningham et al., 2012). A Debye length of 3–4 μm (which corresponds to the distance between the nuclear membrane and the cell membrane) is predicted by the modelling of Cunningham et al. According to Flegr (2009), protons from the cell center are transported through channels of the endoplasmic reticulum to the periphery,

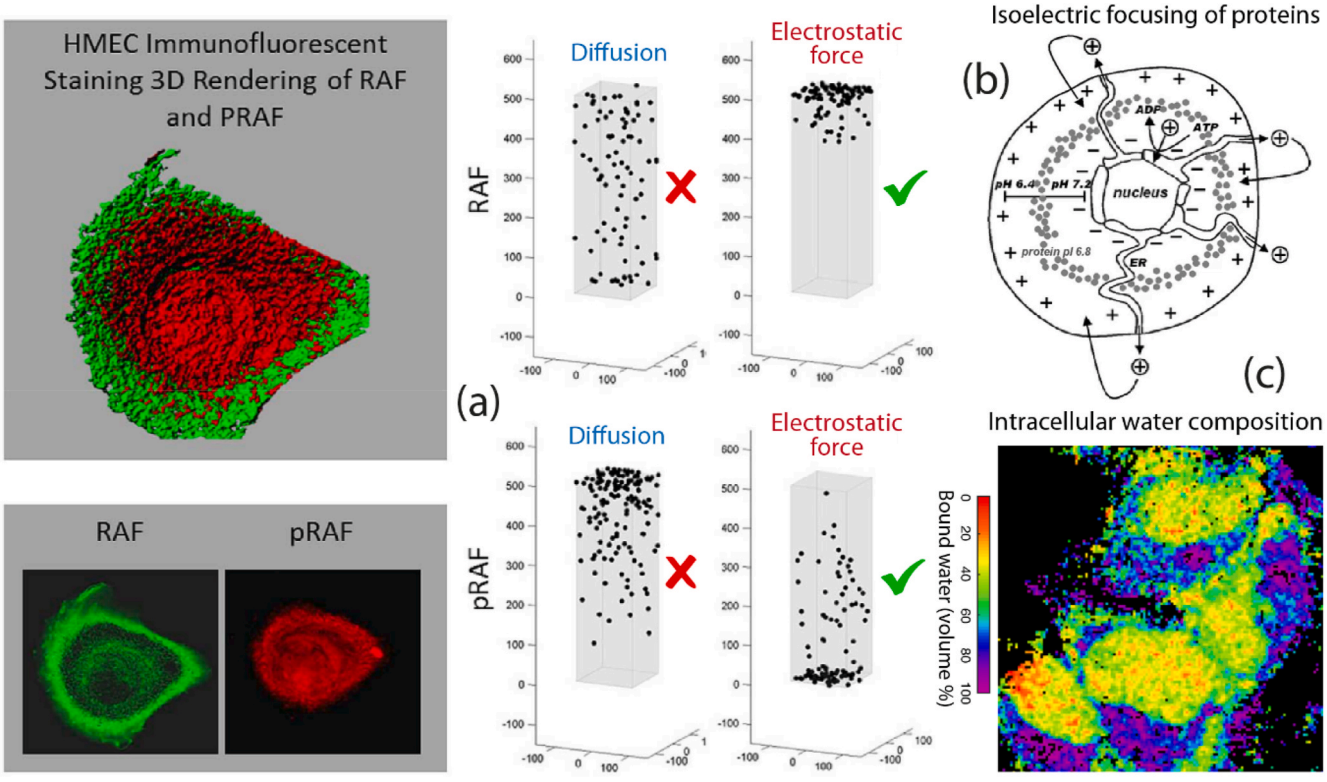

Fig. 9. The role of electrical forces in intracellular sorting of proteins, and the heterogeneity of intracellular water composition. **(a)** It is known that the protein RAC clusters around the cell membrane (green) and the protein pRAF around the nuclear membrane (red). Diffusion cannot explain this *in vivo* observation but taking into account the electrical forces between the charged membranes, the intracellular electrical field and the charged proteins, modulated by the protein's isoelectric point values, the cytosolic pH and the protein's phosphorylation state, can explain it. Reprinted and modified from Cunningham et al. (Cunningham et al., 2012), with permission from the publisher. **(b)** Isoelectric focusing of proteins inside a cell by proton transport through channels of endoplasmic reticule from the center to the periphery of the cell. Reprinted and modified from Flegr (Flegr 2009), with permission from the publisher. (c) The heterogeneity of intracellular water composition: intracellular water is bound to 64% in the cytoplasm and 35% in the nucleus (i.e. the nucleus has more free water) (data for HeLa cells). Reprinted and modified from Shi et al. (Shi et al., 2019), with permission from the publisher.

