

Action potential, bioenergy resource, and the principle of perpetual natural electromagnetic dynamics: the living essence and eternal elegant-beauty— from biology to the universe (I)

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To present biomedical achievements in Medial History and IEEE Milestones (Institute of Electrical and Electronics Engineers milestones)

HaiYing Shen, M.D., Ph.D.

Cardiologist, Biomedical scientist

Spiritual advisor William Harvey (De Motu Cordis (on Circulation)

Motto Royal Society's Nullius in verba (Take nobody's word for it)

Scientific career

Fields Cardiology

Internal medicine

Biochemistry and molecular biology

Medical physiology, electrophysiology

Molecular biology-founded cell electrophysiology

Bioelectricity, bioenergy resource, fine-energy resource

Electromagnetic dynamics

Natural electromagnetic dynamics

Celestial electromagnetic dynamics

Electromagnetic dynamics on natural mathematics

Aesthetics

Institutions

Division of Cardiology, Department of Internal Medicine, Korea University

School of Medicine, Kyung Hee University

Department of Internal Medicine, Seoul National University Hospital



(in white in three photographs)

Academic achievements

Spontaneous high-frequency action potential

Keywords *action potential, spontaneous high-frequency action potential, tachyarrhythmias, atrial fibrillation, wound, denervation supersensitivity, neurogenic pain, hyperalgesia and allodynia, epileptic discharge, diabetic pain, regeneration and development*

The eukaryotic mechanism directed by bioelectricity: creation and enlightenment

Keywords *eukaryotic mechanism, eukaryotic bioelectric excitation, eukaryotic bioelectromagnetic field, bioorganic electricity generation, bioorganic information, bioorganic energy resource; cell electrophysiology, biomembrane, plasma membrane, endoplasmic reticulum, sarcoplasmic reticulum, mitochondrion, nucleus, Golgi apparatus; action potential, neuronal excitation, skeletal muscle excitation, muscle contraction*

Action potential, bioenergy resource, and the principle of perpetual natural electromagnetic dynamics:

the living essence and eternal elegant-beauty— from biology to the universe

Keywords *action potential, bioelectricity, bioenergy resource, fine-energy resource; electromagnetic dynamics, natural electromagnetic dynamics, celestial dynamics; aesthetics, celestial aesthetics, natural mathematics, time; earthquake, seismic wave, cyclone, capillary action*

The electromagnetic spin energy and the electromagnetomathematic differentiation on phase transition

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

The molecular biology-founded cell electrophysiology and electropathophysiology: on signal transduction, immunology, sarcoma and cancer, atrophy and apoptosis, retrovirus, regeneration and ageing

The understanding on 100-year problem: the wisdom of the Heart

Keywords *cardiac electrophysiology, Frank–Starling law, Anrep effect, eccentric hypertrophy, concentric hypertrophy, heart failure, arrhythmia, circulation*

This work is dedicated to my beloved grandparents and parents, family, schoolmasters and schoolmates, alma mater and homeland.

Action potential, bioenergy resource, and the principle of perpetual natural electromagnetic dynamics: the living essence and eternal elegant-beauty— from biology to the universe

Highlight

The perpetual operation of energy in vigorous state, instead of standstill (heat death), is the essential vitality of biology and the universe, what principle of nature operates it? The perpetual refers to the state-in-operation of power system in dynamic homeostasis founded on ground energy, instead of the confusion without energy resource or energy dissipated. To pursue the perpetual dynamic power and energy creation is the summit realm of practical technology. However, it has long been disregarded theoretically and practically. This work starts from the highly developed biological studies, and by utilizing the intrinsic principle refined, explores the intrinsic principle, operating mechanism and energy creation of perpetual electromagnetic dynamic power from biology to the nature in macroscale and microscale. The electromagnetic perpetual motion generates from the relativity of field (thermal field, electromagnetic field and gravitation field) as the ground energy to operate energy conversion of thermodynamics, electromagnetic dynamics and fluid dynamics. It creates the potent energy of electricity and electromagnetic dynamic power. This work historically discovers a new milestone on the generating principle and operating mechanism of perpetual electromagnetic dynamic power and energy creation in biology and the nature. The strict and unified principle dominates the vigorous living state from the biology to the Earth's geological and meteorological phenomena and celestial motions, not obfuscated but clarified, not disordered but in supreme harmony and homeostasis. And it is first time that clearly presents the applicable molecular biochemical model for the digitalized perpetual operation of bioelectricity and bioenergy resource, and provides the practicable reference on the development of harmless fine-energy power, with the purpose learning from and emulating the nature. This study highlights as follows:

i. On the electromagnetic energy resources; the electromagnetic dynamics connotation of natural energy resource. The perpetual electromagnetic energy resource exists in the nature and universe. The perpetual electromagnetic energy resource results from the perpetual operation of electromagnetic convection-exchange coupling in dynamic homeostasis. The creation of electromagnetic convection-exchange coupling is composed of alternating current electricity, complex-electromagnetic signals (analog signal and digital signal), and the characterized torsional electromagnetic power. The connotation of energy resource in this study essentially is the complexity of the combination of energy resources composed of (i) electricity generation, (ii) electromagnetic information (electromagnetic signals), and (iii) electromagnetic torsional (spin) dynamics, which is the creation of natural energy resources. The creation which forms the property of fine-energy power is characterized that (i) it is digitally and informationally maneuverable, and (ii) it operates circularly and infinitely.

