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Biophysical mechanisms complementing "classical" cell biology

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1. ABSTRACT

This overview addresses phenomena in cell- and molecular biology which are puzzling by their fast and highly coordinated way of organization. Generally, it appears that informative processes probably involved are more on the biophysical than on the classical biochemical side. The coordination problem is explained within the first part of the review by the topic of endogenous electrical phenomena. These are found *e.g.* in fast tissue organization and reorganization processes like development, wound healing and regeneration. Here, coupling into classical biochemical signaling and reactions can be shown by modern microscopy, electronics and bioinformatics. Further, one can follow the triggered reactions seamlessly via molecular biology till into genetics. Direct observation of intracellular electric processes is very difficult because of e.g. shielding through the cell membrane and damping by other structures. Therefore, we have to rely on photonic and photon – phonon coupling phenomena like molecular vibrations, which are addressed within the second part. Molecules normally possess different charge moieties and thus small electromagnetic (EMF) patterns arise during molecular vibration. These patterns can now be measured best within the optical part of the spectrum - much less in the lower terahertz till kHz and lower Hz part (third part of this review). Finally, EMFs facilitate quantum informative processes in coherent domains of molecular, charge and electron spin motion. This helps to coordinate such manifold and intertwined processes going on within cells, tissues and organs (part 4). Because the phenomena described in part 3 and 4 of the review still await really hard proofs we need concerted efforts and a combination of biophysics, molecular biology and informatics to unravel the described mysteries in "physics of life".

2. INTRODUCTION

Cells, organelles and molecules have to be synchronized or at least prepared for a compatible cooperation. Thus, the time needed to exchange all the necessary information for the coordination of these processes would be much too long if one would only take into consideration random diffusion of signaling molecules in a watery surrounding. Brownian motion and the random walks of molecules may be speeded up a little by controlling structures like actin filaments or microtubules, however, also passive or even active transport by motor proteins would take too much time to solve this coordination problem (Brown molecular movement in watery solutions: 0.1. µm/s; vesicle transport on filaments: 0.2. - 1µm/s - compare to 50 – 99% speed of light of EMF waves).

Furthermore, cells and tissues adapt very fast and in a coordinated – means also concerted - way to changes in functional and metabolic needs.

This time- and coordination problem alone shows that we have come to an end in explaining all phenomena of molecular and cell biology exclusively with the canonical toolbox of chemistry, molecular biology, genetics, cell biology as well as biology in general! Using only these methods we come to saturation in progress regarding functional analysis of molecules and in the characterization of bio-molecular interactions.

Nevertheless, fantastic achievements now are reached in the description and collection of biomolecules as separate entities. The same is true for the analysis of molecular, chemical and mechanical functions during interaction and in relation to organelle functions. Furthermore, many pathways are revealed even in genetics and in translation into proteomics.

However, as mentioned above, we come to a methodological dead end only in gathering and collecting more and more descriptive facts. If we want to look behind the driving forces of molecular self-organization and characteristics of the living matter, we need to seek for the real mediators in the coordination of living cells and organisms. This is the question, which already Schrödinger posed in 1949: "What is life"! (1) For this we have to add to our sophisticated chemical molecular biology the search for the "physics of life" and use modern informatics to make a leap in categories!

Time has come to do this because we have now a toolbox full of new methods. These are: life cell imaging in highest resolution, molecular detection by high end confocal microscopes (STED, TIRF, PALM, STORM, Miniflux, focal plane-, structured illumination etc.), cryo-electron microscopy and the combination with physical methods of spectroscopy, charge distribution, mechanical and electric force measurements etc. – all combined with cutting edge informatics and visualization.

In the present review, let us gather and tentatively interpret information, which now springs off from all ends. Recently, biomolecules and molecules in general were described e.g. as "active matter" (Vlisek, cited in Popkin – "Physics of life") (2) showing that molecules in many cases have the tendency to group in flocks or patterns – seemingly against the unshakeable principle of entropy growth (the second law of thermodynamics) – which is still obeyed, however guided in living nature by subtle compartmentalization and energy flow. This looks like a new level of the 1970ies and 1980ies findings and debates about self-organization of matter - Bénard´s thermic reaction, Belouzov Zhabotinsky´s chemical reaction, Eigen´s biochemical hypercycles, Prigogine´s steady state and dissipative structures and all the discussions about fractals, deterministic chaos and attractors. Furthermore, recent new findings of Pollack (3–6) regarding water molecules (the so-called 4th phase of water) are in this respect tantalizing news. As mentioned later (see below) Pollack characterized zones of "bound" water molecules coupled to charged surfaces of various materials – also proteins. He called the zone "exclusion zone" because other molecules and even ions (except the charge – oriented water molecules) are excluded from this quasi – crystalline water zone.

All this shows a paradigm shift emerging in thinking also in cell biology. And, as Piers Coleman wrote in an article in Nature (2007) (7) – "we also need to seek the principles that govern collective behavior" in nature. He talked in general about the world between micro – and nanometer scale and also about principles like coupling of electrons into "Cooper pairs" (Footnote[1]) and other phenomena of the quantum world.

Before we try to go down into the world of molecules and smaller particles - even "bosons" means the "exchange mediators" (e.g. photons or gluons) between particle-like entities – like "Fermions" (e.g. electrons or quarks) we first should investigate what is measured already in living cells.

3. AN OVERVIEW ON THE DETECTION OF ENDOGENOUS BIOELECTRICAL PHENOMENA

As a simple and rough example let us first consider electrode experiments, which already Galvani performed in the 16th century using frog legs ("biolectricity" and the discussion about "vis vitalis", the vital force, with B. Franklin). Later on, DuBois Reymond (19th century) performed more focused experiments showing the electric currents circulating in his own body, namely in the wounded forearm. With help of the more sophisticated measuring instruments of his time he clearly could show a wounding potential of 70 mV and more (8). The exact electric phenomena near wounded tissues have been studied not before the end of the 20th century by the McCaig group (9, 10), Pullar (11–14) and others – already using modern cell biological techniques (see below).