generating pH and electrical field gradients inside the cell and thus isoelectric focusing (i.e. the first step of electrophoresis) of proteins (and possibly also low-molecular weight components such as amino acids) (Fig. 9(b)).

Of particular importance is the water in the cells which has specific properties. According to microscopic imaging with stimulated Raman excited fluorescence microscopy, intracellular water is bound to 64% in the cytoplasm and 35% in the nucleus (i.e. the nucleus has more free water) (data for HeLa cells) (Shi et al., 2019) (Fig. 9(c)). The high amount of (gel-like) bound water in the cytoplasm highlights the special biochemical and biophysical state of the intracellular place. Molecules and organelles in the cytoplasm contain a water layer (a hydration shell) that has structural and functional significance, e.g. for protein folding and molecular recognition (Fogarty et al., 2013; Levy and Onuchic 2006). The surface charges on molecules influence the local properties of the water layer, for example dipolar nanodomains are induced in protein hydration shells (Martin and Matyushov 2015).

Bound and free water around molecules have different dielectric properties (Cherkasova et al., 2020). While bulk water has a relative permittivity (dielectric constant) of about 75 (at 35 °C) (Malmberg and Maryott 1956), bound water has a much lower value, e.g. 2–4 in a protein hydration shell (Seyedi and Matyushov 2018). Inside a protein, the dielectric constant is about 6–7 and reaches 20–30 at the surface of the protein (Li et al., 2013). The relative permittivity is important for electrostatic effects since the electrostatic force between electrically charged bodies is inversely proportional to the permittivity of the medium in which they are located. A lower relative permittivity is associated with a stronger electrostatic force. Bound water is therefore able to