ii. On the electromagnetic motive powers; the electromagnetic dynamics connotation of

astrodynamics. The “enigmatic” rotational energy is detected by the magnetic inductors as the electric current is driven by voltage (electric potential), due to the relation of electromagnetic interaction, as described in Ørsted's rules. This rotational power drives the operation of electromagnetic inductors. The operation of electromagnetic convection-exchange coupling makes the rotational power persistently spin in informationized rhythm, which operates the perpetual rotation (spin) of celestial bodies. It presents an endogenous perpetual rotational power to operate electromagnetic inductors with the characteristic digitally maneuverable, which is envisaged for the digitalized mechanical powers.

iii. The electromagnetic dynamics connotation of aesthetics and eternal vitality; the ingenious relativity. If the indeed grand unification theory exists in the nature, the principle on biology should be contained. If what can depict the essence of the lives and the universe (perpetual celestial operation), it has nothing for it but the eternal vitality with elegant-beauty that the lives and universe are not in standstill (heat death) but in the active motional state, motioning not in messy but in the refined operation and harmonious coexistence. The dynamics of electromagnetic convection-exchange coupling in the relationship of inter-variation is contained in natural mathematics, information (involving information entropy and energy level) and biological and universal electromagnetic energy with the natural correspondence, which essentially operates them. The dynamics is not monistic, but is composed of the combination of static- and dynamic interaction, generated from the ingenious creation on relativity by the nature. It is what operates the informationized electromagnetic energy with aesthetics and perpetual operation, creating the eternal vitality with the elegant-beauty in unity from biology to the universe.

Abstract

The lives are continuous and the galaxies are in revolution, in which the perpetual motion of electromagnetic energy in vigorous state forms the essential state of biology and the universe. The bioelectric excitation of action potential is the essential character of the living state of organisms. The highly developed molecular cell biology researches enable the presentation of physical and chemical attributes of each participant of action potential to disclose the intrinsic relation and mechanism on bioelectricity generation. The action potential is operated by electromagnetic convection-exchange coupling with the electromagnetic properties as follows: first as the electric currents of alternating current on electricity generation, second as the oscillation of electromagnetic signals on informationization, and third as the electrically charged fluid that creates the spinning electromagnetic

power on electromagnetic fluid dynamics.

The process, principle and prerequisite on the energy creation of action potential electromagnetic dynamic homeostasis system give the in-depth insight into the principle and prerequisite on the operation of electromagnetic dynamic homeostasis system and its energy creation. Basing on it, the operation mechanism of electromagnetic convection-exchange coupling dynamic system in macroscale and microscale of nature is investigated— because an indeed understanding comes from the thoroughly and deeply done investigations. The rigorous and unified principle dominates the energy creation of electromagnetic dynamic homeostasis system from the biology to the Earth phenomena and celestial motions: the circulated electromagnetic convection-exchange coupling in dynamic homeostasis generates from the prerequisite on relativity, and performs the perpetual operation of electromagnetic oscillation, the spinning electromagnetic power in rhythm, and the interactions between coupling systems. It creates the dynamic homeostasis in elegant-beauty with the property of refinement, harmony, and the combination of statics and dynamics.

Taken together, this work highlights the energy creation of electromagnetic dynamics in dynamic homeostasis generated from the electromagnetic convection-exchange coupling system, and it is what imparts the eternal vitality and aesthetic connotation into biology and the universe.

Keywords

action potential, bioelectricity, bioenergy resource, fine-energy resource; electromagnetic dynamics, natural electromagnetic dynamics, celestial dynamics; aesthetics, celestial aesthetics, natural mathematics, time; earthquake, seismic wave, cyclone, capillary action

Extracts on relativity and the ingenious relativity

(i) The relativity in electromagnetic inter-induction. The process of electromagnetic convection-exchange coupling is essentially the coupling of static- and dynamic electromagnetic inter-induction in the dynamic homeostasis in the relationship of counter-variance & intergrowth, which is operated by the natural principle of static- and dynamic electromagnetic inter-induction as contained in Maxwell's equations with/without sense in spacetime, on the foundation of the ingenious relativity.

(ii) The relativity in thermodynamic entropy. The second law of thermodynamics accounts for

the increase in disorder, i.e., entropy increase, of the system overwhelms the universal natural processes with the irreversibility. On the other hand, it is realized that it exists an energy control mechanism in nature that was antagonistic to entropy increase. Maxwell (*Maxwell's demon*), Josiah Willard Gibbs (*Gibbs paradox*), and Poincaré (*Poincaré recurrence theorem*) are the scientists who tried to violate the second law.

Given the oscillation system of electromagnetic convection-exchange coupling, the result of systemic entropy increase is the increase of frequency and energy level of electromagnetic oscillations, in which the extrema of systemic entropy increase generates the electromagnetic oscillation which trends to the maximized energy level. Hence, the result of systemic entropy increase develops not to standstill of “heat death”, but into the maximized energy level of the oscillation of electromagnetic convection-exchange coupling with the maximized energy level of thermodynamic motion and electromagnetic motion.

(iii) The relativity in energy field. The circulation of electromagnetic convection-exchange coupling in dynamic homeostasis generates from the prerequisites on relativity as follows: the ground substances in different static electromagnetic intensity; the mobile electric charges in different electrostatic intensity which performs the convection motion; and the motivation that motivates the convection motion, which can be achieved by positive or negative pathways that positively to increase the motive force or negatively to decrease the resistance.