At times before these modern studies, only one - electrode or static combinations of electrodes were used in the beginning of the 21th centuries - derivatives of these beginnings were acknowledged as ECG or EEG. The measurements of heart and brain electric function were never questioned. However, concerning an extension of these measurements from organs into tissue – and into cell measurements nearly a ban was imposed on comparable electric studies – possibly because of the misuse and false interpretations of questionable instruments of this time. However, studies of Nordenstroem (15) and Becker

(16–19) could show more clearly the importance of electric currents for tissue health, cancer and regeneration. Furthermore, these authors made first attempts to cure or manipulate regeneration by electric currents. However, all these studies were disregarded and pushed into the “voodoo-corner” by mainstream biomedicine dominated at these times by biochemistry and pharmacy.

A first clear – cut analogue attribution of electrical processes in cell and developmental biology succeeded with very small self-calibrating vibrating micro-electrodes (20, 21). For the first time tissue folding processes going on in very early embryogenesis (like gastrulation) could be recorded electrically and could be compared with the microscopic picture of the folding processes. It could be shown that tissue folds coincide with sharp electric gradients and that the electric gradients even shortly precede the subsequent tissue movements (22–25)!

Over the last two decades electro-, ion- and membrane potential sensitive molecular dyes have been available, which can indicate precisely and during life cell imaging the “electro-molecular” processes going on within the cell, tissues and small organisms. From these tools we got more precise information of the location, spreading and dynamics mostly from the surface of cells and membranes of organelles (especially mitochondria). However, the “electric interior” and charge cooperation between molecules are hardly explored until the present day. Only first attempts were made to analyze intracellular fields using so-called “nano – pebble” voltage sensors (26).

3.1. Membrane potential as universal feature of cells

In general, each cell (not only neural cells!) produces a membrane potential that is specific for its type and tissue. Possibly, this membrane potential was the first guided control system through the cell membrane coming up with the more and more oxygenated atmosphere, about 1.5. billions of years ago. By energy-fueled membrane transport systems controlling osmoregulation within the archaic surrounding this potential through ionic separation has most probably been developed (27). Later on ions like Ca++ could then develop as first messenger and information transmission systems. This should be relevant for single membrane surrounded ancestors of Archaebacteria and Eubacteria. By this, stretch-activated- and electric channels evolved shifting the membrane potential away from being neutral, thus producing a membrane potential. Much later during development of primitive multicellular systems, ionic channels from one cell to the neighboring cell may represent the ancestor of the hormone and nervous systems (28). In vertebrates connexins (gap junction components, see below) are first detected at the 8 - cell stage (29), and gap junctions themselves contribute to conveying electrical information (see below).

Let us go back to the membrane potential in recent multicellular systems: the height of the membrane potential is specific for the degree of differentiation of a cell! Normally, it varies from -40mV to -90mV in differentiated cells and from -8.5.mV in the fertilized egg, -23mV in the four-cell and -25mV in the 16-cell frog embryo (30, 31). Interestingly, tumor cell membrane potentials are also in the range of the embryonic cells (32, 33).

The electric nature of these membrane potentials producing endogenous electric fields (electric fields, EF; direct currents, DC and ultra-low frequency electromagnetic fields, UL-EMF - see also (34)) comes from the segregation of charges by molecular machines like pumps, transporters and ion channels that are mostly situated in the plasma membrane (for reviews see (35)) (Figure 1). Not only small ions like protons, sodium or potassium can be involved in EF formation, but also larger biomolecules like tissue factors, growth hormones, transmitters and signaling molecules like serotonin and others – nearly all biomolecules possess electrical charges besides their chemical and receptor mediated action (36). These charges make possible an enhanced spreading by “micro-iontophoresis” (37, 38). All these factors carry information for a single cell but also for the neighboring cells.

Furthermore, ions and charged molecules can also pass from cell to cell by gap junctions. As a result, ion gradients in tissues and cell assemblies are produced and consequently a larger electric field is generated. However it should be stated again that these endogenous EF are steady or at best slowly changing. Furthermore, they have lower membrane potential values than the typical action potentials in nerve or muscle cells and do not show spikes of electric activities. They are smooth instead and can change over longer periods (from days to weeks – e.g. during wound healing) (9) or form UL - EMF.

Within a cell, the enzyme machinery does not work in a linear manner, as proposed by Rosenspire *et al*. (39, 40). These authors discuss an electrically sensitive, membrane-embedded receptor complex such as voltage-sensitive phosphatase (VSP) that transduces a signal to 1–25 Hz Ca++ pulses. The frequency of the calcium pulses is then compared with fundamental 0.05 Hz metabolic oscillations. Rosenspire *et al*. ((40); see also (34)) argue “the intermediate metabolism of the cell functions as a biochemical bandwidth filter centered at 0.05 Hz.

