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PUZZLES OF THE LIVING CELL ON THE NANOMETER SCALE AND COHERENT COLLECTIVE EXCITATIONS IN SOME BIOMEMBRANE STRUCTURES

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In spite of considerable success achieved in molecular biology due to an overwhelming volume of subtle experimental results, the mainstream philosophy in this field is still confronted with difficulties in understanding the integrative features of the living cell, such as the unparalleled emergence of self-organization and the hierarchies of collective order. A critical analysis of the usual method which consists essentially in dividing the biological systems in their isolated components, evidenced its limitations in promoting a physical theory of the cellular dynamics, as well as the necessity of complementary attempts from a more holistic approach. Examination of subcellular structures showed pregnant patterns of order and symmetry in a range of up to tens and hundreds of nanometers, well-beyond the short-range specific interactions, pointing to the requirements of coherence in the dynamical order of the microscopic components and of long-range correlations in the cell. A brief review of the theoretical attempts initiated in this direction by Fröhlich, Preparata, Del Giudice and by others, with a special emphasis on the collective dynamics of water, illustrated the remarkable potential of this unconventional approach. We suggested further possible applications of these concepts in double- and multimembrane organelles based on the involvement of water and biomolecules' collective dynamics and long-range correlations in the form of coherent oscillations and solitons, in phenomena such as non-diffusive wave-form propagation of heath, the structural stabilization of stacked multimembrane structures, the molecular morphogenesis of the nuclear pore, the formation of spiral and point group symmetric structures of polyribosomes on the surface of the rough endoplasmic reticulum membrane, and the control of membrane-associated proteins involved in apoptosis.

1 .Introduction: beyond molecular biology

In the approach of life, molecular biology and its new-born branches such as genomics, proteomics and lipidomics recorded vast achievements by studying more or less separately the structure of a large number of components of biological systems as well as their interactions when spaced out. This mainly analytical strategy lead also to a rather inspirational definition of life by Monod [1], who described biological objects as "strange objects" exhibiting a phenomenology which can be reduced to the following notes: 1) teleonomy – objects endowed with a project represented by their structure and fulfilled by their performances; 2) morphogenesis – objects conditioned by autonomous and spontaneous internal interactions which result in their macroscopic morphology; 3) invariant reproduction – objects able to conservatively reproduce and transmit the information corresponding to their structure; and 4) complexity above a threshold – the amount of information transmitted from a generation to another surpasses by several orders of magnitude the information associated to any other known system.

Whether these characteristics define life completely or not, they are difficult to translate into physical terms. But they clearly highlight the fact that as compared to the physical world, the phenomenon of life stands out by an unparalleled order in its spatial structure and temporal evolution even in its simplest forms. However, different, even radically opposed meanings were found in interpreting the above image. On one side, from a rather orthodox standpoint of molecular

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[1, 2] and cell biology [3], the ultimate goal of the investigation in this field would be to represent the dynamics of the living cell and multicellular organisms as consisting of chains of events determined by one-to-one instructions coming from the genome. Moreover it was said that life emerged exclusively by a succession of casual microevents. On the other side, such opinions were seriously doubted even by a prominent molecular biologist like Jacob [4] and they raise the question if the described approach could fully explain the living organism itself, as the method consists essentially in dividing the biological systems in their isolated components. Because, as remarked by Niels Bohr, the attempt to determine the wave function of a living object would lead immediately to its death [5]. Such and similar considerations by others of the founders of quantum mechanics as well as by subsequent investigators set up the feeling that in the analytical way of molecular biology we miss some other most fundamental aspects of living matter. To understand the cell as a multi-level feedback self-organizing system where the activity of its molecular components is highly cooperative and do not follow in a simple way from structure, one is compelled to judge together with Kastler that "other forces intervene here" [6]. Of course, this does not mean other physical fields than the existing ones, but factors additional to those usually taken into account by molecular biology. The latter did not induce or promote by itself the onset of a theory regarding the dynamics of living systems – or at least of its main physical hypotheses – and, therefore, complementary attempts from a more holistic approach appeared necessary to account for the integrative features of life.