In action potential dynamic homeostasis system, the setting in relativity generates from the ground substances of negatively charged polymers in different electrostatic intensity. In universal environments, the celestial bodies create celestial thermal field (heat), electromagnetic field and gravitation field, which generate the gradient of field intensity in propagation, leading to the relativity with the difference. The gradient in propagation of the field intensity of thermal field, electromagnetic field and gravitation field plays two roles: (i) it contributes to the ground substances in different field intensity, which function as the exchangers for the sorption of differently charged particles into the asymmetric distributions on counterpart regions which causes the decrease instead of increase of systemic entropy (do as Maxwell’s demon), and this spontaneous symmetry breaking of particles on counterpart regions generates the potential energy gradient for the dynamic energy of thermodynamic diffusion motion in the form of convection; and (ii) it contributes to the ground potential energy generated from thermal field, electromagnetic field and gravitation field, which acts as the motive powers that motivate the convection motions.

Because it needs the motivation that motivates the convection motion, the electromagnetic

convection-exchange coupling is of the forced convection-exchange coupling. However, the motivation is ingeniously designed by natural dynamic system. In action potential bioelectric dynamic system, the resting membrane potential formed by the net outward preferential motions of the ion higher in reactivity forms the potential barrier which plays the two roles: (i) it plays the role like the dams in hydroelectricity that contributes to the dynamic energy of inward diffused ions by raising the potential energy, with the conversion of potential energy to dynamic energy; and (ii) it obstructs the inward ion diffusion by the resistance of resting potential, acting as the sluice that tunes off and on the process of convection-exchange coupling, in which the depolarized resting potential plays the role that endogenously tunes the sluice on. In macroscale dynamic system, the geological deformation which induces geomagnetic and geoelectric effect functions as the motivation for electromagnetic oscillation of earthquake; and the heat caused by the sufficiently warm surface temperatures from solar radiation motivates the convection motion to generate cyclone. In microscale system of capillary action and Marangoni effect (e.g., “tears of wine”), it is the difference in surface tension generates the potential energy which contributes to the dynamic energy to motivate micro-convection along interface. In celestial dynamic systems, the heat of inner core drives the compositional convection at convective zones.

Taken together, the prerequisites on relativity that generates the electromagnetic convection-exchange coupling in dynamic homeostasis are never foisted, but “naturally” and “spontaneously” generated from the physical properties (thermal field, electromagnetic field and gravitation field) contained by the nature. It results from the ingenious utilization on natural physical properties into design and layout. The eternal vitality with elegant-beauty from biology to the universe is created from the relativity with the meticulous and ingenious soul of nature.

(iv) The quantum electromagnetomathematic connotation of time.

The quantized property of time. Grounded on the static interaction between magnetics (space) and electrics (motion), the dynamic interaction between magnetics and electrics forms the circulated electromagnetic convection-exchange coupling with the derivative of curl, which is quantized with the digitalized cycle and frequency (energy level) in rhythm. This quantized spin with the digitalized energy level generates the time, and the proceeding of the circulation of spin generates the evolution of time. Hence, the time is characterized by the properties as follows: the foundation of time is the operation of electromagnetic convection-exchange coupling, the time generates from the dynamic rather than static interaction between space (magnetics) and motion (electrics), the dynamic electromagnetic interaction in circulation generates the electromagnetic spin energy in the form of

digitally and rhythmically quantized time.

The topological property of time. The electromagnetic spin energy formed by electromagnetic convection-exchange coupling is characterized by the inversely conjugated torsion, with the characterized property on the conjugated torsional center and axis, and torsional longitude because the conjugated torsion is the torsion in dimension and is compact, the performance of time is thus stabilized, compact and fine-tessellated (refer to Volume III on celestial rotation), leading to the unit of time with the standardized fine-tessellation.

The relativity of time on entanglement. The entangled interaction among the interacted spinning systems generates the relativity of the time in harmony, like the time of Earth's rotation (solar day) and orbit (sidereal year).

Summary. The dynamic electromagnetic interaction between space and motion of electromagnetic convection-exchange coupling generates the time with the digitally and rhythmically quantized energy level of spin, the standardized fine-tessellation, the relativity of entanglement, and the infinite perpetual operation with refinement and harmony. The time is essentially of the physical-mathematically quantized electromagnetic spin energy created by electromagnetic convection-exchange coupling in the eternal elegant-beauty.

List of topics

Volume I Action potential: the electromagnetic dynamic homeostasis system in biology

Part I The electromagnetic dynamics of action potential: process, prerequisite and rule

I The dynamic homeostasis and endogenous mechanism of action potential excitation

- i. The dynamic homeostasis of action potential excitation
- ii. The endogenous mechanism of action potential excitation
- iii. Summary. The connotation of the relativity in dynamic homeostasis of action potential

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

II-I The relativity in motion: double-diffusion (convection) motion vs. double-exchange motion

- i. The process of action potential: double-diffusion (convection) and double-exchange.
- ii. Diffusion motion: the motion down concentration gradient; diffusion equilibrium

- iii. Exchange motion: the motion against chemical gradient; Gibbs–Donnan equilibrium
- iv. Summary I. The physical connotation on the relativity of the coupled motions of double-diffusion and double-exchange
 - (i) The relativity of motions: double-diffusion (convection) vs. double-exchange
 - (ii) The unity on the relativity of motions: the electromagnetic convection-exchange coupling
 - (iii) The physical attribute of electromagnetic convection-exchange coupling
- v. Summary II. The relativity in the prerequisite for action potential setting

