Organisms
Journal of Biological Sciences

Vol. 3, 1 (July 2019)
ISSN: 2532-5876
DOI: 10.13133/2532-5876_5.8
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ORIGINAL ARTICLE

Field-dependent effects in biological systems

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Abstract

A system's biology perspective implies that, in investigating the logic of complex living organisms, we have to shift from single entities to their mutual correlations. The collective dynamics between cells and their tissues – embedded within a morphogenetic field - makes possible the self-movement of the system, allowing a continuous change of the organism without disrupting its fundamental unity, i.e. preserving hence its internal coherence. Interactions among molecules, usually explained according to a reductionist, ligand-receptor model, occur in a complex biological matrix and their dynamics should be described in accordance with the framework provided by Quantum Electro Dynamics (QED), in order to accommodate with a wide arrays on inexplicable facts (synergy, coherence, long-range interactions, and emergence of ordered structures). Indeed, a vast number of biological processes have already been demonstrated behaving according to Quantum Mechanics rules. Quantum effects are constitutive components of the biological field and they deserve to be carefully investigated to provide a more convincing comprehension of a number of biological phenomena. Within this field, quantum effects alongside with other neglected, weak forces, can participate in shaping critical biological transitions, promoting cooperation between a large number of molecular entities, and leading hence to the emergence of coherent processes.

Keywords: Quantum effects in biology; self-organizing systems; constraints; coherence in biology; water structure

Citation: Bizzarri, M, Monti, N, Minini, M, Pensotti, A, 2019, "Field-dependent effects in biological systems", *Organisms. Journal of Biological Sciences*, vol. 3, no. 1, pp. 35-42. DOI: 10.13133/2532-5876_5.8

1. Controversial findings

A living organism is fundamentally different from a non-living system, mostly regarding two basic aspects. The first one is the capability of self-movement. Namely, a living organism is able to pursue autonomously the direction of its own motion, whereas a non-living object can be only pushed/pulled by an externally applied force, and constitute then a "passive" actor. This statement has huge consequences, as it implies a profound revision of the causality concept in biology. Movement (and consequently self-organization) are the default state of living organisms, and do not require any "cause" to be explained (Soto *et al*., 2016).

The second difference is that the dynamics of each component depends on the simultaneous dynamics of the other components, so that the ensemble of components behaves in harmony in a correlated way. The collective dynamics makes possible the self-movement of the system, allowing a continuous change of the organism without disrupting its fundamental unity, i.e. preserving hence its internal coherence. As a result, this perspective shifts the focus from the single entities to their mutual correlations. The main actor of organism behavior becomes then the ensemble of correlations among different constituents. Again, that argument leads to the logic conclusion that molecular components cannot be longer viewed as "independent" molecules, free to move according to diffusion laws, but are "forced" to follow a "coherent" dynamic, as such dictated by the field. This collective behavior participates in providing robustness to the attractor in which the system dwell, thus protecting the organism's identity from external perturbations. Additionally, given that such "field" is shaped by boundaries, those constraints restraint the degree of freedom of the single entity (Soto *et al.*, 2016). Indeed, while molecules, when considered individually, can interact chemically with any kind of other components, they acquire within the living organism the property of selecting a discrete number of chemical partners, such as those allowed by the field itself. This consideration implies that chemical interactions are highly dependent on the dynamics governing the field, which can modify and eventually supersede classical chemical reactions. As a proof in principle, a very disturbing example has been offered by studies which demonstrated that specific fields allow like charges to attract themselves, instead to be repulsed, as posited by Coulomb force (Larsen *et al.*, 1997; Zhao *et al*., 2016). That finding challenges the ordinary view that condensed matter is held together by electrostatic interactions only and suggest that understanding should include a very different perspective, as such advocated by the Quantum Electrodynamics (QED) (Del Giudice and Preparata, 1998).

2. Quantum Field Theory

QED origin can be traced back to Quantum biology, a field of investigation that emerged from the pioneering book of Erwin Schrödinger, in the far forties (Schrödinger, 1944). Despite most of the current research is still theoretical and subject to questions that require further experimentation, the field has recently gained momentum, given that it has been conceptualized by physicists all throughout the 20th century.

