The dynamics of action potential: the bioelectromagnetized interaction created by cell biology (I)

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Abstract

The bioelectric excitation of action potential is the essential character of the living state of eukaryotic organisms, and it is the principal groundwork of physiology. The science and technology are advancing with the progress of the times, however, the principle on action potential remain stalled at the apparent cognition of last century due to the restriction of that era. Based on the highly developed molecular cell biology researches, this work brings insight into the endogenous mechanism of action potential, detects the every detail of this dynamic system: the physical and chemical attributes of each participant and the prerequisites of layout; and especially, focuses on the intrinsic relation and interaction in it. It gives the bran-new presentation on action potential mechanism and its physical and chemical regulation, and importantly, investigates the in-depth insight on the principle of dynamic homeostasis performed by action potential.

The optimal way to operate action potential dynamic system is in the way of electromagnetic interaction: the action potential is the electric current formed by the motion of mobile charged ions, and the electromagnetic field that drives the motion of electric charges is the interaction between the gridding ground substance meshwork of cell and the mobile ions. Since the description of Maxwell's electromagnetic equations, it is first time that clearly illustrates the practical model for understanding the operation of the interaction between magnetism and electricity. It is the bioelectromagnetic mechanism created by the nature that highlights the prospect of practicable technology on the development of bioenergy resource.

Keywords

action potential, action potential dynamics, dynamic homeostasis, bioenergy resource

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The dynamics of action potential: the bioelectromagnetized interaction created by cell biology

Part I The dynamic homeostasis and endogenous mechanism of action potential excitation

I The dynamic homeostasis of action potential excitation

The excitability of cell presents the two opposite states, static homeostasis and dynamic homeostasis. One is the in the resting state with the static homeostasis, the other is in excitation-standing state with the dynamic homeostasis [1 Shen]. The excitation-standing state is the original state of the pacemaker cells of the heart (rhythmic heart beating), neurons (the arousal state of cerebral cortex), and skeletal muscle cells (the tension of skeletal muscle). In human body, it presents as the continuous electric signals in electrocardiograph (ECG), electroencephalograph (EEG), and electromyography (EMG), functioning as the vital electrophysiological sign of the state-in-living of organisms.

What determines the resting state and excitation-standing state of an excitable cell is the state of the resting membrane potential which plays the role like a "sluice" that turns off and on the initiation of action potential, in which the polarized one (below the threshold potential, known as resting potential) leads to the resting state of cell, while the depolarized one (above the threshold, termed reentry potential) leads to the exciting state of cell. The sustained state "on" causes the continuous persistent discharge of action potential, leading to the excitation-standing state in dynamic homeostasis.

The resting potential is in the state restricted by polarization, while the reentry potential is in the state relaxed by depolarization when the sluice is "on", the excitation-standing state of cell which generates from dynamic homeostasis rather than the resting state derived from the restricted static homeostasis, presents the original essence of cell excitation in physiology.

II The endogenous mechanism of action potential excitation

The depolarized membrane potential that elicits the discharge of action potential can be achieved in two ways, exogenous and endogenous. The depolarization is elicited by the exogenous electric stimuli,

which is the conventional method artificially used under the experimental conditions, this initiation mechanism of action potential is termed exogenous action potential.

Under the physiological conditions, the depolarized membrane potential is achieved in the physiological way, with the physiological principle of membrane potential generation. Membrane potential (also transmembrane potential or membrane voltage) is the difference in electric potential across membrane, which generates from the ratio of exterior/interior ion concentrations across the membrane, and varying the ratio of exterior/interior ion concentrations will vary the membrane potential. To depolarize a polarized resting potential, a reduced positive charges inside or an increased positive charges outside is needed which shortens the transmembrane potential, as demonstrated by Goldman equation. Accordingly, the reduced cation concentration inside can endogenously tune the cell excitability from static homeostatic state (resting state) into dynamic homeostatic state (excitation-standing state).

The significant cation (K+) concentration inside of cell which benefits for a robust outward cation leakage enables the reduced cation concentration inside and the resultant depolarized reentry potential in a great scale. However, an "inevitable" contradiction emerges that the outward transmembrane motion of cation leakage meanwhile hyperpolarizes the membrane, causes the hyperpolarized membrane potential.