II-II The relativity in space: attractive action vs. hydrophilic action— compressible lattice vs. extensible lattice

- i. Latticed space and transformer potential (parasitic potential)
- ii. Attractive action and the compressible lattice
- iii. Hydrophilic action and the extensible lattice
- iv. The screening action: attractive action vs. hydrophilic action
- v. Summary. The relativity of space between the interacted polymers and counterions: transformer potential

II-III The relativity in “spacetime” of action potential

- i. The setting in relativity for generating action potential
- ii. The metal ions (alkali metals and alkaline earth metals) with the competitive reactivity
- iii. The ground substances of negatively charged polymers in opposite responses to metal ions (attractive action vs. hydrophilic action)

II-IV Summary. The connotation on the relativity in the setting of action potential

- i. The foundation of depolarization and repolarization
- ii. The foundation of resting membrane potential
- iii. The foundation of endogenous action potential mechanism: the connotation of resting membrane potential
- iv. The foundation of leakage potential

Part II The informationized electromagnetic oscillation of action potential-electromagnetic convection-exchange coupling

I The connotation of action potential in information: complex-signals, encoding and transmission, Shannon entropy and energy level

i. ii. iii. iv.

II Summary. The character of action potential informationization: standardization and energy level of electromagnetic oscillation of convection-exchange coupling

Part III The electromagnetic fluid dynamics of action potential

I The characterized property of electromagnetic rotational energy field in electromagnetic fluid dynamics

i. ii. iii. iv.

II The electromagnetic fluid property of action potential

i. ii. iii.

Part IV Summary. The energy creation, principle and prerequisite of action potential-electromagnetic dynamic homeostasis system

I The property and energy creation of action potential in electromagnetic dynamics

II The principle of action potential-electromagnetic dynamic homeostasis system in relativity

i. ii. iii. iv.

III The summary on process, principle and requisite of the electromagnetic convection-exchange coupling in dynamic homeostasis

i. ii. iii. iv.

IV The connotation of relativity

Volume II The convection-exchange coupling of electromagnetic dynamic homeostasis system in macro- and microscales of nature

Part I The relativity in the universal property and the prerequisite for electromagnetic convection-exchange coupling

I Second law of thermodynamics, Maxwell's demon and the relativity in the universal property

i. ii.

II The prerequisite for the convection-exchange coupling of electromagnetic dynamic homeostasis system

Part II The electromagnetic convection-exchange coupling in geological and meteorological dynamics: earthquake and cyclone

I The analysis on earthquake: denotation, connotation and seismic waves

II The analysis on cyclone: the principle on dynamic homeostasis in electromagnetic dynamics

III Summary

Part III The electromagnetic convection-exchange coupling of dynamic homeostasis system in microscales

Part IV Summary. The connotation of electromagnetic convection-exchange coupling in energy operation and creation

I The connotation of electromagnetic convection-exchange coupling

i. ii. iii.

II Summary. The energy creation of electromagnetic convection-exchange coupling in macroscale and microscale

Volume III The dynamic homeostasis of electromagnetic convection-exchange coupling in astrodynamics: celestial rotation and gravitation

Part I Celestial rotation and shaping: the topologic operation of electromagnetic spinning energy created by convection-exchange coupling

I Background

II The rigid property of celestial rotation

III Electromagnetic torsion (spin) created by convection-exchange coupling: the topologic operation of celestial rotation and shaping

i. ii. iii. iv. v.

IV Summary. The topologized and informationized operation of celestial rotation created by electromagnetic convection-exchange coupling

i. ii.

Part II The property of celestial gravitation in dynamic relativity

i. ii. iii.

Part III Summary. The essence of gravitation

Part IV The summary on volume I to III. The perpetual natural dynamics of electromagnetic

convection-exchange coupling created by the relativity and the ingenious relativity

Volume IV *The living essence and elegant-beauty of the Nature in aesthetics— the perpetual electromagnetic dynamic homeostasis from biology to the Universe*

Part I *The elegant-beauty: the creation of celestial dynamics in aesthetics*

i. ii. iii. iv.

Part II *The connotation of natural mathematics in dynamics: the logic and beauty created by the dynamics of electromagnetic convection-exchange coupling*

I *The connotation of natural mathematics created by electromagnetic dynamic energy*

i. ii. iii. iv.

II *The relationship of “space, motion and time” between natural physics and natural mathematics*

(i) (ii) (iii)

Part III *The living essence and elegant-beauty from biology to the Universe*

Postscript

i. Harmless and perpetual fine-energy resource and dynamics

ii. Oriental Taiji

iii. Epilogue. Soul course

Action potential, bioenergy resource, and the principle of perpetual natural electromagnetic dynamics: the living essence and eternal elegant-beauty— from biology to the universe

Volume I **Action potential: the electromagnetic dynamic homeostasis system in biology**

Part I **The electromagnetic dynamics of action potential: process, prerequisite and rule**

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

i. The dynamic homeostasis of action potential excitation

The action potential excitation which generates the regular electric currents is the property of the

living organisms to perform the function. The excitability of cells presents dynamic homeostasis in excitation-standing state [1]. The excitation-standing state is the original state of cardiac pacemaker cells (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 “informationized” 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 function as the “potential barrier” that obstructs the depolarization of action potential, playing the role like a sluice that turns off and on the initiation of action potential, in which the polarized one (below the threshold potential) leads to the resting state of cell, while the depolarized one (above threshold) 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.