The classical approach to explain how molecules interact and "communicate" each other in a living system mostly rely on the molecular paradigm, which posits that a living organism is an ensemble of molecules kept together solely by chemical forces, whose dynamics can be reduced to pairwise (covalent or electrostatic) interactions, as epitomized by the ligand-receptor model, as previously discussed. However, this reductionist stance does not get rid of a wide array on inexplicable facts, as those represented by synergistic effects displayed by complex mixture of natural bioactive compounds, or the biological (non-thermal!) effects induced by low electro-magnetic fields (Marino *et al.*, 2016).

Biological interactions are usually entirely explained based on chemically mediated forces (covalent and electrostatics). This static and mechanistic approach implies biological response to be strictly local and linear (the response is proportional to the stimulus), despite some attempts have been carried out to integrate some dynamics concept into that framework, specifically by considering the influence of the association/dissociation rate between ligand and receptor in regulating the biochemical reactivity (Paton, 1961). However, even this model lefts aside some critical issues – namely how selective recognition between molecules occurs and signaling amplification downstream the chemical interaction led to an "organized" behavior – and has been hence criticized (Szent-Gyorgyi, 1960). To be specific, it is quite unlikely that, within cells, biochemical reactions proceed as observed in a test tube and it is unconceivable that specific entities could face up the chaotic Brownian motion, thus accessing their respective receptor only by chance (Rowlands, 1985). As Szent-Gyorgyi (Szent-Gyorgyi, 1957) already postulated, chemical theory cannot forget that molecular interactions occur within complex matrices (including especially water) and the fields (electromagnetic (Adey 1988) as well as gravitational (Klink *et al.*, 2011) in which they are embedded. While modification of the gravity field is a quite unusual occurrence – with the noticeable exception represented by experiments performed on board of the International Space Station (Bizzarri *et al.*, 2015) - subtle changes in the electromagnetic (e.m.) field, as those addressed by Quantum Field Theory – are quite ubiquitous. According to Adey, glycoproteins on the cell surface can act as antennae for e.m. signals (Fröhlich, 1988). After the transmission across the membrane, the signal is propagated to the cytoplasm by cytoskeleton-mediated events, in which again e.m. processes may be involved. Therefore, it is time to look at the biochemical reaction not as a pure chemical process, but instead as biophysical event.

Several evidences point out in this direction. For instance, P. Weiss found that cells of the same type tend to aggregate both in vivo and in vitro with a rate faster than that allowed by the range of attractive forces, despite being mixed with several kind of other cells (Weiss, 1959). Similarly, erythrocytes actively attract each other to form rouleaux when the cell membranes are still 4 μm apart, a distance ten thousand times the range of the known chemical forces (Rowlands, 1988).

These examples prompted Paul in suggesting that a long-range e.m. mechanism, involving coherent electromagnetic states, may be responsible for the recognition between molecules and cells. These phenomena have been recently reinterpreted in terms of a coherent dynamics, according to the framework provided by Quantum Electro Dynamics (QED) (Bischof and Del Giudice, 2013).

As shown in the early seventy for a particular physical system as the LASER, any system of identical atoms and molecules above a given density and below a given temperature goes over to a state that is totally different from what is predicted by the classical condensed matter theory. In coherent matter systems (as living organisms), single entities oscillate in phase and in tune with an electromagnetic field that resonates at their frequency, thus generating a radiation that is coherent both spatially and temporally. The fundamental difference is that in the LASER such state is reached by providing energy from an external source (a pump, needed to give rise to and sustain the atomic oscillations) and by "constraining" the system in a box whose walls are finely adjusted mirrors – the optical cavity – to confine the electromagnetic field resonating with the atoms. In living systems, the coherent state predicted by the QED analysis emerges spontaneously being the system a dissipative system (in which the "dissipation" of entropy allows in preserving the ordered structure), constrained by boundaries furnished by a number of biophysical forces.