How does the nature ingeniously resolve the contradiction? It is by the relativity of membrane. The cation leakage is performed at the local membrane (e.g., postsynaptic membrane) to cause the reduced cation concentration inside and elicit the endogenous depolarization and action potential discharge at the somatic membrane (in contrast to the local membrane) [1 Shen].

The leakage of cation from local membrane acts as the "switch" to turn on and off the sluice of dynamic homeostasis. The ratio of exterior/interior ion concentrations determines equilibrium potential and reversal potential of ions, as refer to Nernst equation and Goldman equation on equilibrium potential and reversal potential, which determines reentry potential (equilibrium potential), and fundamentally determines the parameters of action potential involving amplitude (reversal potential), duration (cycle) and frequency, the amplitude of cation leakage thus act as the tunable switch to control the parameters of action potential (amplitude, duration and frequency) in excitation-standing state. The endogenous action potential so performs the property as follows [1 Shen]:

(i) Chaotic property, highly sensitive to the initial conditions. The action potential parameters, involved the amplitude, duration and frequency, are highly sensitive to and adjusted accurately by the

exterior/interior ratio of ion distributions across the membrane, in accordance with Nernst equation and Goldman equation on equilibrium potential and reversal potential.

(ii) Excitation-standing state. The sustained state of the reduced cation concentration inside causes the sustained depolarized state of resting membrane potential, which is termed “reentry potential” or “remodeled potential” in contrast to the resting potential at the resting state. As up to threshold, the sustained depolarized reentry potential endogenously elicits the sustained spontaneous repetitive discharge of action potential, known as spontaneous high-frequency action potential (SSL action potential) [1 Shen]. Because the depolarized amplitude of reentry potential up to threshold is in a great scale due to the significant K+ concentration inside of cell, the amplitude, duration and frequency of action potential parameters are capable of being greatly shortened (amplitude) and quickened (duration and frequency) compared to that of exogenous action potential, the degree of which is in accordance with the depolarized amplitude of reentry potential caused by cation leakage.

(iii) Check point. During the excitation-standing state, each remodeled reentry potential ahead of each cycle which results from the instant alteration of the exterior/interior ratio of ion distribution and is renormalized by each perturbation, acts as the check point to adjust the variation of action potential parameters. So any interval in excitation-standing state is the quantized inclusion of the digitalized information on action potential parameters. It is the attribute of cerebral cortex neurons which are latest in the evolution of nervous system with the most advanced complexity in excitation.

Part II The relativity in motion and space: the prerequisite of action potential

III The relativity in motion

The course of action potential is formed by the transmembrane motions of mobile ions (mainly positively charged ions), which is composed of two processes: the diffusion process that forms the coupled depolarization and repolarization phase in the form of diffusion motions of counterpart ions down their concentration gradients (the extrinsic part of action potential); and the exchange process that forms the resting phase in the form of double-exchange motion between the counterpart ions against their concentration gradients (the intrinsic part of action potential).

i. Diffusion action— the motion following chemical gradient; diffusion equilibrium

The diffusion motion is that the ions move from the region of higher chemical potential to the

region of lower chemical potential following the chemical potential gradient, which is driven by thermodynamics to get individual chemical potential equilibrium (diffusion equilibrium).

The prerequisite of the diffusion motions of depolarization and repolarization in the counter directions is the asymmetric transmembrane distribution of ions on the counterpart sides of membrane that forms the significant chemical potential difference of ions. This prerequisite is formed by the double-exchange motion between ions.

ii. Exchange action— the motion against chemical gradient; Gibbs–Donnan equilibrium

(The double-exchange (double-displacement), also metathesis reaction, is the ions in the counterpart substrates (ground substances) are simultaneously exchanged from the original regions into the counterparts against chemical potential gradient and in face-to-face direction. The double-exchange results from the systemic electromagnetic equilibrium between substrates and metal ions. It forms the significant chemical potential difference of ions with the asymmetric distribution of ions on the counterpart sides. Gibbs-Donnan equilibrium is used to describe the behavior of charged particles against diffusion equilibrium, which fails to distribute evenly but causes a difference of chemical potential arising between two parts. Via double-exchange, the result of ion distributions after the countered ion diffusions is inversed to restore into the original state.