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, is of 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 resting membrane potential, a reduced positive charges inside or an increased positive charges outside is needed which plays the role that shortens the transmembrane potential difference, as described by Nernst equation and Goldman equation. Accordingly, the reduced cation concentration inside can endogenously tune the excitability of cell from resting state into excitation-standing state.

The significant cation (K^+) concentration inside of cell which benefits for a robust outward cation leakage down concentration gradient enables the reduced cation concentration inside and the consequential depolarized resting 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 undo this contradiction? It is by the relativity of plasma membrane. The cation leakage is performed at the local zone of membrane (junctional zone, e.g., postsynaptic membrane) to cause the reduced cation concentration inside to elicit the endogenous depolarization and action potential discharge at the somatic zone of membrane (in contrast to the local zone) [1]. The action of chemical signals in synapse cleft can cause cation leakage from postsynaptic membrane, and the sustained action of chemical signals caused by the sustained release of chemical signals into synaptic cleft (e.g., the quantal release of acetylcholine at neuromuscular junctions) causes the sustained state of cation leakage.

The leakage of cation from local zone of membrane thus plays the role as the tunable “switch” to turn off and on the discharge of action potential. 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 resting potential, and fundamentally determines the parameters of action potential involving amplitude, duration (cycle) and frequency. The amplitude of cation leakage thus acts as the tunable switch to control action potential parameters (amplitude, duration and frequency) in excitation-standing state. The endogenous action potential so performs the property as follows [1]:

(i) Highly sensitive to the initial conditions. The action potential parameters, involved the amplitude, duration and frequency, are highly sensitive to 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 potential. As up to threshold, the sustained depolarized resting potential endogenously elicits the spontaneous repetitive discharge of action potential, known as spontaneous high-frequency action potential (SSL action potential) [1]. Because the depolarized amplitude of resting potential up to threshold is in a great scale due to the significant K^+ concentration inside of cell, the parameters of action potential are capable of being greatly shortened (amplitude) and quickened (duration and frequency) in accordance with the depolarized amplitude of resting potential caused by cation leakage.

iii. Summary. The connotation of the relativity in dynamic homeostasis of action potential

The resting state of cell is when the depolarization of action potential is obstructed by the sluice of polarized resting potential, while the excitation-standing state is in the state that the sluice is turned on. The physiological significance of resting membrane potential lies in to tune the parameters of action potential with the cation leakage from postsynaptic membrane which is induced by the chemical signals released into synaptic cleft so that the instant state of dynamic homeostasis is under the control of chemical signals in response to the variant physiological states. The state of dynamic homeostasis of action potential is not invariable and ragescent but variable and controllable in the way by forming the relativity with resting potential and with cation leakage from local zone of membrane.

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

II-I The relativity in motion: double-diffusion (convection) motion vs. double-exchange motion

i. The process of action potential: double-diffusion (convection) and double-exchange.

The course of action potential is formed by the transmembrane motions of mobile charged ions (mainly positively charged ions), which is composed of the coupling of two processes: the double-diffusion process that the ions move down concentration gradients forms the coupled depolarization and repolarization phase in the form of convection in which the depolarization diffusion triggers the repolarization diffusion in the counter direction, and the course of convection (depolarization and repolarization) causes the displacements of ions into their counter sides; and the double-exchange process in which the ions move against concentration gradients forms the resting phase in the form of double-exchange, which causes the double-displacement of ions into their counter sides, returning back into their original sides. The course of action potential is composed of the double-diffusion (convection) which forms the extrinsic visible “real part” of action potential with the depolarization and repolarization phase, and the double-exchange which forms the intrinsic invisible “imaginary part” of action potential with the resting phase.

ii. Diffusion motion: the motion down concentration gradient; diffusion equilibrium

The diffusion motion is that the ions move from the region of higher concentration to the region of lower concentration down concentration gradient, which is driven by thermodynamics to get individual thermodynamic equilibrium (diffusion equilibrium).

iii. Exchange motion: the motion against chemical gradient; Gibbs–Donnan equilibrium

The double-exchange (double-displacement) is the ions are simultaneously exchanged from the original regions into the counter sides against concentration gradients in face-to-face direction. The course of double-exchange results from electromagnetic dynamics to get systemic electromagnetic equilibrium between exchangers and metal ions. It forms the significant concentration difference of ions with the selective asymmetric distribution 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 the process of double-exchange, the result of ion distributions after double-diffusion is inversed to restore into the original state.

The double-exchange of ions, which is universally applied in the industrial 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 counterions (cations) with the electrostatic attraction, take effect as the exchangers that support the sorption and exchange 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 [1 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 which are different in electrostatic intensity instead of the single bed 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 positively charged metal ions (and proton) and the electropositive series in reactivity imply that the double-exchange of electrically charged ions is under the dominance of electromagnetic dynamics.

iv. Summary I. The physical connotation on the relativity of the coupled motions of double-diffusion and double-exchange

(i) The relativity of motions: double-diffusion (convection) vs. double-exchange

i. Are all the ion motions move down concentration gradient? The double-diffusion motion is that the ions move from the region of higher concentration to the region of lower concentration down concentration gradient to get individual thermodynamic equilibrium of electrically charged ions; the double-exchange (double-displacement) is the ions move from the region of lower concentration to the region of higher concentration against concentration gradient to get systemic electromagnetic equilibrium between exchangers and cations. They are in reciprocally inverse relation on the direction of movement and the development to equilibrium.

ii. Are all the motions visible with the spatiotemporal feature? The double-diffusion and double-exchange form the relativity in motion: the double-diffusion motion which forms the depolarization and repolarization phase of action potential is extrinsically visible with the spatiotemporal feature, acting as the “real part” of the motions; while the double-exchange motion which forms the resting phase of action potential is intrinsically invisible lack of spatiotemporal feature, acting as the “imaginary part” of the motions.

