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Cellular and subcellular coherent dynamics, biological functional properties, and system-environment interaction

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Abstract: In this *view point* paper, we briefly summarize some of the clinical, biochemical and biophysical results obtained in our research on Relaxation Response. We also qualitatively describe the theoretical biophysical model that could link them. Our work points to a *unified view* of the human biological system activity, joining the *dynamics* ruling the interactions and correlations of the microscopic components to the knowledge of their specific individual properties in the effort of going beyond a purely atomistic approach.

Introduction and Presentation of the Viewpoint

The appearance of property concerns the manifestation of an object to another, it is the relationship between the object and the object in relation that manifests itself. In Biology, we are constantly looking at a relationship through the "keyhole" of a particle, a molecule, a cell or a living being. The biological world is a game of perspectives: a molecule, a cell is like a mirror on which the other molecules or cells with which it relates are reflected.

In this sense, it is not choletserol that close the arteries but the relationship between cholesterol, vascular endothelial cells, hormones, cytokines, neurotransmitters, pollution, mental stress, etc… It is not a bacterium that solely and unequivocally determines an infection, but it is the relationship between the bacterium, the host cell, the immune system, the neuro-endocrine network, pollution, mental stress etc., that can describe how some people get sick or not when exposed to the same "pathogenic" micro-organism.

The world, especially the one observed on a biochemical/biological scale, is not continuous but granular, discontinuous and fluctuating.

In each observation of biological realities, we can draw finite information and, therefore, inexhaustible, not cumulative (Rovelli, 2020). The more an experimental observation becomes precise and "detailed", the more, inevitably, it loses the vision of the set of relationships of which that observation is part.

The more observation is dedicated to the whole, the less "exact" or precise it can be in describing the state of the components. By studying a single bolt inside a car engine, we cannot grasp the movement of the car. Its movement is a property emerging from the interaction of the bolt and all the other mechanical components of the car.

Going back to examine the details of a component inserted in a relationship-net after moving to the observation of the system functional activity, we can find that those details changed … We will find the bolt a little more dilated due to the heat generated inside the engine, but it is the same bolt that varies its structure if inserted in a certain relational dynamics.

The fact is that the functional relationship between the components of the system that we want to explore "comes together" with, cannot be separated by the components of the system itself. And the components can oscillate in several states remaining in the same relationship. It is the functional activity of the system that remains stable and efficient, not the details of the state of the individual components. These remarks, although obvious, are often disgregarded in the practice.

There are no "closed" systems in the universe, each element is "open" to the relationship with its surroundings: the necessary delimitation of variables in a scientific laboratory experiment, although necessary for its great practical utility, represents, however, an important epistemological limit. In general physical systems, and especially in biological systems, structure and function cannot be separated (Vitiello, 1998). This is a view point paper and we can only briefly report results of our research, its theoretical framework and the view which emerges from all that. The interested reader may find the experimental and mathematical details in the cited literature.

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Impact of the View Point in Practice: Study Evidences from Ten Years of Research on Relaxation Response in a Medical Scenario

The general views just described above can be applied to the study of the disease of a living being, shifting the focus from wanting to identify solely the "constitutive causes" determining the disease to the network of relationships between the components of the system that brought out the "disease" phenomenon. In this way, "health" and "disease" become two sides of the same coin: the relationship (adaptive or not) of the biological system (human psycho-physiology) with its environment.

For example, from this perspective, the "ischemic heart disease" is a label that has some cognitive/communicative importance but could be misleading from a therapeutic point of view. In fact, a "myocardial infarction" does not exist as an entity. There is a specific person with myocardial infarction. Each myocardial infarction is different, unique because it is the result of a (maladaptive) relationship between the psycho-physiology of the individual and his environment. Behind each myocardial infarction there is a subject with a network of disadvantageous relationships to maintain health in terms of nutrition, physical activity, social environment, pollution, smoking, etc.

Taking up the introductory example, it is unquestionably generally believed that heart attack depends on high cholesterol. But some patients have a heart attack with normal cholesterol values (Tanabe *et al.*, 1980). Or patients who return to the hospital with a recurrence of the infarct despite having very low cholesterol due to the therapy setting (Dal Lin *et al.*, 2017a). The problem probably lies not in the quantitative modification of cholesterol in "high" or "low", "good" or "bad" but in the network of relationships that causes cholesterol, even beyond its absolute plasma level, to take on a behavior rather than another (changing quality, oxidizing and depositing in the vessel wall or not). The point is that psycho-emotional activity is inseparable from the behavior of body cells and molecules. In fact, psychosocial stress "is written" in the body through a dialogue made up of neurotransmitters, hormones and cytokines acting also on cholesterol and vascular balance. Psycho-neuro-endocrine-immunology (Ader, 2011; Bottaccioli and Bottaccioli, 2017) and epigenetics (Bottaccioli, 2014; Dal Lin *et al.*, 2015a, 2015b, 2018c, 2019) are two disciplines able to describe how mental stress represents a cardinal risk factor for cardiovascular diseases (and all chronic inflammatory degenerative diseases) since it acts in an inflammatory-oxidative sense (Dal Lin *et al.*, 2017a, 2017b, 2017c, 2017d; Fioranelli *et al.*, 2017; Piccoli *et al.*, 2017).