The double-exchange motion of ions, which is applied in the processes of purification, separation, and decontamination to move out and purify ions, are performed by the exchangers (beds) of the ion-exchange resins made of charged polymers. The negatively charged polymers, which contain net negative charged groups to offer high affinity for cations by the electrostatic attraction, take effect as the exchangers that support the sorption and exchange of counterions of positively charged ions (metal ions and proton) onto the surface of negatively charged polymers via the electrostatic attraction in order to gain electric neutrality [2 Crini]. (*The polymers may act as the amphoteric exchangers for exchange both cations and anion, because the component of positive charges is also contained by the polymers; the anion, e.g., chloride ion, may participate in some type of action potential either*)

The process of ion exchange has properties as follows: it is a reversible process that allows ions to freely move back and forth by adding or removing the ions; the polymer exchangers have binding preferences for certain ions compared to others, dependent on their chemical structures; the double-exchange is predominated by the cation higher in reactivity; and the double beds (exchangers) different (competitive) in electrostatic intensities are more efficient for double-exchange.

The reactivity series (or activity series) of metal ions on the application of double displacement reactions and the extraction of metals refers to that the competition of metal ions in which the one higher in reactivity predominates the exchange that it can displace those lower in the reactivity series. The reactivity series of metal ions present analogous to their series in electropositivity, Cs > Rb > K > Na > Li > Ra > Ba > Sr > Ca > Mg > Al > Ti > Mn > Zn > Cr> Fe > Cd > Co > Ni > Sn > Pb > (H2) > Sb > Bi > Cu > W > Hg > Ag> Pt > Au. The counterion attribute of positive charged metal ions (and proton), and the electropositive series in reactivity, imply that the double-exchange motion is under the dominance of electromagnetic field (electromagnetodynamics).

To form the selective redistribution of ions on the counterpart sides of membrane with the significant chemical potential difference of ions transmembrane that enables the ion diffusion motions of depolarization and repolarization in the counter directions, the double exchangers of cations (metal ions and proton) on the either side of membrane are constructed by the ground substances of negatively charged polymers different in electrostatic intensities that electromagnetically interact with the counterions competitive in the relativity, which are required for double-exchange of metal ions.

iii. Summary. The connotation on the relativity of metal ion motions (diffusion action vs. exchange action)

The action potential is composed of the extrinsic part of the countered ion diffusions (depolarization and repolarization) and the intrinsic part of double-exchange between mobile ions, in which the result of intrinsic double-exchange plays the role prerequisite for extrinsic depolarization and repolarization diffusions of action potential. The system of materials for generating action potential consists as follows:

(i) The water to provide aqueous solution for ion motions; (ii) the mobile couterions (metal ions and proton) with the competitive reactivity; (iii) the ground substances (negatively charged polymers) with the different electrostatic intensities in response to couterions; and (iv) the lipid bilayer membrane to separate the ground substances and function as the “potential barrier” that separate the metal ions.

Note that (i) both ion motions of diffusion and exchange are essentially of physical processes driven by the thermodynamics and electromagnetodynamics, which can “naturally” act lack of the participant of chemical catalyzers; and (ii) the chemical action of guest molecules, typically the ester guest molecules (e.g., acetylcholine and ATP) and aromatic guest molecules (e.g., norepinephrine), can vary the size and shape of the lattices of polymers via chemophysical action to take effect on ion

motions.

IV The relativity in space

i. Latticed space and parasitic potential

Each pair of electrically charged particles interacts through electrostatic forces (Coulomb force). The opposite charges attract each other and are held together by electrostatic forces under the electromagnetic action.

The metal ions (especially alkali metal and alkaline earth metal) are positively charged. They act as the counterions that can be attracted, "captured" by the negative charged polymers (porous coordination polymers), with non-covalent interaction that bind loosely in a reversible process of sorption. Under the action of electromagnetic field, the metal ions doped into the negatively charged polymers do not usually exist on their own, but bind with the negative charges carried by the polymer molecules in regular arrangement into the coordinated space of crystal lattice structure.