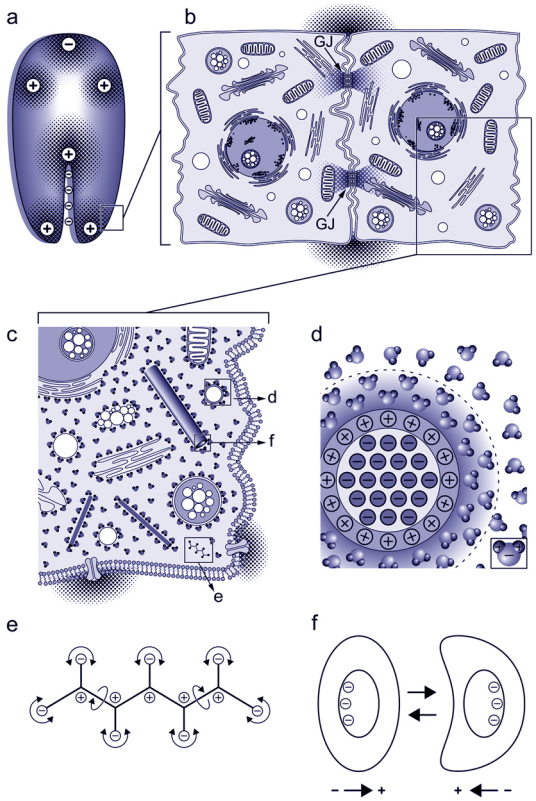

Figure 1. A. Local charge domains appearing temporarily within an early embryo (general example) measured at the surface (see also Becker 17 and Funk 34). Insert see b. B. Two surface (epithelial) cells with their own local charge domains (grey field lines) and gap junctions (GJ). Insert see c. C. Part of a cell in b; with cell organelles - e.g. nucleus at the bottom, charged particle with polarized water molecules (d), lipid molecule (e), microtubule (f). Note the oriented (polarized) water molecules symbolized in the vicinity of the organelles (bound water or exclusion zone, EZ, in d). D. Principle of the polarized "bound" water molecules (symbolized at the bottom right – note the typical +/- charges at 120 degree angle) around a charged particle. Note the alignment of the water molecules within the EZ (dotted line). E. Example of a molecule with charges at the backbone and side chains. Arrows indicate possible mechanical vibrations. By moving charges (phonon – photon coupling) an electromagnetic wave is elicited mostly with the THz till IR range of the EMF – spectrum. F. Conformational change (back and forth) of a protein, caused by charge – driven (EMF – driven) electron delocalization within a hydrophobic pocket. By such EMF – "domains" (or electron spin interactions), quantum informational coupling can occur.

In this way, the 0.05 Hz electrical pulse-frequency domain of interest is seen to arise quite naturally."

3.2. Situations where bioelectric fields can be detected

During early development of amphibian and chicken embryos, endogenous ionic currents can be measured. Those currents and related fields are actively generated by Na+ uptake from the environment that leads to a transepithelial potential difference (TEP). Within the early stages of a developing organism, differences in TEP between various regions form intra-embryonic voltage gradients. The arising endogenous static EF is on the order of 1–5 V/cm. Therefore it is well above the minimum level needed to affect morphology and migration of embryonic cells *in vitro* (31, 41, 42).

However, already within a fertilized egg and in the subsequent 2, 4, 8 etc. stages Vandenberg and Levin (36) showed patterns of a changing membrane potential arising within the cell surfaces, sometimes reaching from one to the neighboring cell. So *in toto* a patterned surface of the *morula* and in the later stages appeared. These EM patterns can be followed in smaller animals like the flatworm *planaria* also during later stages, e.g. in front-end and right-left polarization (37–40). Furthermore, organ fields become demarcated like the eye field and others. And functionally and for time coordination it is very important that the EM fields precede - as was actually found - mechanical actions of epithelial folding, gastrulation and even internal signaling and genetic processes such as further cell differentiation and internal cell polarization (28). As an example: first the position of the eye field in the whole body plan is marked by the EF, then after typical differentiation markers like Pax 6 can be detected (order of appearance of "biomarkers", see below in more detail).

Sources of current loops are TEP differences in further development. In axolotl embryos outward

currents are found at lateral edges of the neural ridges and at the blastopore, whereas inward currents are found at the center of neural groove across the wall of neural tube and at lateral skin (9, 10).

An example for further development in organs is the eye lens. Here also, driving forces are EF. They are produced by basolateral membranes of anterior epithelial cells via Na+/K+ pumps (42). Using published values for equatorial and polar lens resistivity (0.5 and 500kO/cm) Wang et al. (42) have calculated that lens currents give rise to steady DC EF of between 0.2 and 6V/cm - a normal physiological range. The main current efflux is concentrated at the lens equator, where important aspects of lens physiology, such as growth of new cells, take place. During adult life, lens epithelial cells move towards the equator, probably by active migration, proliferate and differentiate into lens fiber cells (see also (43)).

Endogenous EM fields are found not only in development and in pre – sketching the classical and already described cell biological phenomena within a developing organism but also in wound healing and regeneration.

In wound healing an enhanced TEP is generated immediately upon wounding with the cathode at the wound center. This EF is the earliest detectable signal that an epithelial cell receives to initiate directional migration of cells into the dermal wound bed (21, 44). This wound-induced electrical signal comes very early and lasts for many hours (10, 45). It regulates different cell behaviors within 500 µm to 1 mm from the wound edge. After complete covering by the epithelium the signal fades. In corneal epithelial wound healing, the electric field lines control even the orientation of the mitotic spindle in the proliferating epithelial cells as well as the orientation of the re-growing nerve sprouts (10). Also in cultured hippocampal neural and glial cells the cleavage planes were oriented perpendicular to the DC-EF field lines (46). Kucerova *et al.* (47) demonstrated that the EF after wounding trigger only initial signals like polarization of cells. Later on other factors (like growth factors etc.) take over. The electrical short-circuiting thus is the accelerated signal together with the signal of autonomic sensory nerves and diffusion of signaling molecules and hormonal actions normally are much slower.

All these examples together show that the mentioned small DC electric fields are ideally suited to bridge the information gap for short time periods and for the spatial dimensions between the short-range action of molecules e.g. by local hormones, growth factors etc. and the far reaching control from the organism e.g. via hormones distributed via blood stream and the autonomic nerves.