If an individual's maladaptive relationship with his environment causes him to become ill, restoring a balance should improve health. It has been widely demonstrated that nutrition and exercise are essential in this regard (Bottaccioli and Bottaccioli, 2017). Less is known from the point of view of psycho-emotional balance. However, if mental stress undermines health, as widely recognized in clinical observations (Ader, 2011; Bottaccioli and Bottaccioli, 2017), relaxation should promote it, as effectively described in scientific terms for several years and as handed down in historical medical literature from ancient times (Dal Lin *et al.*, 2020b). To try to better understand how some molecular axes of this phenomenon could work, we have pursued since ten years researches related to the Relaxation Response in healthy subjects and in patients suffering from myocardial infarction.

During a 20 min session of Relaxation Response-RR-(thus, only changing psychological/brain activity) we observed: the modification of vital signs (lowering of heart rate, body temperature, blood pressure) (Dal Lin *et al.*, 2018b), the reduction of heart ejection fraction with the maintenance of cardiac output and the increase of coronary flow reserve (Dal Lin *et al.*, 2018b); we documented the reduction of several stress hormones, inflammatory cytokines and oxidative stress markers (Dal Lin *et al.*, 2018b, 2020a, 2021b) and a changing of the expression of the NfKB, TLR4, p53 genes (Dal Lin *et al.*, 2018b), through the modification of the levels of some circulating microRNAs (Dal Lin *et al.*, 2018a, 2021b) and the activity of telomerase (Dal Lin *et al.*, 2021b; Pavanello *et al.*, 2019). Moreover, we described a probable attenuation of the cellular senescence and biological ageing process (Dal Lin *et al.*, 2021b; Pavanello *et al.*, 2019).

During the RR the levels of protein carbonyl groups and von Willebrand factor polymers vary (Dal Lin *et al.*, 2021a) as varies the transparency of the plasma of each subject (Dal Lin *et al.*, 2021b). We have also analyzed the blood pH, its electrical conductivity and the emission of ultra-weak photo-induced light emission (in the following refereed to as biophotons) persisting up to a few minutes after a light source has stimulated the studied material (Jursinic, 1986; Niggli, 1993; van Wijk *et al.*, 1993; Brizhik *et al.*, 2001), managing to find, in all the subjects, after the RR, electrical conductivity decrease and linear logarithmic curve of the biophoton energy emission vs biophoton frequency (Dal Lin *et al.*, 2020c) (the linear logarithmic curve signals the relation with coherent dynamics, see next section "The Theoretical Modeling").

The reduced timing in which the observed molecular activity occurs and its persistent recurrence in all the analyzed different subjects suggest that such an activity could not be accounted only by random molecular collisions and diffusion mechanism of biochemical substances. Since molecules present in human plasma often carry electrical dipoles and charges, and therefore generate and are affected by electromagnetic fields, then a sort of wave guided molecular motion could be induced by electric dipole wave field excitations present in the same molecular environment, thus realizing the view of the above described system-environment unavoidable interaction. More on such a theoretical modeling is presented in the following section. The model provides a possible description of the observed changes in the plasma transparency, its electrical conductivity and pH behavior, biophoton emission and the functional dependence of their energy on the frequency. The observed physiological improvements in the subjects undergoing RR experience suggests the basic hypothesis that the mental activity associated with RR is able to determine effects at a biomolecular level (Dal Lin *et al.*, 2021). On such a line of thought, data of statistical relevance have been also collected on the changes in linguistic expressions, such as recurrence and choices of specific words, in subjects after RR sessions. Due to the required brevity of the present "vision" paper, there is no room here to present details of these results, which however have been reported in Dal Lin *et al.* (2020a). See also Piattelli-Palmarini and Vitiello (2015, 2017a, 2017b), Vitiello (2020) for a study of linguistic problems in relation to brain activity.