However, the chemical structure of biomolecules cannot provide by itself the required strength supporting intermolecular recognition interactions (Bistolfi, 1991). In addition, they differ in the way they resonate when stimulated. That is to say that their molecular structures (and not only their paramagnetic nuclei) oscillate between different electromagnetic patterns, inducing hence, through long-range, frequency-dependent interactions, specific changes in the configuration of complementary molecules, finally generating an electromagnetically induced geometrical "template" of the two molecular regions (Frazer and Frazer, 1987). Indeed, shape, electromagnetic configuration (including the charge distribution of valence electrons that define the chemical potential) and stability of molecules, are highly dependent of the interaction with the e.m. field as well as with the neighbouring compounds (Cosic, 1994). Any change in the e.m. field ultimately ends up in shaping the e.m. envelope of the molecule and its interaction potential. It has been showed that as long as two (or more) atoms or molecules remain within the coherence volume (in which electron waves are coherent) (Li, 1995), they can be arbitrarily far apart (i.e., sufficiently separated that no electron wave function overlap is possible), while still exhibiting some correlation effect. Within this "coherence volume", photons emitted by single entities are completely delocalized (Li, 1994). The exchange of photons between the particles builds interference patterns, the basis of a communication linkage among the particles, which thereby form a complex cooperative system that has to be considered as a whole. According to this framework, molecules recognize their targets by electromagnetic resonance, and resonance behaves like an attractive force in influencing and attracting molecular patterns, when it is coupled with an e.m. field at rest, i.e. entrapped within a self-produced cavity. Occurrence of such cavities is provided precisely by water, whose essential role is habitually neglected in biological modelling.

We can appreciate the importance of such "cavities" by considering the functioning of the laser by analogy. In the laser, the appearance of a coherent field occurs when the system is supplied with both an external source of energy and a cavity, whose size allows us to select a specific wavelength of the coherent field. Yet, in living systems can be provided from the outside.

According to Dicke (Dicke, 1954), for distances between two emitters smaller than the wavelength of the light emitted, the emission must happen cooperatively, and the field between the emitters cannot be random but has to be coherent. The emitters then cannot be considered as independent individuals, because they are embedded in and interacting with a common radiation field. Being coupled with the same e.m. field, they are part of a communicating system. These preliminary hints have been developed in full by the QED, which describes a physical system in terms of a matter field, which is the space-time distribution of atoms/molecules, coupled to the gauge field with the possible supplement of other fields describing the non-electromagnetic interactions, such as the chemical forces. An extraordinary mechanism that creates order locally, by lowering the entropy of the atomic-molecular system, if the prevailing thermodynamics conditions are appropriate. It is not difficult to recognize in all this the crucial characters of the mechanisms of life, where a complex network of reactions and interactions works with an energy expenditure and an external interference that are negligible.

The atomic-molecular system that above the critical temperature has the chaotic features of a gas (where the discontinuous particle aspect of modern condensed matter, together with its intuitive plausibility is completely re-established), in the coherent state acquires the typical characters of a macroscopic wave, described by an amplitude and a phase, varying with continuity in space and time. A physical system of this kind behaves in a manner completely different from a more or less chaotic ensemble of a large number N (typically 10^{-23}) of atoms-little balls. According to QED, matter oscillations in phase with those of a particular mode of the electromagnetic field produce "coherent" effects (akin to laser)[1] that under certain conditions are proportional to N^2 and not to N.

Such fluctuations involve a network of interactions that include the overall matter in a macroscopic spatial region, and not only the few atoms that surround that point (as classical condensed matter theory posits) (Preparata, 1995). This scenario discloses new and utterly unexpected perspectives to understand the behavior of biological processes, namely those involving self-organization and synergistic response to complex mixtures of "active" pharmacological-like substances. However, to deal with is challenging task we have to depart from classical theories while addressing a number of critical issues, including basic notions about the structure of water, the origin of coherence in cell and tissues, and the extent/efficacy of the interaction among low frequency magnetic fields with ionic system of the cell, just to mention a few.

3. QED and Water structure

According to QED framework, water is not a simple "solvent" medium, displaying short-range interactions, but it is a complex system organizing itself in Coherence Domains (CD) (Arani *et al.,* 1995) of the size of 10-5 cm, in which a few million molecules oscillate in phase with the coherent electromagnetic field. Such CD's, like islands in a sea, are surrounded by interstices (whose size increases with temperature) of incoherent liquid, a sort of high-density gas of molecules kept together by short-range forces.