Biological objects distinguish themselves not only by the complexity of the detailed molecular dynamics, but also by the apparent simplicity of their global functions at the macroscopic level. This is due to the hierarchic organization of these systems, where more or less distinct structural domains with collective dynamics can be identified. Briefly, in the living matter evolve "hierarchies of collective order" [7], and this suggests that the emergence of the unusual macroscopic properties of biological objects should be due to coherence in the dynamical order of their microscopic components [6]. Coherence and collective motion might be the key to bridge the gap between non-living and the living (or its prerequisites), and biological objects should perhaps not be looked at so much as "strange" but to a large extent, although they are ubiquitous on Earth, as an unique form of "exotic" physical objects.

There are many puzzling questions in many fields of biology - such as the evolution, the embryogenesis and the morphogenesis at macroscopic level, the neurogenesis, the problem of finality, etc., - which we will not approach here as they refer also to living systems with dimensions beyond the nanometer scale. In the following we shall limit our discourse to a few examples on coherence and collective in various chain-like biomolecules and their aggregates, membrane subcellular structures; and water (as it forms 50-80 % of the cell mass), and we will articulate some suggestions for a number of multimembrane systems. A first issue which is typical to structures measured in nanometers concerns the occurrence of local subcellular order.

2. Quasi-long range order in the cell and the problem of long-range correlations

Cells are objects usually of 5-100 μm diameter, and even a small prokaryotic (e.g. bacterial) cell contains about 4.10^{10} molecules of water and about 5.10^{8} molecules of various chemical constituents; the latter include one or a few DNA double helixes and large numbers of RNA, proteins, lipids, sugars, ions and small molecules. A higher organism (animal or vegetal) prokaryotic cell is about 500 times larger [2, 3, 8].

On a micrometer scale a prokaryotic cell does not show any rigorous spatial order but evidences some topological order between its subcellular structures (nucleus, organelles, plasma membrane) which is invariant under mild strain, as the cell may be considered a special case of soft matter.

However on shorter spatial ranges various order properties emerge inside the cell, and symmetry is among the most striking of them. On a 10-100 nm scale one can observe the aggregation of many different biomacromolecules (globular proteins either cytoplasmic or membrane-bound) or of their supermolecular associations (ribosomes, messenger RNA-bound polyribosomes, microtubules and microfilaments) in well-defined central symmetric arrangements. Also, on the same scale most cell organelles (mitochondria, chloroplasts, endoplasmic reticulum) show parallel double structures stacked in multimembrane arrays [3] with translational quasi-

symmetry. Going deeper at about 5-10 nm scale one finds the allosteric protein oligomers formed of a few polipeptidic protomers assembled in the so-called quaternary structure, such as hemoglobin, exhibiting clear point group symmetries [1-3, 8]. In their turn, these oligomers as well as the monomeric protein molecules exhibit certain quasi-symmetries in their constitutive segments endowed with a secondary structure - the alpha helix and beta sheet structures about 0.5 nm thick with periodicities of 0.54 and 0.66 nm – folded in unique biologically active tertiary structures as compact globules of 2-6 nm diameter. On about the same scale one finds the famous DNA (and RNA) double helix about 2 nm thick with a pitch of 3.4 nm, but which unlike proteins are not subject to rigorous requirements of tertiary and quaternary spatial structures for their biological activity. At the deepest biologically significant level one finds the water molecule about 0.4 nm in diameter, whose physical properties may be approximated to be spherically invariant when free in the bulk but which undergo a spontaneous symmetry breaking to a lower, axial invariance in the cell due to the alignment of its electric dipole by the polar groups on the surfaces of biopolymers and biomembranes.

The occurrence of various rotational, point group, helical and translational symmetries in the 0.5 – 100 nm range outstandingly contrasts to the apparent lack of spatial symmetries on the 5 – 100 □m range of the cellular dimensions. This may suggest that the symmetries existing in the cell are maximal at (comparatively) very short distances but on passing to longer distances they are hidden due to a spontaneous breakdown, similarly to many situations met in physics from elementary particles to condensed matter. Of course, some of the mentioned symmetries of proteins and nucleic acids are explained at least in part by biochemical factors, like the stereochemistry of the peptide bond and of the polynucleotides. Also, the symmetries of allosteric proteins are associated to the advantages of scaling their regulatory function like a c^n cooperative effect (where c is the concentration of the biochemical effector and n is the number of identical subunits in a protein with C_n point symmetry). And generally, the biosynthesis of n units in a subcellular structure is by far more economic when they are identical, which is a strong adaptive advantage [1, 3]. However, the spatial range of the subcellular symmetries may be a well-grounded argument to suggest the existence of certain correlations acting considerably beyond the short-range (< 0.3 – 1 nm) of the Van der Waals and hydrogen bond forces involved in the molecular contact recognition.