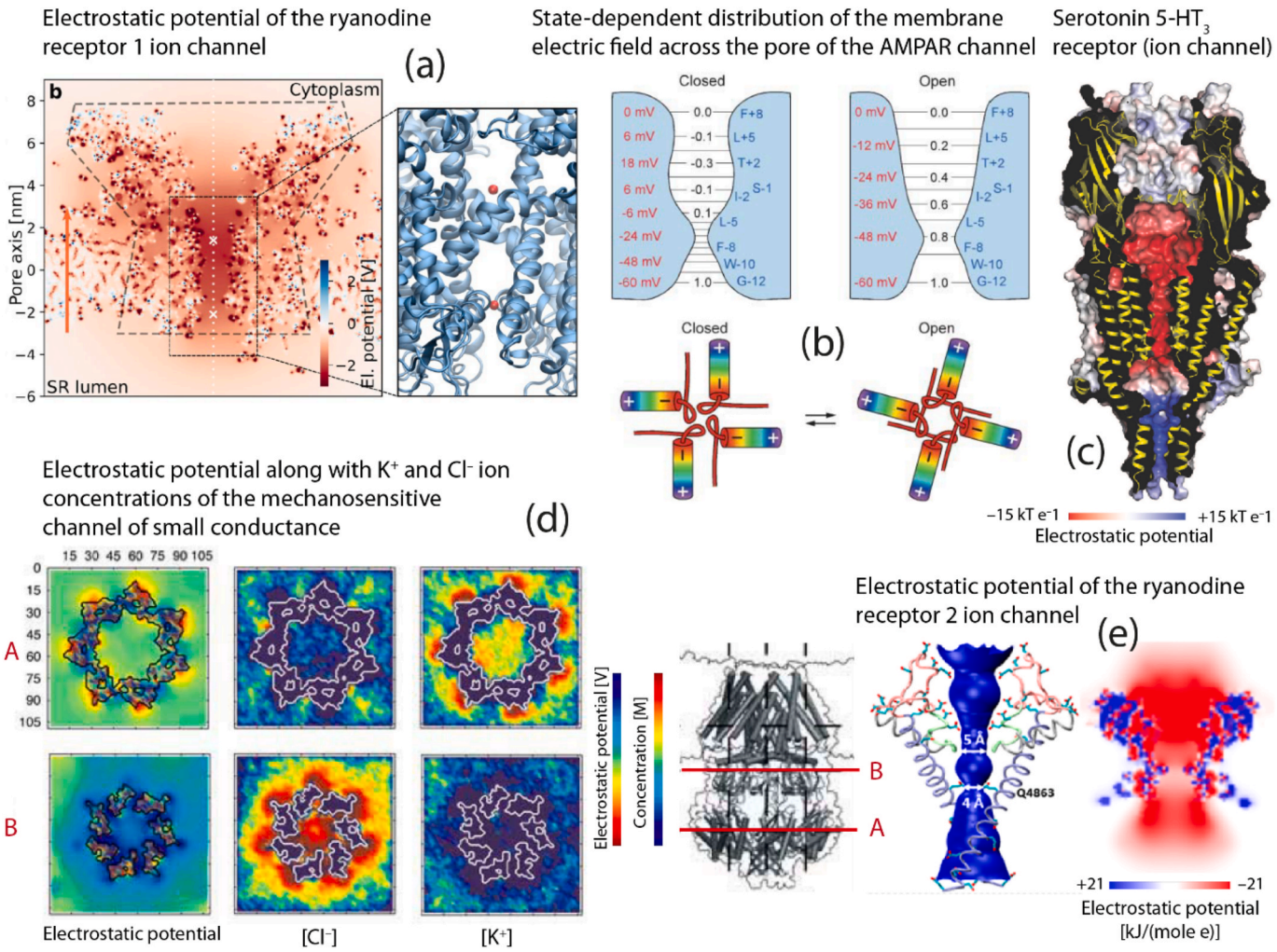

Fig. 10. Electrostatic properties of ion channels. **(a)** Electrostatic potential on a slice of the ryanodine receptor 1 (RnR1) Ca^{2+} ion channel (found in mammalian skeletal muscle). The outline of the channel is marked with dashed lines. The orange arrow shows the direction of the Ca^{2+} ion current (Heinz et al., 2018). Reprinted and modified from Heinz et al. (Heinz et al., 2018), with permission from the publisher. **(b)** State-dependent distribution of the membrane electric field across the α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid receptor (AMPAR) channel pore (Sobolevsky et al., 2005). The M2 loop dipoles seem to move during the transition from closed to open. The cylinders represent the polar α-helical regions of the M2 loops (blue: positively charged N-terminal end; red: negatively charged C-terminal end). Reprinted and modified from Sobolevsky et al. (Sobolevsky et al., 2005), with permission from the publisher. **(c)** Electrostatic potential of the mouse 5-HT_3 receptor (ion channel) (Hassaine et al., 2014). Note the negatively charged transmembrane core which facilitated the passage of the positively charged serotonin molecule. Reprinted and modified from Hassaine et al. (Hassaine et al., 2014), with permission from the publisher. **(d)** 2D sliced through a mechanosensitive channel of small conductance (MscS) showing the electrostatic potential along with the K^+ and Cl^- ion concentrations. The electrostatic potential is positive at the transmembrane region of MscS and the distal C-termini while it is negative at the distal zone of the cytoplasmic domain. Reprinted and modified from Sotomayor et al. (Sotomayor et al., 2006), with permission from the publisher. **(e)** Electrostatic potential on a slice of the ryanodine receptor 1 (RnR1) Ca^{2+} ion channel (found primarily in cardiac muscle). The structure of the ion channel is shown left, the corresponding electrostatic potential map of the channel right (Miranda et al., 2018). Reprinted from Miranda et al. (Miranda et al., 2018) with permission from the publisher.

mediate stronger electrostatic interactions. It also enables specific charge (e.g. proton) movement along biomolecules (Gascoyne et al., 1981).