The emergence of coherent domains accounts successfully for the vapour-liquid phase transition and for the thermodynamics of water, as confirmed by an impressive body of evidence (Marchettini *et al.,* 2010). In the coherent part (highly structured in tetrahedral shapes), water forms magnetic structures capable in principle to interact with weak electromagnetic signals, and store the "information" they carry. That remark can help explain some strange magnetic properties that are known since long (like the decalcarization of water subject to appropriate magnetic fields) and, as such, are incomprehensible within the classical paradigm. In the incoherent part, which endows water with a remarkable plasticity, there linger the ions' systems. Overall, the "ionic traffic" can be significantly influenced by the cross talk between these two compartments (coherent versus incoherent domains), and any factor – e.m. field, solute that can modify such balance can shift the equilibrium of the Quantum Electrodynamical field.

According to the framework sketched above, it is unlikely that molecular encounters occur through random diffusion movements. Instead, they are driven by extended e.m. fields arising from the collective dynamics of water whose decisive role in the biological dynamics has been at last recognized. Consequently, a living organism cannot be conceived any longer as a mere collection of independent molecules mutually coupled by chemical interactions only, but must be seen as a coherent ensemble, a matter field, whose evolution is driven by long-range e.m. fields emerging from the coupling molecule interactions with the biophysical and electrodynamics feature of the "biological field".

Water molecules, which account for the vast majority of molecular components of the organism, organize themselves into extended coherence domains where e.m. fields having a well-defined frequency are trapped inside. These coherence domains are able to collect chaotic energy (high entropy) from the environment and store it in the form of coherent excitations (low entropy) which change the frequency of the trapped e.m. fields. When this frequency matches the frequency of some (non-aqueous) molecules present in the surroundings, those molecules are attracted to the boundaries of the water CDs, coating them and possibly producing membranes or other biological effects (Del Giudice and Preparata, 1995). The attracting forces obey to the following scheme: two molecular entities able to oscillate at the respective frequencies v1 and v2 when embedded into an e.m. field oscillating at v0, develop an attractive force (within the range of the field). However, the

[1] Living systems cannot be properly considered as lasers in the conventional sense, as they are tightly dependent on energy provided by the dissipative system that can fluctuate even dramatically. This occurrence would eventually oblige the system to face with the inverse problem, i.e. de-coherence. The analogy of living organisms with lasers should therefore be considered as a metaphor.

attractive force increases exponentially when the three frequencies no not differ significantly and are below the thermal noise *kT*. A molecule is able to participate in the coherent dynamics driven by water if and only if it displays a frequency v_i , such that:

$$H \left| v_i - v_{CD} \right| \leq kT \quad (1)$$

When molecules satisfy the constraint put by equation (1), they can steal energy from the thermal noise in order to resonate with the frequency of the CD and thus be involved in the coherent dynamics. Therefore, water CDs are devices able to store large amounts of energy, collected from the environment, and transform them in coherent energy; in a nutshell, CDs are able to transform n quanta having a frequency ν into one quantum of frequency n ν. This happens since lifetimes of the coherent excited levels of CDs are very long (Del Giudice and Preparata, 1998) so that many excitations produced by the external noise could pile up in the CDs producing higher and higher coherent excitations.

Overall, this implies that to a biomolecule to have an impact on biological structures it should have in its spectrum a frequency contained in the range of the values of frequencies the water CD can assume, according to Eq. (1). It is worth of notice that several molecules of interest display spectra just in the range estimated to be that of water CDs (Arani *et al*., 1995). In turn, it should also hypothesize that only molecules able to resonate within this range of frequencies can be effectively "incorporated" in the organism, where they exert their effects, while others are "discarded", the structural similarities notwithstanding[2] . According to this framework, "biological" water appears as an essential tool for long-range communications, being able to change its supramolecular organization according to the interaction with the environment. The electromagnetic fields trapped in the CDs produce electromagnetic potentials governing the phase of the whole system, which in turn gives origin to selective attractions among the solute molecules (Del Giudice *et al*., 2010).