On the dynamic side of this picture, in the crowded environment of an eukaryotic cell we find $\sim 10^5$ chemical reactions occurring each second at the right place and time and involving $\sim 10^4$ different types of substrates as well as a roughly equal number of specific types of enzymatic catalysts amounting to a total of $\sim 10^8$ molecular specimens [2,3,8]. Also, a protein as soon as synthesized "chooses" in $\sim 10^{-3} – 10^3$ seconds to fold in one and only one biologically active globular conformation out of about 10^{112} theoretically possible spatial conformations [9]. In fact this astronomical figure is drastically reduced by various mechanisms (hierarchies, systematic local folding patterns, etc.) which restrict the number of possible conformations and lead to the concept of pre-determined folding pathways, but the physical basis of protein folding is not yet fully understood, and direct simulation and protein modeling are not generally feasible. To conclude this short gallery of examples about the complexity of the living systems, we remind that the evolution selected in the human genome just the information needed to specify only $3 – 4.10^4$ proteins, while the number of possible genes ("one gene = one polypeptide chain") amounts to 4^{1500}, which is by far much larger than the total number of different genes existing in the whole biosphere since the apparition of life [2]. From such examples, one is tempted to consider also the possibility that the apparently irregular aspect of the cell on the micrometer scale patched with locally symmetric structures at the level of nanometers – with the ensemble of components interconnected not only in a very complicated spatial design but also in a strict functional order – would be the expression of multiple correlations in the momentum space.

In the conceptual framework of molecular biology all such phenomena of unique complexity are interpreted by a corollary derived from the concept of molecular morphogenesis (feature no. 2 from Monod's definition of biological objects [1]), saying that the cell is nothing more than "a machine" building itself by short-range forces between molecules randomly encountering each other due to Brownian diffusion and recognizing among themselves due to direct contact between spatially- and electrically-fit surfaces. It is quite obvious that for the alternative view centered around coherent collective dynamics, such short-range and random walk recognition, notwithstanding important, hardly could be a complete explanation. Rather, the phenomenology observed in the living cell – including such quasi-long range order properties and local symmetries

as mentioned above – may be expected to result by selective arrangements of molecules at the right places and times due to physical factors ignored in the mainstream of biological research, such as long-range resonant forces and correlations in the coordinate and/or momentum space.

3. Models of collective dynamics in bulk and confined water in relation to an active functional role for the cytoskeleton-associated water

Water, the pervasive environment of biomolecules in the cell, shows itself properties of cooperativity, long-range correlations and collective excitations even as bulk pure H_2O. Strongly directional intermolecular correlations exist in water due to hydrogen bonds and they are responsible for many anomalous properties of this compound as compared to other nonmetal hydrides. Also, H-bonds – which can be described by a three term potential consisting in a Lenard-Jones potential plus a dipole-dipole electrostatic interaction – show a cooperative character as the bonding of two molecules favors the binding of a third one and so on, and this extends correlations to longer distances. Theoretical studies accounting for the density fluctuations in liquid water proposed the existence of high-frequency collective excitations – the so-called fast sound – propagating with a velocity much higher than the ordinary sound [10-12]. These predictions were confirmed by studies using inelastic neutron scattering [13] and synchrotron radiation inelastic X-ray scattering [14], which revealed strong evidence for collective acoustic-like excitations of $\sim 10^{13}$ Hz in liquid water propagating with a speed of 3300 ms^{-1}, a value twice that of ordinary sound. This fast sound involves the whole H_2O molecule and, as for its physical origin, it was suggested to be related to fast librational oscillations [11] or to the interplay between the electrostatic and the Lenard-Jones terms in the intermolecular potential [12]. One remarks tangentially that the existence of a second sound may put forward an analogy to superfluid helium; note also that in the latter and in other strongly correlated systems like superconductors, heat does not propagate in a diffusive way but in a wave form [15, 16].

On the other hand water in the cell, especially in the internally more structured eukaryotic cells, is confined on the nanometer scale and layers of both strongly and weakly associated (bound and vicinal) water molecules surround biomolecules, playing a critical role in structural and dynamical processes. In such small cavities water manifests specific collective dynamics. It has been shown by far infrared dielectric measurements that water confined in inverse micelles exhibits collective surface modes or shape oscillations originating in the vibrational degrees of freedom [17]. Pronounced resonances absent in bulk water were found to depend sensitively on the size of free water pool at the center of the micelle, and when this parameter increased from 1 to 9 nm, the resonant frequencies decreased asymptotically from 7 to 2.10^{11} Hz.