The latticed space is constructed by the interaction between negative charge carried by the chain of polymer molecules and positively charged metal ions. In this sense, the density of metal ion distribution, and the resultant chemical potential (also thermodynamic potential) of metal ions are confined by the latticed space. Parasitic potential (derivative potential) is used to describe that the thermodynamic chemical potential of metal ions is defined and determined by the space (size) of lattices that metal ions locate, which derives from the interaction between positively charged metal ions and negatively charged chains of polymer.

ii. The relativity of negatively charged polymers interacted with metal ions: attractive action and hydrophilic action— compressible lattice and extensible lattice

Attractive action and the compressible lattices. The electron has the smaller mass and thus larger space-filling property. The spatial distance between the negatively charged carriers are much expanded due to the electrostatic repulsion between their electron clouds, the spatial size (spatial extension) of negatively charged polymers are thus much larger than that of parent molecules. The spatial distance can be compressed in significant degree by the positive charges, because the electrostatic attraction between positive- and negative charges resists the electrostatic repulsion, and the negative charges can be pulled pretty approach to each other by their attraction to positive charges.

This character is termed “like-charge attraction induced by counterions”. The counterions play a central role in like-charge attraction is given intense theoretical scrutiny over the last 30 years. It is discovered by various techniques (using x-ray diffraction or others) that like-charge attraction between polyelectrolytes is induced by counterion charge density waves, and typically that metal ion arrangement in the “zipper-like” mode enables the closed bounding of polymers together [3 Angelini,4 Nagornyak].

As the positively charged metal ions are captured by the strong negatively charged polymers, the size of polymer lattice turns to be compressed in response to the existence of metal ions. And the more metal ions attracted to the negative charges, which locates surround the negative charge in the more dimensions, causes the greater compressed lattice size between the adjacent negatively charged carriers.

Hydrophilic action and the extensible lattices. In aqueous solution, the electronegative oxygen atom of water molecule would be attracted electrostatically to the positive charge of metal ions. Under the action of electromagnetic field, the metal ion acts as the coordination center, and the water molecules surround metal ion in the array of first (primary) and second coordination sphere, known also as hydration shell or hydration sphere [5 Dudev]. The shell can be several molecules thick, dependent on the charge of metal ions, and their distribution and spatial dimensionality [6 Ball P].

As the positively charged metal ions are captured by the weak negatively charged polymers, because of hydrophilic action that the layers of water molecules are attracted surrounding the metal ion, the size of lattice constructed by metal ion and polymer is significantly expand, especially alkali metals and alkaline earth metals that have the intensive metal character and electropositivity. It is described as “egg-box” mode of metal ion arrangement that enables the expanded space between polymers [7 de Kerchove]. And the more metal ions attracted to the intensive negatively charged polymers, which locates in the more dimensionality, causes the greater expansion of lattice size between the adjacent negatively charged carriers.

iii. The relativity in space: attractive action vs. hydrophilic action— the competition of screening action

The screening action refers to the electromagnetic field of charged particles is counterbalanced and shielded by the additional charges, that when the unequal oppositely charged particles meet and attract each other, the electromagnetic field action of the weakly charged one is counterbalanced and screened by the electromagnetic field of strong one, and which electromagnetic field of positive- or

negative charge predominates is dependent on the intensity of charges.

As the positively charged metal ions are captured by the negatively charged polymers, the size of crystal lattices constructed by negatively charged polymers and metal ions results from the competition of the charge intensity between metal ions and polymers: the strong negatively charged groups carried by polymers counteract and shield the positive charges carried by metal ions so that the attractive action predominates, in which metal ions play the role that pull the counterpart negative charged polymers closer with the compressed lattices; in contrast, the weak negatively charges carried by polymers are counteracted and shielded by the positive charges carried by metal ions so that the hydrophilic action predominates, in which metal ions play the role that extends the lattices with the additional water molecule layers.

iv. Summary. The connotation on the relativity of the interacted space (attractive action vs. hydrophilic action)

The interaction (attractive action and hydrophilic action) between negatively charged polymers and cations are highly sensitive to the electrostatic intensity of negative charges carried by the polymers in the dose-dependent manner. The lattice space constructed by negatively charged polymers and cations being compressed or expended is dependent on the intensity of negative charges; and the amplitude of variation (compressed or expended) is elastic in the dose-dependent sensitivity and the reversibility in response to adding or removing ions, in which the greater concentration causes the greater amplitude of variation and vice versa.