4. Quantum effects in biology

Until recently, it has been argued that living systems are too "warm" to support quantum effects. However, new studies indicate this is not necessarily always the case, as quantum coherent transport in photosynthesis (Engel, 2007) and magneto-reception in birds to quantum olfaction (Lambert *et al.*, 2012) and single-photon effects in vision (Fleming *et al.*, 2011) are already well established. In particular, occurrence of coherent phenomena in photosynthetic systems, at temperature nearing the physiological one (Panitchayangkoon *et al*., 2010) and in a wide array of proteins containing a chromophore core, in plants (Schlau-Cohen *et al.*, 2012), bacteria (Ostroumov *et al*., 2013) and even mammals. It is indeed worth of notice that tubulin, a key component of cytoskeleton, owns a network of chromophoric tryptophan (Trp) amino acids. The fluorescence quantum yield for both pure Trp (0.14) and wild type tubulin (0.06) at room temperature are comparable to those observed in bacterial light-harvesting complex (Sardar *et al.*, 2007). In addition, energy transfer from Trp to Trp has been observed in tubulin (Weber, 1970), and this mechanism can reliably serve as potential conduction pathways supporting quantum effects (Hameroff et al., 2002). Broadly speaking, electronic coherences may be a general property of any system of compact nearly static chromophores coupled to the environment (Hayes et al., 2013). We may confidently hypothesize that quantum-dependent quick signaling through coherent energy transfer in microtubules may coordinate the complex remodelling of cytoskeleton during critical cell phase transitions. Actually, microtubules have been shown to reorganize in a dose-dependent manner after exposure to UV light (Krasylenko *et al.*, 2013), and these effects may explain the observed apparent UV mediated cell-to-cell influence on cell division (Fels, 2009). It is tempting to speculate if other kind of energy supply, as that provided by QED mechanisms or "extracted" from environmental noise fluctuations (Mohseni *et al*., 2008), could also participate in doing similar rearrangements. It should be outlined that cytoskeletal proteins are good candidate structure for this kind of energy transmission (quantum tunnelling effect) (Craddock *et al.,* 2014)[3]. Giving the pervasive presence of cytoskeleton components within the cell and the role they play in transducing so many processes, such a mechanism deserve to be investigated in depth, as suggested by the seminal book of Hameroff and Penrose (Hameroff and Penrose, 1996). Namely, both tubulin and actin possess

[2] A case in point is represented by amino acids. We know almost 100 amino acids, but quite surprisingly only 20 are represented in biochemistry. Why the remaining 80 are neglected?

[3] Quantum mechanical phenomenon where a subatomic particle passes through a potential barrier. Quantum tunneling is not predicted by the laws of classical mechanics where surmounting a potential barrier requires enough potential energy. QED can instead provide sound explanation of this phenomenon, as the required energy is precisely furnished by the water organization into discrete CDs. Electrons can get over physical/thermodynamic barrier

a Trp density that, in principle, can support resonance energy transfer. It is worth noting that, while the interaction between a tubulin molecule and its immediately neighbouring one along a protofilament is mainly due to hydrophobic interaction, its interaction with all the remaining tubulin molecules can be expressed by a periodic effective potential, and as such can be ruled by QED formalism (Chou *et al.*, 1994). Nowadays we recognize that electron tunnelling is a key factor in many biochemical reactions (including photosynthesis, cellular respiration and microtubule/actin remodelling) (Gray *et al.,* 2003) as well as enzymatic catalysis while proton tunnelling is a key factor in spontaneous mutation of DNA. In particular, enzymes may use quantum tunnelling to transfer electrons long distances, thus increasing the percentage of the reaction that occurs through hydrogen tunnelling (Nagel *et al*., 2006). Long distance (15–30 Å) electron transfers between redox centers through quantum tunnelling plays important roles in enzymatic activity of photosynthesis and cellular respiration in physiological conditions. Without quantum tunnelling, organisms would not be able to convert energy quickly enough to sustain growth (Lambert *et al.,* 2012). Aggregates of solutes, including those provided by complex herbal mixtures, by fostering a redistribution of water molecules around themselves, could affect the structure of water inside the cell. This effect can be either destructive or, alternatively, constructive, i.e. it may help in promoting/restoring a proper CDs architecture.