3.2. Ion transporters and ion channels

It is not surprising that electrostatic and electrodynamic phenomena play a major role in the transport of ions through membranes. Ion transporters and ion channels, which consists of charged proteins, are the structural elements responsible for this. The surface of the ion transporters and ion channels are electrically charged, establishing an electrical surface potential between the transporter/channel and the water which is inside them. The surface potential attracts positively charged solutes (counterions) and repels of like charges, structuring the surrounding outside and inside these transporters/channels (Green and Andersen 1991). In the following, a few examples will be given about the electrical aspects of these ion-transporting structures.

The active ion transporter and transmembrane protein Na^+,K^+-ATPase, member of the P-type ATPase family, is present in the plasma membrane of all animal cells. The electrostatic interactions between the cytoplasmic N-terminus of the protein's catalytic α-subunit and the adjacent membrane is responsible for the E1-E2 conformational shift which regulates the protein's activity and which depends on the ionic strength and modifications of the protein, e.g. phosphorylation by protein kinases (Jiang et al., 2017).

Another active ion transporter is the F(1)F(o) ATP synthases in mitochondria which uses the proton-motive force, consisting of the transmembrane proton concentration gradient (ΔpH) and the membrane potential, to generate ATP. Interestingly, the proton gradient and the membrane potential have different effects on the functioning; the membrane potential seems to be responsible to induce a rotary torque in the ATP synthase (Dimroth et al., 2000). Electrostatic free energy is driving the rotary mechanism of this enzyme (Mukherjee and Warshel 2011).

The electrical surface potential and electrical field inside ion channels play a fundamental role for their functioning (Fig. 10), enabling the opening and closing of the channels as well as the ion-selectivity. The activity of the channel can be regulated by the membrane potential (voltage-gated ion channels) which is an essential feature of excitable cells/tissue. These channels open and close depending on the membrane potential. Voltage-activated ion channels are expressed in non-excitable cells as well (Kaestner et al., 2018). Red blood cells, for example, contain the Ca^{2+}-activated K^+ channel (Gárdos channel) that is controlled by the membrane potential (Bennekou and Christophersen 2003; Maher and Kuchel 2003).

Ion channels can be also sensitive to electromagnetic fields. For example, the cellular Na^+ ion channel is predicted to exhibit an electrical nonlinearity at microwave frequencies which affects the function when excited by an amplitude-modulated electric field (a nonthermal electromagnetic biological effect) (Stoykov et al., 2004). The activity of voltage-gated Ca^{2+} channels have been found to be able to be modulated by an electromagnetic field exposure (Bertagna et al., 2021).

What should also not go unmentioned is the fact that the electric properties of ion transporters and ion channels can be modelled and understood generally within the classical electrodynamic framework but for a deeper comprehension, quantum physical effects (e.g. quantum tunneling, quantum coherence) need to be taken into account (Moradi et al., 2015; Salari et al., 2017; Seifi et al., 2022; Song and Jiang 2021; Summhammer et al. 2012, 2018, 2020; Vaziri and Plenio 2010). The existence of a quantum-confined ion superfluid (QSF) wave along the neuronal axons during nerve signal transmission has been proposed (Zhang and Jiang 2019). The passage of ions through ion channels can be also modelled as a QSF phenomenon (Wen et al., 2018). The ionic superfluid formation in ion channels seems to be the results of an confinement-induced attraction-repulsion balance of charged particles (Zhang et al., 2021).

3.3. Cells

At the cellular level of organization the most prominent feature is the cell's electrical charge, i.e. their type and state specific electrical membrane potential (Levin and Stevenson 2012; Yang and Brackenbury 2013). As already discussed in Chapter 2, the charge of the cell is dependent on many factors, including the type of cell and state of cell cycle.