(ii) The unity on the relativity of motions: the electromagnetic convection-exchange coupling

Are the double-diffusion (convection) and double-exchange irrelevant? On one hand, the double-exchange motion which causes the individual concentration difference (chemical potential) of ions in the opposite regions is the cause of thermodynamic double-diffusion motion of electrically charged ions to get individual thermodynamic equilibrium; and the double-diffusion which causes the systemic electric potential difference is the cause of electromagnetic exchange motion to get systemic electromagnetic equilibrium. The double-exchange and double-diffusion are interacted cause-and-effect reciprocally. On the other hand, because the thermodynamic diffusion motion of electrically charged ions performs the motion of electric current, the double-diffusion (convection) motions of electric current in the counter directions causes the induced magnetic field, which in turn induces the coupled negative electromotive force to contribute to the inverse motion of electrically charged ions in the form of double-exchange (Faraday's law of induction and Lenz's law), restoring the original distribution of ions. The double-diffusion and double-exchange are coupled together by the electromagnetic property of electrically charged ion motions. It is because the electrically charged attribute of ions that the double-diffusion motion of ions causes the induced electromotive force for

the double-exchange of electrically charged ions, and it is the electromagnetic interaction (induction) that generates the coupling of convection and exchange.

The above interaction between double-diffusion and double-exchange of electric charged ions in unity in the form of electromagnetic convection-exchange coupling is under the prerequisite formed by the relativity in the ground substances with the different electrostatic (electromagnetic) intensity and the relativity in the mobile counterions with the different electrostatic reactivity. The excitation-standstill state of action potential results from the interplay between electrically charged convection and electromagnetic double-exchange, which forms the unity and circulation of electromagnetic convection-exchange coupling in dynamic homeostasis.

(iii) The physical attribute of electromagnetic convection-exchange coupling

Is the electromagnetic convection-exchange coupling dependent on chemical catalyzers? Note that (i) both ion motions of diffusion and exchange are essentially of physical processes driven by the thermodynamics and electromagnetic dynamics (electromagnetic induction), which can “naturally” and “spontaneously” operate 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.

How do the guest molecules efficiently take effect? The operating principle is physical, and the guest molecules take effects that modify the physical principle in the chemophysical way.

v. Summary II. The relativity in the prerequisite for action potential setting

The prerequisite for the electric convection currents which are formed by the diffusion motions of depolarization and repolarization of electrically charged cations down concentration gradient in the counter directions is the selective asymmetric distribution of cations on the counterpart sides of membrane which generates the significant concentration difference (chemical potential gradient) of cations between two sides. To form the selective asymmetric redistribution of cations on the counterpart sides of membrane with the significant transmembrane concentration difference, the double exchangers for cations on the either side of membrane are constructed by the negatively charged polymers different in electrostatic intensity which can electromagnetically interact with the counterions competitive in the reactivity are required.

So, to generate the double-diffusion and double-exchange process of action potential, it requires the

layout of the double ground substances made of the negatively charged polymers different in electrostatic intensity on the either side of membrane and the mobile counterions in different reactivity.

II-II The relativity in space: attractive action vs. hydrophilic action— compressible lattice vs. extensible lattice

i. Latticed space and transformer potential (parasitic potential)

Like charges repel and unlike charges attract, as described by Coulomb law of electrostatics. Due to the electropositive property, the counterions (metal ions and proton) are “captured” and attracted non-covalently and reversibly with electronegative polymers through electrostatic interaction in the way of sorption. The counterions so act as the crystal nodes of lattices to connect the negatively charged groups between polymers, and the size of crystal lattice space is determined by the interaction between negative charges group of polymers and counterions. In this sense, the thermodynamic chemical potential of counterions (metal ions and proton) is determined by the spatial size of lattice that metal ions locate, termed transformer potential (parasitic potential), which derives from the interaction between negatively charged group of polymers and counterions.

ii. Attractive action and the compressible lattice

Because 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, and the spatial size (spatial extension) of negatively charged polymers are thus much larger than that of parent molecules. Because the electrostatic attraction between positive- and negative charges resists the electrostatic repulsion, the size of lattice constructed by counterions and polymers can be compressible in significant degree by the positive charges, 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” and 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, in which the size of polymer lattice turns to be compressed in response to the existence of metal ions [2 Angelini, 3 Nagornyak]. And the more metal ions attracted to the negative charges, which locate surround negative charges in the more dimensions, causes the greater compressed space between the adjacent negatively charged carriers.

iii. Hydrophilic action and the extensible lattice

In the context of 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 [4 Dudev]. The shell can be several molecules thick, dependent on the charge of metal ions, and their distribution and spatial dimensionality [5 Ball].