5.Quantum and morphogenetic fields

Insights provided by QED may significantly help in understanding the nature of the morphogenetic field, that is to say that "biological field" in which all biological processes do take place. The idea behind the "morphogenetic field" stems from early speculations on the laws of form, developed in the seventies by some exponents of the Royal Society (Thompson, 1942) convinced that mathematical description of living shape could help in identifying the generative agents of such forms (Løvtrup *et al.,* 1988). At the beginning of the 20th century, the belief emerged that these agents could be organized within a "field of forces", the morphogenetic field (MF). The concept of the MF emphasizes that biochemical processes occurring in that field are modulated, constrained and eventually amplified or nullified by those forces and physical constraints that are in that very field. Indeed, field's boundaries are just those defined by the range of (biophysical) interacting forces acting upon it. The MF describes an anisotropic, asymmetric space, where topological relationship, coupled with forces distribution (including mechanical as well as electromagnetical), contributes in driving cellular processes. The "sum total of local and long-range patterning signals that impinge upon cells and bear instructive information that orchestrates cell behavior into the maintenance and formation of complex 3-dimensional structures" (Levin, 2012).

Accordingly, MF became a heuristic metaphor for grasping the correlation between organizing principles and organized structure within a unified concept, usually by referring to physical (especially electromagnetic) models. However, until recently, scientific community do not go beyond the analogy, thus leaving the exact nature of the fields an open issue. However, since the seminal contribution made in the eighties by Goodwin and Scott-Gilbert, the concept of MF has been rescued from the ambiguity, becoming an adequate basis for a unified theoretical biology (Gilbert and Sarkar, 2000; Goodwin, 1994). Moreover, updates in quantum biology and in QED above mentioned, altogether with the appropriate appreciation of mechanical forces (Bizzarri *et al.,* 2013) and constraints (Montévil *et al*., 2015), help us in formulating a more sophisticated framework within the new perspective advocated by Systems Biology (Bizzarri *et al.,* 2013). Furthermore, an impressive body of evidence (reviewed in Tyler, 2014), has provided solid experimental evidence that MF as a concept is now mature to turn in a useful theoretical and methodological tool. This is especially relevant when considering that a number of complex natural mixtures do not seems to recognize a specific target, while inducing dramatic effects, though (Bizzarri *et al.,* 2011a). That is to say, that some complex molecular blends may exert their "pharmacological" effects by targeting some biophysical properties of the field, instead of single, well-recognized molecular targets. A paradigmatic case in point, showing how chemical solutions could be sensitive to even mild physical forces, is provided by studies investigating chirality occurrence in a previous racemic solution. Sodium chlorate (NaCl03) crystals are optically active although the molecules of the compound are not chiral. When left to spontaneously crystallize from an aqueous solution, statistically equal numbers of levo (L) and dextro (D) NaClO3 crystals were found, as predicted by classical chemical theory. When the solution was softly stirred, however, almost all of the NaClO3 crystals (99.7 percent) in a particular sample had the same chirality, either levo or dextro (Kondepudi *et al.*, 1990). This result represents an experimental demonstration of chiral symmetry breaking or total spontaneous resolution on a macroscopic level brought about by autocatalysis and competition between L- and D-crystals under the influence of a mild (turbulence) physical force. Given the relevance that chirality assumes in biological field, it is tempting to speculate to what extent the overall chemical reactivity can be significantly modulate by biophysical – not chemical – factors.

Quantum effects are intrinsic, constitutive components of "field's effects" and they deserve to be carefully investigated to provide a more convincing comprehension of a number of biological phenomena, still poorly understood. Within a biological field, quantum effects alongside with other – often non-conventional, neglected, weak – forces can participate in shaping critical transitions, promoting cooperation between a large number of molecular entities, and leading hence to the emergence of coherent biological processes (Fröhlich, 1983).

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