It has been also very interesting to find that the stimuli used to induce RR (phonemes, musical sounds) have a fractal structure. We analyzed the acoustic spectra of the sounds we used in our works and their fractal features and observed that they are able to directly act on the cardiac cellular biomechanics, modifying the cytoskeleton organization (Dal Lin *et al.*, 2020d). In fact, it's known that mechanical vibrations affect the behaviour of different cell types and the functions of different organs. Pressure waves, including acoustic waves (sounds), could thus affect cytoskeletal molecules changing their spatial organization and mechano-transduction signaling. Cardiac muscle HL1 cells were exposed *in-vitro* to these different sounds and were stained for cytoskeletal markers (phalloidin, beta-actin, alpha-tubulin, alpha-actinin-1), and studied with multifractal analysis (using FracLac for ImageJ). A single cell in culture was live-imaged and its dynamic contractility changes in response to each different sound were analysed (using Musclemotion for ImageJ). We found that different sound stimuli directly influence the contractility and the spatial organization of HL1 cells, resulting in a different localization and fluorescence emission of cytoskeletal proteins. Since the cellular behaviour appears to correlate with the fractal structure of the sound used, we hypothesized that it can influence the cells by virtue of the different sound waves' geometric properties that we have photographed and filmed (Dal Lin *et al.*, 2020d).

In the next section we analyze the physical characteristics of the environment in which biomolecular activity occurs and briefly sketch the main lines of the theoretical modeling.

The Theoretical Modeling

As said in the previous section, the observed molecular and cellular behaviors appear strictly related to the extracellular and intracellular environment. This is characterized by the water molecules which constitute the great majority of the present molecular species (in number more than 80/90%, in weight more than the 70%). The oscillating electrical dipoles of the water molecules play the crucial physical role briefly described in the following. More details can be found in Fröhlich (1968, 1970), Del Giudice *et al.* (1983, 1985, 1986, 1988, 2015), Vitiello (2001), see also Pietruszka (2021a, 2021b), with respect to temperature conditions (homeostasis) which remains in line with the reasoning of this manuscript.

The molecular dipole dynamics is described in quantum field theory (QFT) by field equations invariant under spherical symmetry transformations. Indeed, there is no preferred direction along which dipoles are oriented. External, even weak perturbations, due, e.g., to ions or currents in the dipole environment, may produce the breakdown of the spherical symmetry producing the dipole in-phase oscillations along a preferred direction, namely a non-zero polarization density P(x,t). Although there is no room to go into details, however, we briefly mention that the Goldstone theorem in QFT, largely confirmed by experimental observations, predicts that long-range correlations are dynamically induced among the dipoles as consequence of the spontaneous symmetry breakdown. This is in fact the dynamical origin of the formation of domains of non-zero polarization density P(x,t) (Del Giudice *et al.*, 1983, 1985, 1986, 1988; Del Giudice and Vitiello, 2006; Vitiello, 2001). The domain formation is described in terms of coherent condensation in the system ground state of the boson quanta, called Nambu-Goldstone quanta, or in the present case, dipole-wave-quanta (dwq), associated to the long-range correlations (according to the de Broglie relation). "Coherent condensation" means that the long-range correlations do not interfere among themselves in a destructive way. This means that the system elementary components undergo an in-phase collective motion, so that the knowledge of the "phase" in one space-time point of the system allows the knowledge in other space-time points. Mathematical details can be found in quantum mechanics and quantum field theory texbooks, see, e.g., (Perelomov, 1986; Umezawa and Vitiello, 1986; Blasone *et al.*, 2011).

The space-time evolution of P(x,t) determines many of the observable effects described above (Dal Lin *et al.*, 2018a, 2018b, 2020a, 2020c, 2020d, 2021; 2021a, 2021b; Pavanello *et al.*, 2019). An interesting further example of such effects, is the one presented by McDermott *et al.* (2017), where the discovery is reported, made by the use of chiral sum frequency generation (SFG) spectroscopy, of a robust chiral water superstructure surrounding the DNA helical structure. Water molecules form a coating mold of DNA (and in general of biomolecular chains) whose "electromagnetic image" is produced by the water dipole oscillations (Kurian *et al.*, 2018; Montagnier *et al.*, 2017). At room temperature, the authors observe that "DNA imprints its chirality on the surrounding water molecules, generating a chiral SFG water response. This […] further shows that the chiral structure of biomolecules can be imprinted on the surrounding solvation structure" (McDermott *et al.*, 2017). Remarkably, their laboratory observation shows that "a change in the hydration state can lead to dramatic changes to the DNA structure" (McDermott *et al.*, 2017), which confirms the dynamical interdependence between biomolecules and their environment of water electrical dipoles (Dal Lin *et al.*, 2018a, 2018b, 2020a, 2020c, 2020d, 2021, 2021a, 2021b, Pavanello *et al.*, 2019).