Counterions interact with negative charged polymers in the opposite actions (attractive action and hydrophilic action) imply that the negative charges carried by polymers are different in the electrostatic intensities. It has the sharp significance on the exchangers for double-exchange. As aforementioned, the double exchangers of the negatively charged polymers different in electrostatic intensities, which are set on the either side of membrane, is required for the double-exchange of action potential (the prerequisite of ion diffusion) that metal ions (and proton) are selectively redistributed into the counterpart side of membrane. And due to the electromagnetic attribute of double exchange, the greater difference in electrostatic intensities between the exchangers the greater asymmetric redistribution with the greater chemical potential gradient of ions on the counterpart sides of membrane.

So as the double exchangers separated by the membrane are set with the attractive action predominated polymer and the hydrophilic action predominated polymer on the either side of

membrane, it results in the maximized asymmetric redistribution and the consequent thermodynamic chemical potential gradient of ions on the counterpart sides, which is the optimal prerequisite for the depolarization and repolarization diffusion of action potential.

Part III The relativity in “spacetime” of action potential dynamics

— As the prerequisites on relativity had been set, how design to achieve the motion of metal ions into the adjustable dynamic homeostasis of oscillation system?

V Materials of action potential

(i) Water; (ii) the mobile metal ions (alkali metals and alkaline earth metals) with the competitive reactivity; (iii) the ground substances (negatively charged polymers) with the conflicting property in response to metal ions; and (iv) the lipid bilayer membrane to separate the ground substances.

i. The metal ions (alkali metals and alkaline earth metals) with the competitive reactivities.

The ions of alkali metals and alkaline earth metals (K+, Na+, Ca2+) are highly electropositive and mobile, and highly reactive for cation exchange. Due to the strong electropositivity, they are capable of binding to the negatively charged polymers, and capable of attracting water molecules with hydrophilic action.

The reactivity series shows K+> Na+ > Ca2+. During the process of cation exchange, due to the higher reactivity of K+ compared to that of Na+ and Ca2+, K+ acts as the active one that predominates the exchange, while Na+ and Ca2+ act as the passive ones whose exchange are under the domination of K+.

ii. The ground substances (negatively charged polymers) in opposite responses to metal ions

The plasma membrane separates extracellular matrix and intracellular matrix. The ground substances of extracellular matrix are constructed by polysaccharides. The ground substances of intracellular matrix are constructed by cytoskeletal proteins, which extend throughout the cytoplasm, from nucleus to plasma membrane. The cytoskeletal proteins involve microfilaments (also called actin filaments), microtubules, and intermediate filaments. All the ground substances that construct extracellular- and intracellular matrix are made of high negatively charged polymer meshworks that have large net negative charge densities distributed over their surfaces [8 Janmey, 9 Janmey PA,].

The actin filament proteins are arranged with the barbed-end of each filament attached to the cell's peripheral plasma membrane. The ground substances of polysaccharides (outside) and actin filaments (inside) are separated by plasma membrane into the counterpart side.

(i) Polysaccharides

Glycosaminoglycans (GAGs) are the ground substance extending and filling in extracellular matrix, which are long unbranched polysaccharides consisting of a repeating disaccharide unit, which contain carboxyl or sulfate groups that carry negative charges [10 Seyrek]. The presence of both carboxyl and sulfate groups gives a high density of negative charges along the chains so that polysaccharides are highly negatively charged. Due to the electrostatic attractions, the negative charges noncovalently attract a condensed counterion cloud of positively charged metal ions (K+, Na+, and Ca2+) [11 Salehizadeh].