Regarding regeneration, it has been known for a long time that during wound healing and regeneration the cells of the injured tissue dedifferentiate and fall back into embryonic stages. This is especially true for the so-called blastema - the regenerating tissue in wound and bone fracture healing. It has been reported in a paper by Adams *et al*. (48) that H+ pump (V-ATPases)-dependent changes in membrane voltage are an early mechanism, which is necessary and sufficient, to induce tail (spinal cord, muscle and vasculature) regeneration in Xenopus. After amputation, the normal regeneration bud depolarizes, but after 24 h it repolarizes due to V-ATPase activity. More recently, our group (49) demonstrated that ion contents in the axolotl tail blastema change dynamically during regeneration and, in most cases, are still fluctuating at 48 h *post amputationem*. After 6 h the membrane potential was depolarized by five-fold in the bud region blastema compared with other regions and the uncut tail. The further time line was investigated by Tseng *et al.* (50): 6 h after amputation a V-ATPase dependent proton extrusion occurs, followed by an increased Na+ influx in the regeneration bud and after 24 hours activation of downstream pathways (BMP, Notch, Msx, Wnt and Fgfs). After 7 days the regeneration is completed.

To sum up the hitherto well-known endogenous electric phenomena: we find them within all three situations where fast changes of tissue remodeling are needed: embryology, wound healing and regeneration. Here, the pre – formative capacity EM field contains the major component of early information and coordination.

At cell-, organelle- and molecular dimensions we find that DC – EF can induce changes in position of the Golgi apparatus (GA) and nucleus. Also cytoskeletal proteins are affected such as the microtubule organizing center (MTOC), actin and microtubules (MT) proper (46, 51–53). Furthermore, plasma and mitochondrial membrane potentials change (54). Regarding directional migration, MTOC, GA and actin were reoriented into the direction of the leading edge of the cells, while the MT accumulated in the rear edge of the cells. Also the nucleus was located at the back of the cells.

Saltukoglua *et al*. (55) found a spontaneous and electric field–controlled front–rear polarization of human keratinocytes. The EF - directionality targeted the plasma membrane molecules. This finding fits well with the notion that the EF effects are connected to the outer surface of the plasma membrane due to the high resistance of the plasma membrane (37).

During migration also differences in pH between the front and the rear end have been observed. In a previous study, we reported on patchy

accumulations of physiologically active sodium-hydrogen exchanger (NH3). In addition, H+ bubbles were seen outside the cell membrane particularly at the leading edge of migrating cells. Furthermore, ß-actin accumulated inside the leading edge membrane (56). After NHE3 silencing, cells lost their characteristic polarity and orientation (56). In a previous paper, we found that the directional information of NHE3 is transferred via mechanisms involving PIP2 maintaining electrotaxis (56). Furthermore, we found that pNHE3 forms complexes with both protein kinase C (PKC) isoform η and γ-tubulin at filopodia, suggesting that these molecules may regulate the microtubule-organizing center. Our data further suggest that PKCη-dependent phosphorylation of NHE3 and the formation of pNHE3/PKCη/ γ-tubulin complexes at the leading edge of the cell (55, 56). Thus, we could reveal major components in molecular events in electrotaxis.

4. GOING DEEPER INTO MOLECULAR LEVEL

Using “nano—pebble” voltage sensors Tyner *et al*. (57) and Lee and Kopelman (26) demonstrated that the membrane potential of mitochondria and inside the cytoplasm can be measured and determined to be present over a much wider distance than it was predicted and calculated using the parameters for shielding and damping by stochastic Brownian movement of random water molecules. How can it be explained, such longer EF exist dwarfing their predicted ranges based on calculated values?

Modern cryo-electron microscopic pictures (unfixed and not pre-treated before cryo-cutting!) have revealed that cytoplasm and organelles are stuffed with proteins, glycoproteins, lipids, nucleic acids and all other (1%) “important” molecules (58). The 99% water *molecules* (not the percentage of body water weight!) fill all the gaps between and within these important molecules. However, cryo EM implicates that most of water molecules are bound water molecules not free water. They are arranged in the well-known layers of Helmholtz, Stern, Debye layers forming also a Zeta potential (33). This is a well – known fact in material science and engineering. And because of the charge moieties of nearly every molecule, a characteristic bound water - “exclusion” zone (EZ) for random water is formed, according to Pollack (3, 5, 6). With the method of EMF vibrational spectroscopy it was found that practically no free, bulk water is found in many animal cells and even more in plants (here 70% partly bound and 30% tightly bound water) (59). The EZ can be many water molecule layers thick and has an ordered (charge polarization of molecules) structure excluding not only random oriented water molecules but also ions and other molecules.

In many aspects bound water differs from random, free or bulk water: the density is 0.97 instead of 1 (bulk water), the heat conductivity is much higher and the dielectricity-related frequencies are 2 GHz compared to 19 GHz (bulk water) (60). Recent publications demonstrate that bound water has significantly shorter NMR spin lattice and spin – spin relaxation times (23, 21 in Chaplin (61)).

There is much work to be done to study bound water within the realm of a cell, within cell´s compartments, around organelles and membranes and all around biomolecules! On the other hand, future models (e.g. for EF transduction) have to take into account this bound water – not only around biomolecules but also in the vicinity of cell membranes. Phospholipid bilayer membranes lying at the border of the cell and also around cell organelles help to create compartments – also by the bound water all around. In addition to this, a watery interface is described directly at the outer side of the bilayer, about 4 nm thick with about 40% occupied by the aqueous (hydrophilic) region (62). Cell membranes do not only separate by their direct membrane potential due to its sealing and separating different electrochemical areas by a very thin border (see Smith (63)). What is more that the differences between membrane bound water and intracellular water alone create a large charge potential compared to the more bulky extracellular water (64).

In the molecular arrangement bound water thus has a quasi – crystalline structure and also has other electron conducting properties than “normal” water (3–6, 65). So, also EFs are also transduced for much wider distances than expected (see 54). Regarding interactions with EMF, bound water has the following features – although more precise studies are urgently needed within this field: it has an absorption maximum in the wavelength of 270 nm. IR increases the EZ maximally (59) and in general, external electric fields should enhance the differences between these both forms of water (11, 86 in Chaplin (66)). Thus, EZ water can be created also due to some electromagnetic interaction within cells. Furthermore, through the enlargement of the “antenna – radius” of molecules the areas of bound water may act as additional receiver for EM patterns or signals coming from inside or outside the cell.