As the positively charged counterions are captured by the weak negatively charged polymers, because of the hydrophilic action that the layers of water molecules are attracted surrounding the metal ion, the size of lattice constructed by counterions and polymers can be 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 [6 de Kerchove]. And the more metal ions attracted to the negatively charged polymers causes the greater expanded space between the adjacent negatively charged carriers.

iv. The screening action: attractive action vs. hydrophilic 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 electrostatic intensity of charges.

As the positively charged metal ions (and proton) are captured by the negatively charged polymers, the size of 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 charged groups 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.

v. Summary. The relativity of space between the interacted polymers and counterions:

transformer potential

The interaction (attractive action and hydrophilic action) between negatively charged polymers and cations causes the transformer potential of mobile charged cations which 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 expanded is dependent on the intensity of negative charges; and the variation (compressed or expanded) is elastic and reversible in the dose-dependent sensitivity in response to adding or removing ions, in which the greater concentration causes the greater amplitude of variation and vice versa.

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

II-III The relativity in “spacetime” of action potential

i. The setting in relativity for generating action potential

The setting in relativity for generating action potential are composed as follows: (i) the ground substances of negatively charged polymers with different electrostatic intensity; (ii) the mobile counterions (metal ions and proton), and especially alkali metals and alkaline earth metals, with the different reactivity; and (iii) the lipid bilayer membrane to separate the ground substances with the

differentiation of local zone of membrane (junctional zone, e.g., postsynaptic membrane), which contributes to tune “on” of action potential.

ii. The metal ions (alkali metals and alkaline earth metals) with the competitive reactivity

The ions of alkali metals and alkaline earth metals are highly electropositive and highly reactive for cation exchange. Due to the strong electropositivity, they are competent to bind to the negatively charged polymers as mobile counterions, and competent to attract water molecules with hydrophilic action.

The reactivity series shows $K > Na > \dots$. During the process of cation exchange, due to the higher reactivity of K^+ compared to that of Na^+ , K^+ acts as the active one that predominates the exchange, while Na^+ acts as the passive one whose exchange is under the domination of K^+ .

iii. The ground substances of negatively charged polymers in opposite responses to metal ions (attractive action vs. hydrophilic action)

The plasma membrane of cell separates extracellular matrix and intracellular matrix. The ground substance of extracellular matrix is constructed by polysaccharides. The ground substance of intracellular matrix which attaches to the cell's peripheral plasma membrane is constructed by microfilaments (actin filaments) which are arranged with the barbed-end of each filament attached to the cell's peripheral plasma membrane. The ground substances of polysaccharides (outside) and microfilaments (inside) are separated by plasma membrane into the counterpart sides.

(i) Polysaccharides

Glycosaminoglycans (GAGs) are the ground substance extending and filling in extracellular matrix. They are long unbranched polysaccharides consisting of a repeating disaccharide unit, which contain carboxyl or sulfate groups that carry negative charges [9 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 Ca^{2+}) [10 Salehizadeh].

Because the metal ions (K^+ and Na^+) are osmotically active, the polysaccharides are strongly hydrophilic, and form the highly hydrated porous gels. The pores of hydrated porous gels are formed in "egg-box model" [6 de Kerchove], and the size of pores are evidently enlarged by the increased concentration of metal ions (and proton) [6 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 [7 Janmey, 11 Edelstei, 12 Nancy], 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 [12 Nancy]. Its underlying mechanism is described as “like-charge attraction between polyelectrolytes induced by counterions” [2 Angelini], in which counterions are found that play a central role for generating attractions.

Microfilaments are composed of two helical, interlaced strands of actin [13 Grimard]. Actin carries around 11 net negative charges at neutral pH [7 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 [2 Angelini, 14 Lin, 15 Priel]. The zipper-like charge alignment enables the close bundling of actin filaments together, pulling them “attracted” closely [2 Angelini, 16 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 [17 Kang, 18 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 [16 Shikinaka, 19 Tang]. In the presence of high concentrations, multivalent linear waves of counterions condense [2 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 actins is generated and intensified by electrostatic interactions with counterions [13 Grimard, 20 Hase].

II-IV Summary. The connotation on the relativity in the setting of action potential

i. The foundation of depolarization and repolarization

The negatively charged double-exchangers are set with the polymer of which the attractive action predominates and the polymer of which the hydrophilic action predominates, which are separated by the membrane. It results in the maximized asymmetric redistribution of the metal ions with the competitive reactivity on the either side of membrane, and the consequential thermodynamic chemical potential gradient of metal ions across the membrane, which is the optimal prerequisite for the depolarization and repolarization diffusion of action potential.

The maximized asymmetric redistribution of mobile cations on the counterpart sides of plasma membrane (Na^+ exterior/ K^+ interior) generates the significant transmembrane concentration gradient of ions to enable the ion diffusions of depolarization (Na^+) and repolarization (K^+) in the form of convection.

ii. The foundation of resting membrane potential

The metal ion higher in reactivity, rather than those lower ones, dominates the exchange and presents the net preferential transmembrane motion with the higher permeability that overwhelms other ions.