The membrane potential is specific for different types of cells (Levin and Stevenson 2012) (Fig. 1(a)), changes with the cell cycle (Yang and Brackenbury 2013) (Fig. 1(c)) and is associated with phenotypical changes of the cell – for example, the transition from an anti-inflammatory phenotype of a macrophage to a pro-inflammatory one (from depolarized to hyperpolarized) (Joshua and Mariah, 2016) (Fig. 1(b)). All cell organelles have a specific membrane potential (and pH value) (Fig. 1(c)) as well (Bagkos et al., 2014; Koivusalo et al., 2011; Steinberg et al., 2007; Tyner et al., 2007), giving rise to a complex intracellular environment with respect to bioelectric currents and forces. The membrane potential is not just an "epiphenomenon" but a causative agent, being able to act in a top-down manner on downstream biochemical and biophysical processes taking place inside and outside the cell – it not only plays an important role in excitable cells (e.g. enabling electrical signalling in the nervous system) but has also significant biological functions in non-excitable cells, which are increasingly researched and discovered (Abdul Kadir et al., 2018).

In excitable cells, the membrane potential can change quickly (in sign and amplitude). Interestingly, non-excitable cells also show fluctuations of the membrane potential and cancer cells in particular. More aggressive cancer cells show a larger and more pronounced fluctuation (Quicke et al., 2021). The biological significance the membrane potential fluctuations in cancer cells is just beginning to be explored and novel cell imaging approaches "open a new window onto the 'electro--excitable' pathophysiology of cancer" (Quicke et al., 2021).

Due to the relatively high membrane potential, the cell membrane acts like a Faraday cage. With a membrane potential (V_m) for a typical non-proliferating mammalian cell of −70 mV and a membrane thickness (d) of 5 mm, the electrical field strength (E) across the membrane is in the order of kV/m ($E = V_m/d = 70$ mV/5 nm = 200.000 V/m). The cell is therefore generally shielded from external electromagnetic influences and disturbances. However, ion channels, membrane proteins, lipid rafts and other parts of the cell membrane are influenced by the direct electromagnetic environment and can play an interface between cellular function and external physical influences, such as currents and electromagnetic fields (Bersani et al., 1997; Galvanovskis and Sandblom 1997; McLeod et al., 1992; Panagopoulos et al., 2002; Stanley and Friedman 2019).

Since the distribution of ion channels and various physicochemical properties of the cell membrane can be inhomogeneous/heterogenous (involving the formation of macroscopic domains as well as micro- and nanodomains) (Efremov 2021), there will also be inhomogeneities in the spatial distribution of the cellular membrane potential. Such spatial variations have been measured for example in the mitochondrial membrane potential (Wolf et al., 2019).

Molecules attached to the cell surface also play an important role for the electrical properties of cells. For example, incorporated in the red blood cell (RBC) membrane are glycoproteins (mainly glycophorin A which is rich in sialic acids) that create a negatively charged RBC surface (Lima et al., 2020; Suzuki et al., 1998; Varki and Varki 2007). A RBC in suspension is characterized by a structuring of charges, ions and molecules surrounding it. The driving force for this structuring is the electrical charge of the membrane. Two ionic layers and an electrical potential between them (Zeta potential) are created (Fernandes et al., 2011) (Fig. 11(a)). Changes in the ionic composition of the intracellular and extracellular milieu as well as changes in the composition of molecules integrated or attached to the membrane (like the electrically negatively charged glycoproteins) lead to changes in the surface