Recently, it was convincingly shown in experiments by Pollack and others (3, 5) that light´s electromagnetic energy builds potential energy in this EZ. Pollack writes: „Photons recharge the EZ by building order and separating charge. They do this by splitting water molecules, ordering the EZ, and thereby setting up one charge polarity in the ordered zone and the opposite polarity in the bulk water zone beyond“.

Because especially infrared light (3 till 15µm) has the highest capacity to enlarge the EZ, this may have also implications for IR and Low Laser Level (LLL) therapy. Here, only in a few words: by IR the EZ around collagen, cartilage and other tissues can be "re -ordered" again. Furthermore, one can extrapolate that the bound water molecules in functionally active molecules, e.g. around reaction centers within enzymes enhance the radius of action of the "important" molecules. One example: Karu (67) and many others after her (68–73) showed that the right wavelengths (mostly between 670 and 820nm) could enhance the activity of the cytochrome oxidase (Cco) a part of the respiratory chain within mitochondria or in ectopically respiratory sites. Cco is sitting just "in front of" the ATP producing molecular motor ATP synthetase and delivers "proton fuel". So the bound water molecules might have also enhanced the stimulating effect of IR on the heme-molecule of Cco.

4.1. Spectrum and frequencies of resonances

Till now, we painted an idealized picture for an absolutely still molecule exhibiting no thermal motion. However, at least in homoeothermic organisms with relative high temperatures we have a considerable thermally activated movement of any molecule – being much higher than the temperatures where experimentally modeled "exotical physical" phenomena occur (quantum coherence, energy sinks of coherent areas etc.) that we later even transfer to biology. However, we have some hints, how tricky nature can circumvent the presumptive constraints by higher temperature and entropy.

Referring back to the molecular movement: every analytical chemist knows that nearly every molecule has a characteristic pattern in "back-scattering" of infrared radiation (Raman scattering) leaving a spectral pattern, which characterizes the molecule. It depends on the lengths of side chains coming into vibration, vibration property of the carbon backbone etc. (see (74)). So we find vibrational signatures characteristic for each molecule type. These vibrational signatures can also be used for resonance and energy transfer to other molecules of the same type by IR or THz transfer of photons, thus imprinting the excitations mode to the respective molecules ((75) see (74) and review Jaross in this issue).

If we just hold in and look to all endogenous frequencies of organisms and cells, which we have touched in this article, we found nearly constant (DC) - EF or slowly fluctuating EF till UL – EMF in the endogenous fields produced during early embryonic development, wound healing and regeneration. Frequencies in the low Hz range are to be found in metabolic situations (biorhythm of cell reactions, e.g. 1–25 Hz, Ca++ pulses in combination with 0.5 Hz metabolic oscillations, see Funk *et al*. and Rosenspire *et al*. (34, 40)). Then we come to range of the action of cells by motion, like it is slow in smooth muscle cells, faster in heart muscle with its ECG and higher till hundreds of Hz in neurons (EEG and cerebellum neurons).

Within the kHz till MHz range we will find ionic shifting, and then within the MHz range, dipolar wiggling and tilting takes place (see e.g. Kandori *et al.* (76)). At higher frequencies, first supramolecular and then molecular vibration comes into play.

The next step (kHz till MHz) is found in chemical and enzymatic reactions and from MHz on, supramolecular structures like microtubules, filaments and DNA come into vibration. Here the range touches at the high frequency – end the upper GHz till THz band (see (77, 78)). A special point – for organizing spaces, compartments and structures within a cell are the so-called eigenmodes (natural vibration of a system such that various parts all move together at the same frequency – in electrodynamics "shape of a field having a specific frequency", see Cifra (79). According to Cifra, these eigenmodes are within a THz range (79).

Again, Cifra *et al*. (80) presented a comprehensive compilation regarding frequencies of cellular signals emitted by different organisms (algae, yeast, frog muscle, crab nerve etc.) and listed frequencies from kHz till MHz and at higher frequencies in wavelengths of mm till visible and UV light. Here, also distant interaction wavelengths of biosystems were listed in wavelengths or frequency tables (compare also with frequencies of external radiation exposures: Blackman (81) and also Leszczynski *et al*. (82)).

At THz till IR molecular vibrational spectra are working (see Jaross (74) and Jaross in this issue) and at higher frequencies all "typical" biophotonic phenomena within the NIR, visible and UV range are happening – at the shortwave of visible and UV and higher, typical photon absorptions and de-excitations by electrons take place (see Cifra (79) and for photon cell to cell communication see Prasad *et al.* (83)).

By most of the listed frequencies charged parts of molecules can be set into resonance by this vibration (sometimes coherent with others) producing adequate EMF frequency patterns. Next, we have to consider those molecules surrounded by the EZs and the molecule swinging together with the bound water layers. This all makes the radius of molecular interaction much longer than previously thought (3). By these phenomena a pre-formative level can arise, where molecules swinging in a similar mode can find each other in a more facilitated way and by this they may cluster more easily.

This resonance phenomenon can also be found in enzymes, which have special turnover frequencies characteristic for each enzyme. They can have ranges from 0.5 Hz up to 1 MHz in their active center (see also above and "light harvesting in photoactive plants", below). The turnover frequencies, however, can also be manipulated from outside by adequate EMF frequencies (84). In reality, the situation is much more complex because other proteins are around the enzyme reaction center(s) and thus many additional vibration modes appear.