The two above features of liquid water point on two more physical facts: the coupling of the collective modes in water to electromagnetic radiation, and the existence of two phases of water in various systems. Both appear to be interconnected in the theory of Preparata which employs the ideas of quantum electrodynamics (QED) to account for the properties of condensed matter in general [18], and which opens new perspectives with respect to water in biological systems. The idea of two types of water in the liquid state in which clusters of "ice-like" matter are dissolved in a fluid that behaves normally was proposed first by Röntgen [19] to explain the large number of its puzzling anomalies (density, compressibility, viscosity, etc. and their dependence on temperature and pressure) which are essential to the existence of life. This intuitive model has been mistrusted initially because it does not support apparently the quantum mechanical identity of water molecules [20], but it was revived by the consideration of the highly directional electrostatic forces of hydrogen bonds, assuming that each pair of molecules has a probability p_{HB} to be connected by an H-bond, whose lifetime is τ_{HB}. As a result a "flickering" low-density gel-like structure of H-bonded molecules coexists with the unbounded molecules, that in certain conditions may nest in the cages of structure and in its interstices [21 - 23]. However this generally accepted description is merely phenomenological, as evidenced by a theoretical analysis. In subsequent Monte Carlo simulations of the dynamics of water effective molecular pair potentials have been introduced, but such a description "will never be completely realistic, because of the existence of many-body forces and the complexity of water" [22]. Another question is how the water molecule can give rise to the highly directional H-bonds, as the electron cloud of the H_2O ground state has a smooth, potato-like structure [24]. Then, how is it possible that an electrostatic interaction emerges in a highly mobile

environment? In order to find the theoretical foundation of the current phenomenological model and thus to settle better its physical grounds, the QED approach assumes that the molecules in the condensed phase are in a ground state that differs from the ground state of the isolated molecule. In this new ground state their electrons' cloud would then be so distorted as to produce the observed binding, and to increase the values of molecular parameters such as the effective radius and the dipole moment, as known from experiment. Accordingly, liquid water is looked less than as a "molten ice" but more as a "condensed vapor". The theory considers the evolution of an assembly of initially independent molecules that by the QED instability of their electrons' ground states are driven toward a coherent dynamical state, where large intermolecular attractions emerge, capable of accounting for the observed thermodynamics of water.

To understand the emergence of coherence in this multi-molecular system, one has to remind that in the QED picture [25] both matter and radiation are regarded as "quantum fields", namely as objects fluctuating in space and time and showing the wave-particle complementarity. In a two-body interaction between atoms or molecules mediated by electromagnetic (EM) field, only static fields are important. But in the general case of N-body interactions, the time-dependent radiative part of the EM field is no longer negligible and, as a result, the small individual fluctuations of many individual components may superpose coherently (in phase). Considering an ensemble of N molecules mutually coupled through an EM field, the fluctuations of the EM field whose frequency matches the energy difference between two energy levels of the molecules can couple to corresponding fluctuations of the matter field. Beyond a threshold of molecular density, the coupled fluctuations of both the EM and matter fields will be damped no longer, and the two fields will share a common oscillation. Thus a coherent oscillation of matter and EM fields arises, described by a unique wave function in which it is impossible to trace the individual components.

In the case of water, the theory [18] shows that liquid water consists of two interspersed phases, a coherent and an incoherent one. The incoherent phase comprises water molecules in the molecular ground state (as observed in the gas phase) packed in a highly dense state in the interstices around large clusters (of the size of 75 nm) in which the water molecules perform hindered rotations and interact coherently with a large electromagnetic field. Thus the coherent phase is built up by the collection of such "coherent domains" that at a given temperature have survived the disordering attacks of thermal fluctuations. In the coherent phase, due to the oscillations of the water molecules between the ground state and an excited state at 12.06 eV – whose relative probabilities are about 0.87 and 0.13 – the volume occupied by each molecule is definitely larger than the volume occupied by the molecules of the incoherent phase, thus rendering the coherent phase density (0.92 g cm^{-3}) much closer to the density of ice. The energy gap that protects the molecules from "evaporating" from the coherent phase into the incoherent, "gaseous" one, allows to assume a roton-like excitation phase of "liquid" water. (Note that although liquid water is not superfluid, an analogy to liquid ^{4}He is possible.) Also, a difference in the electrostatic energy between coherent and incoherent phase is expected and evaluated to a small negative difference $\delta_{es} \sim -0.022$ eV.