Due to the higher reactivity of K^+ and the higher concentration of K^+ on the interior side of plasma membrane rather than exterior, the resting potential of plasma membrane predominantly arises from the electrochemical equilibrium potential of K^+ , which results from the net outward flow of K^+ down chemical potential gradient, so that the resting potential is in the polarized state (positive outside but negative inside) at the value of K^+ equilibrium potential (equilibrium potential is the membrane potential at which there is no net flow transmembrane, refer to Nernst equation).

iii. The foundation of endogenous action potential mechanism: the connotation of resting membrane potential

The resting membrane potential (positive outside but negative inside) caused by the ion (K^+) higher in reactivity and higher concentration inside forms a “potential barrier” that obstructs the inward flow of the ion (Na^+) lower in reactivity and higher in concentration outside.

The potential barrier formed by K^+ equilibrium potential plays the role that (i) it raises the potential energy gradient of the inward diffused ion (Na^+) to enhance inward diffusion down potential gradient, taking the effect like the dams in hydroelectricity that it provides the dynamic energy that converts from potential energy for inward diffusion to motivate convection; and (ii) it obstructs the inward ion diffusion with the resistance of resting potential, acting as the sluice that tune off and on the process of convection-exchange coupling, so that the inward diffusion of Na^+ down chemical potential gradient (depolarization) is under the control of the height of potential barrier formed by K^+ equilibrium potential, by which varying the K^+ equilibrium potential by varying the ratio on the exterior/interior K^+ concentrations (refer to Nernst equation), in the way of local leakage due to the higher K^+ concentration inside, acts as the endogenous sluice to turn off and on the inward depolarization diffusion of action potential.

iv. The foundation of leakage potential

The higher reactivity of K^+ which permits the preferential transmembrane motion and the higher concentration of K^+ inside are competent to outward leakage motion of K^+ . The local leakage causes the reduced interior concentration which causes the spontaneous depolarized resting potential at the somatic membrane, functioning as the tunable switch to control the endogenous initiation of action potential, in which the greater leakage causes the greater depolarized resting potential, and the greater shortened amplitude and duration and the faster frequency of action potential, refer to Nernst equation and Goldman equation on equilibrium potential and reversal potential.

Part II The informationized electromagnetic oscillation of action potential-electromagnetic convection-exchange coupling

I The connotation of action potential in information: complex-signals, encoding and transmission, Shannon entropy and energy level

i. ii. iii. iv.

II Summary. The character of action potential informationization: standardization and energy level of electromagnetic oscillation of convection-exchange coupling

Part III The electromagnetic fluid dynamics of action potential

I The characterized property of electromagnetic rotational energy field in electromagnetic fluid dynamics

i. ii. iii. iv.

II The electromagnetic fluid property of action potential

i. ii. iii.

Part IV Summary. The energy creation, principle and prerequisite of action potential-electromagnetic dynamic homeostasis system

I The property and energy creation of action potential in electromagnetic dynamics

II The principle of action potential-electromagnetic dynamic homeostasis system in relativity

i. ii. iii. iv.

III The summary on process, principle and requisite of the electromagnetic convection-exchange coupling in dynamic homeostasis

i. ii. iii. iv.

IV The connotation of relativity

Volume II The convection-exchange coupling of electromagnetic dynamic homeostasis system in macro- and microscales of nature

Part I The relativity in the universal property and the prerequisite for electromagnetic convection-exchange coupling

I Second law of thermodynamics, Maxwell's demon and the relativity in the universal property

i. ii.

II The prerequisite for the convection-exchange coupling of electromagnetic dynamic homeostasis system

Part II The electromagnetic convection-exchange coupling in geological and meteorological dynamics: earthquake and cyclone

I The analysis on earthquake: denotation, connotation and seismic waves

II The analysis on cyclone: the principle on dynamic homeostasis in electromagnetic dynamics

III Summary

Part III The electromagnetic convection-exchange coupling of dynamic homeostasis system in microscales

Part IV Summary. The connotation of electromagnetic convection-exchange coupling in energy operation and creation

I The connotation of electromagnetic convection-exchange coupling

i. ii. iii.

II Summary. The energy creation of electromagnetic convection-exchange coupling in macroscale and microscale

Volume III The dynamic homeostasis of electromagnetic convection-exchange coupling in astrodynamics: celestial rotation and gravitation

Part I Celestial rotation and shaping: the topologic operation of electromagnetic spinning energy created by convection-exchange coupling

I Background

II The rigid property of celestial rotation

III Electromagnetic torsion (spin) created by convection-exchange coupling: the topologic operation of celestial rotation and shaping

i. ii. iii. iv. v.

IV Summary. The topologized and informationized operation of celestial rotation created by electromagnetic convection-exchange coupling

i. ii.

Part II The property of celestial gravitation in dynamic relativity

i. ii. iii.

Part III Summary. The essence of gravitation

Part IV The summary on volume I to III. The perpetual natural dynamics of electromagnetic convection-exchange coupling created by the relativity and the ingenious relativity

Volume IV The living essence and elegant-beauty of the Nature in aesthetics— the perpetual electromagnetic dynamic homeostasis from biology to the Universe

Part I The elegant-beauty: the creation of celestial dynamics in aesthetics

i. ii. iii. iv.

Part II The connotation of natural mathematics in dynamics: the logic and beauty created by the dynamics of electromagnetic convection-exchange coupling

I The connotation of natural mathematics created by electromagnetic dynamic energy

i. ii. iii. iv.

II The relationship of “space, motion and time” between natural physics and natural mathematics

(i) (ii) (iii)

Part III The living essence and elegant-beauty from biology to the Universe

Postscript

i. Harmless and perpetual fine-energy resource and dynamics

ii. Oriental Taiji

iii. Epilogue. Soul course

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