The quantum variables are the vibrational dipole fields of water molecules. Their quantum nature is established as customary (Eisberg and Resnick, 1974) by comparison of the volume $V = \lambda^3$, associated to the de Broglie wavelength $\lambda = h/p$ of the molecular dipole field, with the volume $V' = d^3$, where d is the mean intermolecular separation, $d = (V'/n)^{1/3} = [18/(N \times \rho)]^{1/3}$. Here h is the Planck constant, n the number of molecules in V', 18 is the water molecular weight, N is the Avogadro number, ρ the water density in standard conditions at $T \approx 300$ Kelvin, p denotes the momentum, $p = (3m^2\ k_B\ T)^{1/2}$, with kB the Boltzmann constant and m is twice the electron mass. For $\lambda^3 \geq d^3$ quantum wave effects are expected to be important (Eisberg and Resnick, 1974). By using the values for the various quantities, we find $\lambda^3/d^3 >> 1$, which shows that quantum effects of the dipole field dynamics may indeed appear.

As said, the coherent condensation of dipole wave quanta in the system fundamental state manifests as the polarization density P(x,t) (dipole ordering). The transition from the microscopic to the macroscopic level is thus dynamically obtained through the formation of the coherent state of the dipole wave quanta. P(x,t) acts as the order parameter; i.e., it provides a measure of the microscopic molecular dipole ordering. Space-time evolution in P(x,t) describes thus phase transition processes through differently ordered micro-configurations. It can be shown also that the coherent state has fractal self-similarity properties (Vitiello, 2012, 2009). An isomorphism it thus established between fractal self-similarity and coherent states, so that the linear functional logarithmic dependence of the spectral power density on frequency, which typically characterize fractal self-similarity (the fractal dimension is given by the angular coefficient of the straight line in the log-log plots), signals that a coherent state dynamics underlies the system. This is indeed observed, e.g., as said in the previous section, for the electrical conductivity linear logarithmic curve of the biophoton energy emission *vs.* frequency (Dal Lin *et al.*, 2020c, 2021).

In perspective, the vision emerging from our studies is quite promising, as suggested by its capability to describe, as a further example, the dynamical formation and spatial organization (Dal Lin *et al.*, 2020d) of microtubules, of which cytoskeleton is made, of central importance of course in all the metabolic activity. QFT predicts that the propagation of, e.g., an electric perturbation wave-field within a coherent state occurs by self-focusing of the field (the Anderson-Higgs-Kibble mechanism) (Blasone *et al.*, 2011; Matsumoto *et al.*, 1975), which thus propagates in filamentary fashion opening its way through the ordered medium, provided that its strength is able to break the ordering correlation on its channeling path (not too much high strength which would fully destroy the ordering; on the contrary, very low field strength would not channel through, but in such a case the carried energy will be stored in the coherent correlations summing up till the threshold for the self-focusing is reached) (Del Giudice *et al.*, 1986; Vitiello, 2001). The field is zero outside the channel. A transverse force is then generated by the field gradient perpendicular to the channel path. This force is repulsive or attractive on surrounding molecules according to a frequency resonant pattern (Del Giudice *et al.*, 1986). In this way, a selective polymerization process is generated by which attracted molecular species form coating strata over the channel (within which the field propagates). The computed microtubule internal diameter is $\delta \approx 146$ Å, which fully agrees with the observed 140 Å (14 nm); (the external diameter is 25 nm). For more details see (Del Giudice *et al.*, 1986; Dal Lin *et al.*, 2020a, 2020c, 2020d, 2021; 2021a, 2021b). We quote this result, not elsewhere derived in the literature, since it shows the powerfulness of the proposed "vision", which finds its mathematical formulation in the QFT approach to living matter. In this manuscript, the authors attempt to outline indeed that the collective coherent dynamics of the cellular and subcellular components influence biological functional properties. A final comment might be about the possibility to influence, e.g., for therapeutic tasks, cellular processes by tuning the dipole moments of surrounding water. We thank the anonymous reviewer for posing such a question. In principle, such a tuning of dipole moment collective mode should be possible. At the present stage, however, an adequate knowledge and the corresponding technology is not available. In this connection, it comes to our mind the discussion on acupuncture and meridians within the present theoretical modelling presented in Brizhik *et al.* (2019).

In conclusion, our work points to a unified view of the biological system activity, as a many level functional system (Dal Lin *et al.*, 2021), joining the dynamics ruling the interactions and correlations of the microscopic components to the knowledge of their specific individual properties in the effort of going beyond a purely mechanistic and atomistic approach. The last one is absolutely necessary. However, it is not sufficient for the understanding of biological systems.

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