The model predicts the specific heat and compressibility of supercooled water at T = 230 K, the specific heat of liquid water, the boiling temperature and the latent heat of vaporization in good agreement with experiment, and allows a qualitative understanding of the density anomaly of water as due to the superposition with temperature dependent weights of two temperature dependent densities, as well as of the critical volume, as the largest molar volume above which no QED coherent process can spontaneously take place.

Thus in a natural way the clusters of water molecules from the phenomenological model of "flickering" H-bonded network in liquid water appear to be the coherence domains, where the molecules evolve in phase with a coherent EM field. Moreover, in the biological perspective the QED theory of water seems to reveal far-reaching consequences, as implicitly remarked by Preparata when saying that "it is not impossible to imagine that such ordered structure may retain and release electromagnetic information that it has aquired in some way or other" [18]: supposedly, this may be also a prerequisite for the emergence of coherent features in the dynamical order of the living cell.

Indeed, from the first step inside the cell one is compelled to contemplate the water dipoles aligned in their interaction with the polar groups on the surface of biopolymers and biomembranes. As a result, the rotational SU(2) or spherically invariant O(3) symmetry of the free water dipole undergoes a spontaneous breakdown to the U(1) subgroup of rotations around a given direction, leading to the emergence of collective Goldstone modes and to the appearance of permanent electric

polarization around the inhomogeneities with electrical activity in the cell, as well as to a self-focusing mechanism of propagation for the electromagnetic field inside the biological systems [26, 27]. Del Giudice and colleagues point further to the fact that coherence domains of water shaped as filaments of calculated 29.2 nm diameter will form in spatial regions contiguous to the ends or surfaces of biomolecular chains, and they will entrap the electromagnetic field of a Goldstone dipole-wave quantum of finite mass of 13.6 eV [27]. Around such filamentous domains of coherent water, localized most likely on the chain-like proteins of *the cytoskeleton*, particularly on the actin filaments of the latter of 8 nm diameter (Fig. 1), the EM fields will produce high electric field gradients which in their turn would develop frequency dependent, non-linear forces of the form:

$$F \sim \{ (\omega_o^2 - \omega^2) / [(\omega_o^2 - \omega^2)^2 + \Gamma^2 \} \nabla E^2 \quad (1)$$

where ω_o is the oscillation frequency of a dipolar biomolecule from the cytoplasm, ω is the frequency of the coherent oscillations inside the water domain, Γ is the damping of the oscillations with frequency ω_o, and E is the electric field intensity in the domain's region. The form of the above force ("dielectrophoretic force") is given for a molecule located just on the boundary of the water filament and the force may become very important and long-range acting when there is a strong field gradient and when $\omega = \omega_o$, i.e. it has a resonant character. Moreover, small changes of ω and/or ω_o could change an attractive force into a repulsive one. Therefore, specific molecules can be brought in contact in a non-diffusive way to react at a given time on the surface of water coherence domains around the cytoskeleton while the reaction products may be repelled subsequently. Such long-range correlations may offer an explanation for the large number of well-coordinated biochemical reactions occurring in the cell [28].

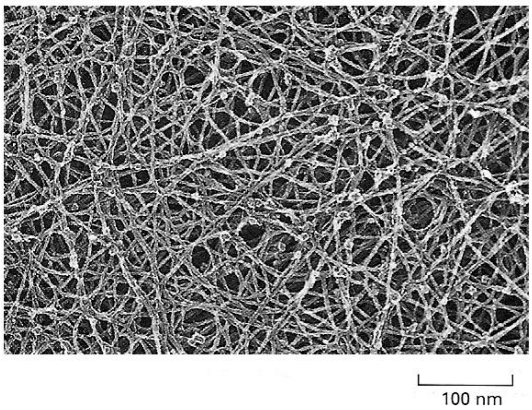

Fig. 1. A network of actin of the cytoskeleton underlying the plasma membrane of an animal cell. Deep-etch electron micrograph by John Heuser; modified after [3].