A kind of resonance (exciton-related, see below) energy transmission plays a role in the antenna complexes of plant photosynthetic systems, too. The antenna pigments of photosynthetic systems are excited by the absorption of light. This energy is transmitted radiation-free onto the adjacent pigments by Förster resonance (FRET, see below). Only when the pigment-dimer in the reaction centre was brought into an excited state by the transfer of excitons, an electron transfer takes place. Then, one of this molecule - pair delivers an electron which is replaced by an electron from the photolysis of water. An important finding was gathered by 2D electronic spectroscopy that the electronic excitations of photo-pigments travel through photosynthetic proteins as quantum mechanical wave packets keeping their phase coherence, rather than by incoherent diffusive motion as has usually been assumed (85). This functions effectively also when the photopigments are farther apart than is expected (86) – this wave like energy transfer was firstly described in the Fenna–Matthews–Olson bacteriochlorophyll complex in green sulphur bacteria (87).

For the antenna complexes in photosynthetic algae and for the use of light (light harvesting by coherent molecule action) in these complexes Kolli et al. (88) argue „The main feature allowing these systems to take full advantage of fast vibrations is the near-resonance between vibrational frequencies and the energy gaps between excitonic states (see above). An important implication of this close energy match is that quantum-coherent evolutions (means that quantum coherence evolves – see below) can then tune the resonances and direct excitation energy in a preferential manner." Therefore, Kolli et al. (88) argue, "in photosynthetic complexes where transport is vibration-activated, a fundamental biological function for quantum coherent contributions to dynamics is to support resonances that promote a fast and effective energy distribution. "

All these phenomena make it more probable that changes in molecule conformation also "transfect" other similar molecules by wave like patterns of photon transfer (e.g. by THz or IR). Possibly, this is also the case in pathological situations like in amyloid plaques or ß – sheet conformation or in the case of other "misfolded proteins" like alpha synuclein in the pathogenesis of Parkinson´s disease (89). Thus, the described phenomenon is reminiscent on an infectious conformation imprinting at molecular level.

However, let us go back to our picture of an enlarged range of interaction during "molecule radiation" - compared to the classical assumption of random movement and stochastic key – lock interactions of molecules and only if one calculates with typical ranges of molecule binding (which diminishes with distances in proportion to r^6 !). In our new picture, the molecules are more comparable to resonating quartz molecules, which are set into vibration by the thermal and infrared "energy". These molecules as well as the wave – like patterns are the whole system. However, this motion picture of reflected and scattered waves is extremely complex. It is comparable to complicated interference patterns – with a kind of "moiré" – effects. And if reference vibration "beams" would be present (possibly there are present, but there has not been precise enough the instrumentation to measure them till now) this could even represent complex holograms (90). If this were the case, one could easily imagine the near infinity of molecular topographies.

Now, let us consider this already long known biochemical library of molecular forms and combinations in context with the surrounding water molecules and charge patterns. This beauty of topography and nm-exact architecture can recently be admired directly in cryo-EM pictures (58). The molecular components further are constructing channels, vesicles, enzyme clusters, organelles etc. all structures cooperating in a quasi-crystalline manner.

Up to this point, the present text may appear as only a chain of theoretical analogies transferred to the molecular biological situation. However, Raman scattering is an experimentally validated full-proof tool based on the phonon – photon coupling which is nothing new or strange but a physical reality. The same is true for interference patterns and bound water. Only their combinations and the situation within a cell seem to make these facts impossible. It may appear that these observations are an affront against the currently accepted tenets of cell biology. However, cell biology largely uses only Newtonian mechanics with a little addition of thermodynamics - transferred erroneously directly from macro- to nm- and even smaller scales. Hence one should consider a completely different conceptual background for binding and basic forces on these spatial and temporal scales.

4.2. The role of energy fueling of the above mentioned processes

Regarding the energetic situation and thermodynamics there exists a way out of the 2nd law

of thermodynamics that demands an entropy increase for defined locations and defined compartments. If all molecular vibrations are at random and no new orders or patterns arise there exists no problem. Then, everything within a cell would be energy consuming and no function or new structuring could happen - except ATP burning and the way into higher entropy. However, new structures arise "finding their locations by themselves", vesicles know their way, fuse with the cell membrane at the right place and time (91, 92) – all is coordinated. Furthermore, we have an open dynamic system in a steady state turnover (dissipative structures; steady state equilibrium) also between most of the compartments. And, there is another effect: if there exists an irradiation with ordered, coherent EMF, say IR, then there is more order coming into the compartments or into CDs than is the order of the reflected beams - in this sense the total entropy can increase again.

Let us further consider a coordination of molecular vibrations into a coherent swinging mode. Coherent means, molecules swing within the same frequency and phase. This is a new order and this state can normally not persist very long without additional pumping of energy against entropy.

Forming additional compartments again, can partly circumvent this problem. Further additional energy pumping like in a laser would solve the problem – however in a cell we have only thermal "noisy" energy. Nevertheless, there exists a kind of self – pumping of energy into coherently swinging areas – an effect described by Dicke ("subradiance", see below) with the further refinement by Li (93–95). Superradiance, in contrary, is the cooperative decay of excited dipoles, e.g. molecules with charges. The number of dipoles participating and their distance influences superradiant effects. Thermally excited atoms emit light randomly. The emitted intensity is the function of the number of atoms n. When the dipoles are coherently radiating in phase with each other, the net EMF is proportional to n and the emitted intensity is then n^2. Subradiant states represent states – opposite to superradiance, which are at a lower energy level and instead of emitting more energy by coherence, represent a sink of thermal energy. Using the mechanism of destructive interference with cancellation of force vectors, the system can trap photons and thereby store energy. Between molecules this radiative trapping can occur when the distance between particles becomes smaller than the wavelength of the transition (96, 97). These calculations describe an energetic self-pumping sink because here, the molecules are coherent and exist within the lowest energy state - a situation, which somewhat resembles Bose-Einstein condensates. However, in the situation of CDs an energy trapping self-pumping sink is present. As a result, it is possible that a self-patterning coherent field emerges.