Because the metal ions (K+, Na+, and Ca2+) are osmotically active, the polysaccharides are strongly hydrophilic, and form the highly hydrated porous gels. The pores are formed in "egg (metal ion)-box model" [7 de Kerchove], and the size of pores are evidently enlarged by the increased concentration of metal ions (and proton) [7 de Kerchove]. Due to the highly hydrated space, the polymers adopt highly extended conformations so that occupy a huge volume relative to their mass. It creates a swelling pressure which enables the matrix to withstand compressive forces, and provides mechanical support primarily.

(ii) Microfilaments (actin filaments)

The cytoskeletal proteins of microfilaments (actin filaments), microtubules and intermediate filaments all contain the highly negatively charged groups. Opposite to extracellular matrix protein polysaccharides, they are hydrophobic instead of hydrophilic, and they are not extended but the rod-like (aggregated) polymers that bundle together as in the cell [9 Janmey, 12 Edelstein, 13 Woolf], which seems to violate the Coulomb law of electrostatics in which like charges repel.

It is because these protein filaments are not in the circumstances of vacuum, but in the solution of intracellular environment where they are surrounded by the positively charged counterions which condense upon their charged surface (due to the opposite charges attract), leading to their rod-like bundling by overcoming the repulsive forces [13 Nancy]. Its underlying mechanism is described as “like-charge attraction between polyelectrolytes induced by counterions” [3 Angelini], in which counterions are found that play a central role for generating attractions.

Actin filaments are composed of two helical, interlaced strands of actin [14 Grimard]. Actin carries around 11 net negative charges at neutral pH [8 Janmey]. Through nonspecific electrostatic effects, a condensation of positively charged counterions is attracted by the negatively charged groups along the actin strands with the zipper-like arrangement on the surface and along the longitudinal axis of actin filaments; which is critical to actin filaments sustaining ionic conductances [3 Angelini, 15 Lin, 16 Priel]. The zipper-like charge alignment enables the close bundling of actin filaments together, pulling them "attracted" closely [3 Angelini, 17 Shikinaka].

Cations binding on actin along its length drive actin to incorporate into polymerization, and determine the filament flexural rigidity, depending upon the type and concentration of cations [18 Kang, 19 Kang]. A threshold concentration of polycations is required to the assembly of actin filaments, which counteracts the repulsion between negative charges and forms lateral aggregation (attraction) of filaments [17 Shikinaka, 20 Tang]. In the presence of high concentrations, multivalent linear waves of counterions condense. [3 Angelini]. Increasing the concentration of positively charged counterions causes a significant increase in the intercalation (attraction) of the actin within the microfilament molecules, indicating that the intercalation of actin is generated and intensified by electrostatic interactions with counterions [14 Grimard, 21 Hase].

(iii) Summary

The ground substances on the either side of plasma membrane are constructed by negatively charged polymers, which are competent for the cation double-exchange. And the outside and inside ground substances are in the opposite responses to the counterions, in which polysaccharides interact with metal ions with the extended size (repelling away) while the microfilaments with compressed size (pulling close).

Besides, the ground substances of negatively charged polymers, both outside and inside of cell (polysaccharides and microfilaments), have the commonness in response to cations. First, the dose-dependent and reversible property, that the responses are highly sensitive to the variation of cation dose, which are intensified by the increased cation dose, and vice versa [8 Janmey, 22 Weisenberg, 23 Wolff]. Second, the competition (selectivity), that as adding several different ion species simultaneously, the competitions between metal ions binding onto the surface of polymers take effects in accordance with metal reactivity, which reveals the polyelectrolyte nature responsible for the counterion attraction [24 Dammann, 25 Block].

VI Setting for plasmalemma action potential

VII Processing of action potential in a typical neuron

VIII The relativity in the regulation by guest molecules in cardiomyocytes

Part IV The new concept on the bioelectromagnetic field: the interaction and relativity in generation

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X The mechanism of bioelectricity derived from bioelectromagnetic field: the relativity in inter-variance

XI The relevance between bioelectromagnetic field and Maxwell's electromagnetic mechanical model

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XIII The informatization mechanism of SSL action potential in relativity: the encoded and digitalized coupling-proceeding of analog signal and digital signal

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