In fact a large number of the biochemical reactions in the cell are spatially associated to the actin filaments of the cytoskeletal network [29]. Note that the highly disordered structure of the cytoskeletal actin filaments shown in Fig. 1 provide an "equal opportunity" condition for very different biomolecules involved in a large diversity of chemical reactions; thus it granted the random access to the closest biopolymer chain when "called" by the resonant forces on the surfaces of coherent domains of water. And also, a high disorder in the coordinate space may be associated to long-range correlations in the momentum space. We should mention also, that dielectric relaxation frequency studies on the hydration of actin filaments (F-actin) [30] provided recently direct evidence of very unusual, "dual" properties of water, absent in the case of myoglobin (i.e., the representative example of globular proteins). Thus, apart from the water molecules with lowered rotational mobility that make up a typical hydration shell, there are other water molecules around the F-actin which have a much higher mobility than that of bulk water. In addition, the long-range forces at the cellular level have been evidenced to act between the red blood cells membranes at distances of up

to 4-5 μm [31] as well as between various types of cells and small particles of insulating non-biological materials [32].

The above theories emphasize at the microscopic level a more general concept of resonant and cooperative polarization excitations in systems of oscillating electric dipoles developed by Fröhlich. His rate equations showed that coherent oscillations occur in a dipole set with macroscopic occupation of specific modes provided that metabolic energy is supplied at a rate above a certain threshold, and they can be associated both with biopolymers and with membranes [33]. Later he suggested also another type of collective excitation, by which large electric fields arising on metabolic energy release induce biomolecules (e.g. globular proteins) into highly excited metastable states with much larger dipole moments than near the fundamental state [34]. Such models succeeded in understanding some overall biological attributes – self-preservation by metabolism (or far-from-thermal-equilibrium relative stability), a characteristic type of order, cell division, contact inhibition – and opened the way for other specific applications. Note that while Fröhlich stressed that biological order "*expressed itself* in long-range correlations", he very carefully pointed out that this phenomenon only "*has considerable similarity* with the low-temperature condensation of a Bose gas" [33]. In fact the low-temperature condition is not met in biological systems. But it has been shown that the non-thermal excitations proposed by Fröhlich can still exist in a regime in which the Bose condensation fails [35, 36]. The requirement of a metabolic (chemical) energy supply at a rate above a threshold is imposed also in the microscopic approach of Del Giudice [27, 28], as the above collective phenomena are dissipative and they create order while they release all the incoming energy. This aspect is strongly supported by the fact that many proteins in the cellular structures, including the cytoskeleton, are endowed with ATP-ase activity and thus with a diversity of bioenergetic functions [3, 8]. In the following, we advance some suggestions for a role of long-range correlations in a few membrane phenomena occurring in the cell.

4. Some suggestions for the role of water collective dynamics in multimembrane bioenergetic systems

Water in the multimembrane organelles of the cell

The collective excitations of water raise questions about their possible implications in the water immersing quasi-parallel membrane stacked structures in the eukaryotic cell. Vital cellular organelles are formed by such oriented stacks of flattened vesicles or cisternae (Fig. 2), having a tight luminal space between apposite membranes (e.g. ~10 nm in mitochondria, 10-15 nm in chloroplasts, 20-30 nm in rough endoplasmic reticulum), with translational quasi-periodicity (of ~15-20, ~50, and 30-60 nm in the same structures, respectively). Also the photoreceptor cells in retina are stacked structures with a periodicity of 16 nm. Thus such structures confine water in narrow spaces with size of the same order as the inverse micelles leading to the mentioned collective dynamics of water domains' shape [17]. Therefore, resonant oscillations of vibrational origin with frequencies in the $\sim 10^{11}$ Hz range might exist in the multimembrane organelles. Moreover if the second sound demonstrated in bulk water [10-14] exists also in the cell water, we can hypothesize that oscillatory propagation of thermal disturbances may occur through these periodic structures, as suggested earlier to take place along filamentous biopolymers undergoing coherent electric vibrations [28]. Both types of collective excitations may be highly advantageous in these multimembrane systems as they are involved in intense bioenergetic conversion processes.

We remark that the assumption of some collective phenomena related to superfluidity occurring in the cell (and which would involve ultimately coherent wavefunctions), should not be completely ruled out only on the ground of the high temperature of living organisms (~300 K). These pronouncedly anisotropic piles of water confined in thin layers in the stacked membrane structures may be regarded as composed of essentially bidimensional systems, and it has been shown that a bidimensional atomic gas may undergo a transition into a superfluid phase with quasi-long-range order at a temperature above the threshold where a Bose-Einstein condensate forms [38-40].