To find out more about these phenomena in living cells or in molecular arrangements we have to refine our methods. On the other hand, some hints regarding self-ordering at least of single molecules already exist, e.g. in aligning of molecules like actin, tubulin or by self-cooperating, in the form of biomolecular condensates – all seen directly by cryo-electron microscopy or modern life imaging fluorescent microscopy (91, 92). Here, Förster resonance (FRET) can visualize a direct molecular cooperation in distances of about 3–7-nm (98).

The following phenomena are expected to be involved in irradiation energy or expressed more commonly, regarding temperature. CDs of "important" molecules with water or biomolecular condensates are at a higher degree unstable than membrane bound vesicles at typical body temperature because of the Brownian motion, which increases with temperature. However, the above-mentioned mechanisms of self-pumping and self-ordering help to stabilize them. On the other hand, if the temperature increases above a certain threshold (e.g. associated with high fever) these molecular associates cannot be stabilized, thus the molecular movements get more and more chaotic. Although at smaller increases of temperature, the cell is fighting against with the enhanced production of "heat shock" proteins (99). So in sum, a relatively constant temperature up to a certain level is important for the functioning of cells or more important for complex nervous systems such as the human brain.

4.3. EMF facilitate quantum cooperation

In the next step that we try to climb, everything becomes even more "weird"! A well-known fact in quantum physics is that EMFs facilitate quantum cooperation (100–102). This also means that EMF facilitate states of quantum coherence and by this quantum calculations of probabilities are affected (102). Here also a misunderstanding concerning "biophotons" (103) often occurs. We should go more for the real meaning of "photon" as a "boson" or transmitter of an exchange: a photon can range from 0.0….Hz to cosmic radiation in the EMF spectrum. In addition, T. Görnitz – a student of CF Weizsäcker - expressed it in a recent seminal paper: "Any reaction in a biological system is an electro-magnetic phenomenon. Actually, any biochemical reaction (here are electrons acting, too) involves an exchange of photons, more specifically, of real and virtual (see below) photons. The motion of ions, electrically charged molecules or atoms, is often described as a response to the action of electro-magnetic forces. According to a precise – i.e. quantum physical – description, it is the action of virtual photons. Real photons are emitted when the motion of charges is not uniform, e.g., when being accelerated from rest or slowed down. In view of the small energies acting in the living brain, it is often assumed that one might

ignore quantum aspects and only consider here electromagnetic waves. For a mere pragmatic description this may sometimes be appropriate, though not for a real understanding of those processes"…and again, he quoted: "*In the field of biology all of the interactions among atoms, ions, etc. are transmitted by real and virtual photons"* (101). *These virtual photons describe interactions of "particles" in a field: e.g. if two electrons are interacting they exchange virtual photons. If two electrons are passing near each other (think the electrons more as ripples within the electron field) they produce a transient fluctuation – a perturbation (a jiggling) of the respective field causing a kind of repulsion of the electrons (see respective Feynman diagrams).* "Biophotons" as real photons of light are mostly found in cells during production of radical oxygen species and other processes with deviating radicals – means often when things go wrong within a cell.

To sum up again, EM fields facilitate quantum coupling and quantum calculation with no time delay – this explains the reason why there is such a strong effort these days to build quantum computers. First positive attempts of quantum computing are underway and this shows that in principle this is a feasible approach – and; why living nature should not evolve and use such a technique over the billions of years of evolution on Earth?

The general problem in quantum computing is the read out and translocation from the seemingly "virtual" and "instantaneous" (without delay) level into the classical EMF information level, whose maximum speed is the speed of light. Possibly, nature has solved the problem via paramagnetic influence of electrons held by London forces in hydrophobic pockets as argued by Hameroff, Penrose and Tuszynsky (104–109). In general, these authors built up a big framework of observations, calculations and theoretical extrapolations of related quantum processes to explain modern aspects of the biological nature of consciousness. Now, in this short review we can only briefly touch upon this field of quantum calculation in neurobiology. The famous neurophysiologist Sherrington stated in 1957 (110) that unicellular organisms possess by definition no nervous system - the cytoskeleton should serve instead as a "nervous system".

This is why Hameroff and Watt (105) suggested in their first interpretations that distinct tubulin dipoles and conformational states in cytoskeletal microtubules should represent the center of information processing. Here, patterns of conformation changes should represent two-dimensional Boolean switching matrices with input and output computation occurring via microtubule associated proteins (108). The main question that emerges is how to read out such quantum coherence after a collapse of this in molecular terms? How can decoherence of quantum states lead to a "classical" signal? Hameroff described biological quantum phenomena by shifted (delocalized by London-force electric dipole interaction) electrons. Later on, he proposed *magnetic* dipoles, which could be related to electron spin—and possibly related also to nuclear spins. These spins can remain isolated from their environments for long periods of time. Spin is inherently quantum in nature, and quantum spin transfer through aromatic rings can occur also at body temperatures (111). This is a further advantage over London-force electric dipole interaction involving charge separation. 'Spin-flips' might perhaps relate to alternating currents in related cell structures like microtubules (111).

Analyzing the speed and complexity of the neural operations within the brain, Görnitz came to the conclusion too, that brain would "cook" if all this information quantity and speed, which a human brain is processing within the 1.5 kg brain mass would run in a "classical" way (101). This seems realistic if we compare it to the energy consumption of super - computers. So this should only work by quantum computing, which solves this energy problem.

Therefore, many hints point to the fact that quantum coupling and calculations occur at room - or body temperature. But on which time frame would the read out happen into classical EMF signals? At molecular levels (spin flips or paramagnetic shift of electrons in hydrophobic pockets by London forces, e.g. in ring-like molecules) frequencies were calculated in the THz to IR ranges (108). Already Fröhlich (112), a real biophysics scientists´ protagonist and later his students and followers such as Smith (113), Pokorny (114) and Cifra (80, 115) claimed - and later on directly measured - coherent vibrations of biomolecules within the THz and IR range – all frequencies, which may represent a read out for pre-informative quantum processes (see frequency panel listed above). However, it should be noted that the molecular vibration frequencies must not be necessarily the frequencies of decoherence or readout because it is the size of the particle, which dictates the period of quantum coupling (see below)!