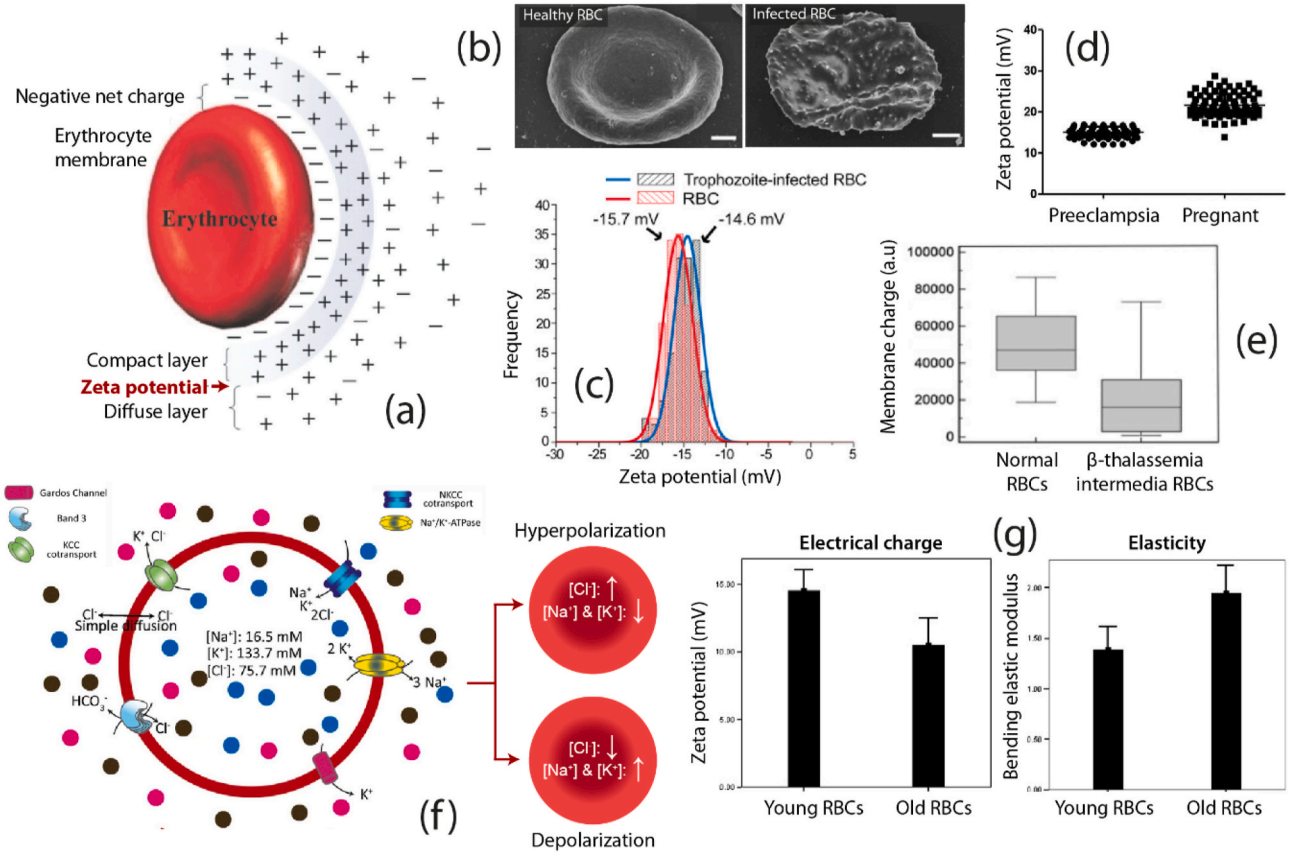

Fig. 11. Electrical properties of red blood cells (RBCs). **(a)** Charge distribution around a RBC with the zeta potential and the two ionic layers (compact layer and diffuse layer). The compact layer comprises cations and the cloud-like diffused layer of a mixture of anions and cations. Between the two layers there is a sheer plate, Reprinted and modified from Fernandes et al. (Fernandes et al., 2011), based on Pollack et al. (Pollack et al., 1965) and Rouger and Salmon (Rouger and Salmon 1981), with permission from the publisher. **(b, c)** The effect of *Plasmodium falciparum* infection on the electrical properties of RBCs. **(b)** Electron microscopy images of healthy and *Plasmodium falciparum*-infected RBCs. **(c)** *Plasmodium falciparum*-infected RBCs have a lower zeta potential compared to healthy RBCs. **(b)** and **(c)** reprinted and modified from Tokumasu et al. (Tokumasu et al., 2012), with permission from the publisher. **(d)** RBCs of women with preeclampsia have a reduced zeta potential of RBCs compared to the RBCs of healthy pregnant women. Reprinted and modified from Karemore et al. (Karemore and Avari 2019), with permission from the publisher. **(e)** RBCs of patients with β-thalassemia have a reduced membrane charge. Reprinted and modified from Lima et al. (Lima et al., 2020), with permission from the publisher. **(f)** Visualization of driving forces for RBC plasma membrane potential changes. "The low cation permeability in the RBC plasma membrane prevents osmotic swelling and lysis. K^+ and Na^+ transport is mainly driven by Na^+/K^+-ATPase, and their respective intra and extracellular concentrations are very marked. Conversely, chloride anions (Cl^-) are highly permeable with differences in intra and extracellular concentration which are not so marked. During hyperpolarization, there is a prominent increase in intracellular negative charges (Cl^-), with a less evident increase in positive charges. The opposite is observed in depolarized RBCs, where intracellular Cl^- anions decrease considerably, while intracellular cations increase slightly. The dynamically orchestrated variation of cytosolic ion concentration depends on the turning on-off of several pumps and membrane transporters like Na^+/K^+-ATPase, Band 3, NKCC, and KCC. Some voltage-dependent anion channels also participate in plasma membrane potential variation." (Balach et al., 2019). Reprinted and modified from Balach et al. (Balach et al., 2019), with permission from the publisher. **(g)** Older RBCs have a lower surface charge and are less elastic. Reprinted and modified from Chen et al. (Chen et al., 2007), with permission from the publisher.

potential of RBCs (Fig. 11(f)), resulting in either depolarization or hyperpolarization (Balach et al., 2019).

The negative electric charge of RBCs causes an electrostatic repulsion of the RBCs, preventing RBC aggregation. RBCs with reduced electrical charge show a different behaviour when flowing through vessels (i.e. axial accumulation in flow direction) and tend to aggregate (i.e. Rouleau formation) (Suzuki et al., 1998).

RBCs of patients from β-thalassemia have a decreased negatively electrical charged membrane and are less elastic, compared to RBCs from healthy controls (Lima et al., 2020) (Fig. 11(e)). The reduced charge is possibly involved in the adherence of RBC to endothelial cells with subsequent disturbances of the microcirculation, as observed in β-thalassemia patients (Haghpanah and Karimi 2012; Hovav et al., 1999; Musallam et al., 2012). A reduced electrical charge of RBCs has been also been found in women who experienced preeclampsia compared to women with a pregnancy without complications (Karemore and Avari 2019) (Fig. 11(d)). Furthermore, a lower membrane potential is also observed in infected RBCs such as RBCs infected with the protozoan parasite *Plasmodium falciparum* (causing severe malaria) (Tokumasu et al., 2012) (Fig. 11(a)). The infection leads the formation of protrusions on the RBC membrane which are positively charged (+20 mV) in contrast to the negatively charged RBC membrane (Aikawa et al., 1996). The reduction in membrane potential and the presence of these positively charged "knobs" in the surface possibly increase the electrical attraction between the infected RBCs and the (negatively charged) endothelial cells of the blood vessels, seemingly underlying the cytoadherence observed by *Plasmodium falciparum*-infected RBCs (Duffy et al., 2014). The hypercoagulable state observed in cerebral venous and dural sinus thrombosis in severe falciparum malaria (Krishnan et al., 2004) might be also linked to these altered electrostatic interactions between infected RBCs and RBCs with other cells and molecules.

Aging of REBc is also associated with a change in the electrical properties of RBCs (Chen et al., 2007) (Fig. 11(g)): older RBCs have a lower surface charge than younger ones. A decrease in the elasticity of

RBCs with aging is also happening.

Interestingly, blood clothing can be also seen from an electrical point of view (Mommaerts 1945): fibrinogen is negatively changed, thrombin positively and profibrin has a pattern of positive and negative charges. The polymerization of profibrin to fibrin is a result of an electrostatic interaction between the charges (positive and negative) of the profibrin.

Form the subcellular to the cellular scale, the cell is generally functioning as an integrated complex system with hierarchically nested electrical components, charges, currents and fields, forming a "bioelectric circuitry of the cell" as recently proposed (Tuszynski 2019).

4. Summary, conclusion and outlook

In this first installment of our three-part review, we discussed the significance of bioelectricity in relation to the structural levels of biological organization that are characterized by charges, atoms, molecules, macromolecules, cell organelles, the intracellular space, ion transporters and ion channels as well as cells. As shown, electrical aspects play a central role here.

Not only are the chemical composition of the molecules and their topography decisive for their interaction but also the charge distribution and electrical processes. The above-mentioned examples show the functional implications of molecular charges and their interactions, also as an outlook for the coming chapters. In the following part (part 2), we will show that electrical phenomena also play a fundamental role for tissues, organs and organ systems.

Declaration of competing interest

None.

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