Why are there different time periods of readouts? The smaller the mass of the quantum coherent objects the longer it is possible to hold them in this "exotic" quantum coherent state. This means that electrons or even more photons or other very tiny entities can be held very long (perhaps forever under some conditions) in this state. And by this the quantum coherence is much more complex with many partners in these long coherent periods in small particles compared to larger objects. So the relationships and the "paths of possibilities" get more and more complicated the smaller the partners of quantum coupling are.

This means the things do not become simpler as we go down to particles like atoms or electrons – in quantum coupling it becomes more complicated (101). And - if the quantum coupling of a very small entity (e.g. electron, photon) completely defines its state then a complete transition from quantum coupling to entanglement (e.g. in spin state) takes place (see literature Jaeger *et al*. (116) and Streltsov *et al*. (117)).

The periods of quantum coherence and decoherence can be calculated as following; the heavier the shorter: a cat - like the neither dead nor living "Schrödinger´s" cat, say with the weight of 2 kg can be quantum coupled only for about 10^{-27} sec. Then, after the so-called de-coherence a real state exists: either dead or alive – or more in general, 1 or 0 in digital terms. For molecules this quantum coherent state can be held for microseconds – measured directly in molecules of the photosynthetic chain in plant cells. And, experimentally quantum coherence could be produced in up to 60 (carbon) molecules. So, depending on the size of the objects, kHz to THz to IR ranges, flip flops between coherence and de-coherence are to be expected in biomolecules.

How the read out could be coupled back into molecular biology? From the above-mentioned biophysical phenomena one can expect a vibrational shift into conformation change and a kind of molecular conformation "transfection" to other similar molecules. This constitutes a resonance emission and a transmission back, like it is found in radio-frequency identification (RFID) tags – like the Resonant Recognition model of Cosic (see review of Jaross in this issue of "Frontiers in Bioscience"). These patterns can also induce phonon (soliton – like) wave trains of water and other "important" molecules further forming filament like structures (118–120) which direct actin bundles or direct nucleation of microtubules out of tubulin molecules. On the other hand, such filamentous cytoskeletal elements can serve as leading structures for electron- or proton-trains. For example, proton diffusion in a carbon nanotube can reach 40 times that of ordinary proton diffusion in water (121, 122).

Let us round up the wave like electronic and photonic energy transfer with the novel findings of bound water around "important" molecules and membranes. And, if we think such a resonant recognition model of vibrational molecular patterns together with the CDs and bound water in general, then a thrilling new pictures of molecular cooperation emerges: the molecules can interact in a farther distance, they can cooperate much more than previously thought and they get informed by each other much faster then it was previously depicted in the classical models of molecular interactions within a cell. Another argument for this is that the bound water layers increase in size with radiant energy in the IR and visible range. By this also the CDs can interact more intensely, thus forming larger complexes ("supercoherence" – (120)) and the radiant wave recognition of such complexes should work more efficiently.

Many things and calculations are still needed to study in this respect; e.g. how does this phonon – photon-coupling act to transfer energy into vibrations of molecules and set them in motion. Is it via the Dicke – Li effect? However, the phenomena of "subradiance" (102) are confined to small distances smaller than the wavelength of light. At the quantum level, we are within a mere informative level and therefore very tiny energy changes are necessary. At the thermal movement level there exists also an informative cue, which can help further – the stochastic resonance (115) or molecular 'Brownian' ratchets (123, 124). These phenomena can amplify weak signals more than 1000-fold by using system-inherent noise. Stochastic resonance can actually enhance the information and thus improve sensing and processing of otherwise undetectable signals – also for example in oscillations between different quantum energy levels (125–127).

As an outlook for future studies we have here only scratched the surface and many additional things should be mentioned. Be it the fast information transfer from electrical synapses, the gap junctions, which now are found more and more also in the (human) brain especially in the upper layer of the cortex where many information associations come together. Furthermore, we should study more many other exotic states of bound water molecules around other charged molecules and also the state of coherent domains in biological environments.

5. CONCLUDING REMARKS

So, coming back to the introductory question of this review: how can all the molecular, cellular and upscale processes happen and be coordinated so fast? Our considerations of informational pathways lead to a layered architecture: the slowest information processes are the crawling (m/sec) ionic processes and the slow electrochemical reactions. Much faster are the endogenous electric (EF) processes by charge separation with an information transfer maximum at the speed of light. As EF per definition use photons as transducers (bosons) – as is in the case of the "biophotons" of any wavelength – any information is transduced maximally at the speed of light. The same is true for the vibrational processes of molecules within the IR range. If charges are involved in molecular vibrations then EMF of different wavelengths are produced. Together with bound water molecules, coherent domains (CDs) can appear, representing physical states where all the components of the ensemble moving in unison (102). In molecular states of CDs even quantum computing is possible with

informational speed again higher. Admittedly, it is hard to consider such physical processes together with the classical picture of molecular- and cell biology. However including these topics in cell biology investigations, we definitely need a new framework within which to incorporate refined theoretical and experimental methods in order to arrive at an internally consistent discipline that can be called the “physics of life”.

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Footnotes: [1]Cooper pairs (e.g. electrons or fermions) are “particles” which have passed a threshold where they bind despite the so-called Pauli Exclusion Principle (two particles cannot occupy the same quantum state, means they are not entangled with each other). At very low temperatures this can happen and then, is the reason for the phenomenon of electric superconductivity, too. These types of exotic “strange”, “condensed matter” states may also exist even at body temperature (see text below) in so-called coherent domains (CDs) and under similar conditions in material science (128)(see also text below).

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