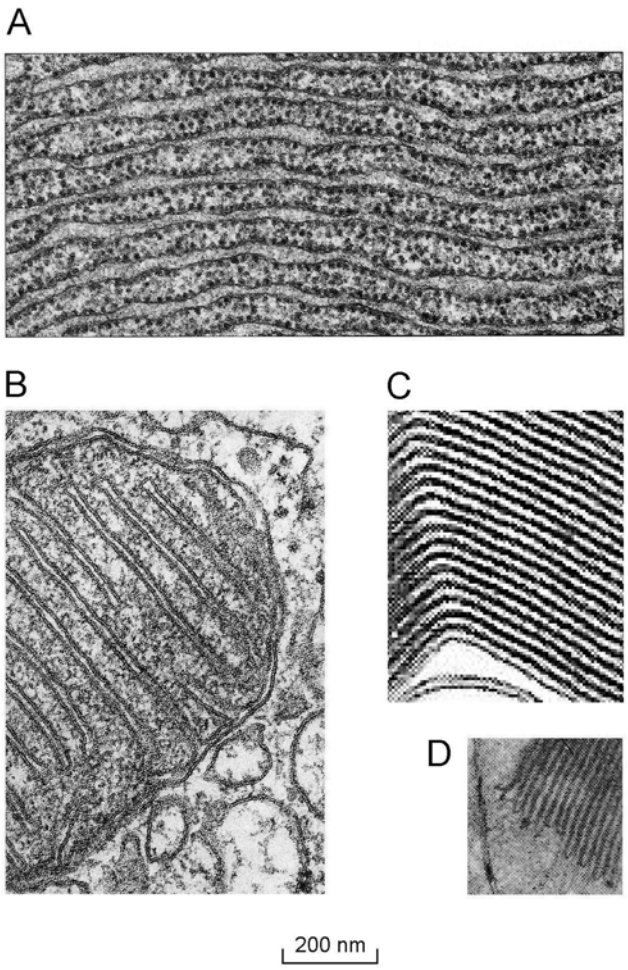

Fig. 2. Quasi-parallel multimembrane structures with specialized bioenergetic and biosynthetic functions in eukaryotic (animal and vegetal) cells. (A) Rough endoplasmic reticulum in a perpendicular section, showing ribosomes on its cytosolic surface. Electron micrograph by L. Orci. (B) Mitochondrion, showing the inner membrane folded in cristae. Electron micrograph by Daniel S. Friend. (C) Fragment of a rod photoreceptor of the retina showing the discs of the photoreceptive membrane. Electron micrograph from [37]. (D) Fragment of a chloroplast showing a granum with the stacked thylakoid membrane. Electron midrograph by K. Plaskitt. The images were modified after [3].

Note finally that long-range Fröhlich-Preparata-Del Giudice correlations and resonant forces may offer a credible candidate in order to explain the stability of the quasi-parallel multimembrane structures. The faces of the apposite membranes are similarly charged and obviously, the electrostatic repulsions must be compensated some way by an opposite force. This may be an attractive or an elastic force. The second alternative supposes that the parallel stacked morphology should be merely the result of a high-curvature bending of the membranes at the margins due to a local heterogeneity in the fluid mosaic, e.g. a locally modified biochemical composition, just as a thin copper wire bends at the point where a little drop of liquid tin is placed on it. But while this assumption would offer a possible explanation for an array of planar parallel membranes bent only at their margins, it can not explain the complex shape of the membranes which in the extended zones follow each other's small meanderings even with curvature sign changes (Fig. 2).

Thus while some role for bending forces is not impossible, the assumption of an attractive force between membranes appears to give a more simple and natural account for the stable stacked morphology. We observe that the range of the intermembrane distances of tens of nanometers is one-

two orders of magnitude higher than the action range of Van der Waals forces or of the hydration and double-layer potentials, while it is well within the reach of long-range resonant forces of the form given by eq. (1). In fact the Gouy-Chapman-Debye-Huckel and related theories predict very small forces at 10-20 nm between two lipid bilayer membranes which, in addition, are repulsive forces [41]. Then it is straightforward to suppose that attractive forces may originate mostly from coherence domains of water located between membranes and may thus contribute substantially to the morphological stabilization of multimembrane cell organelles.

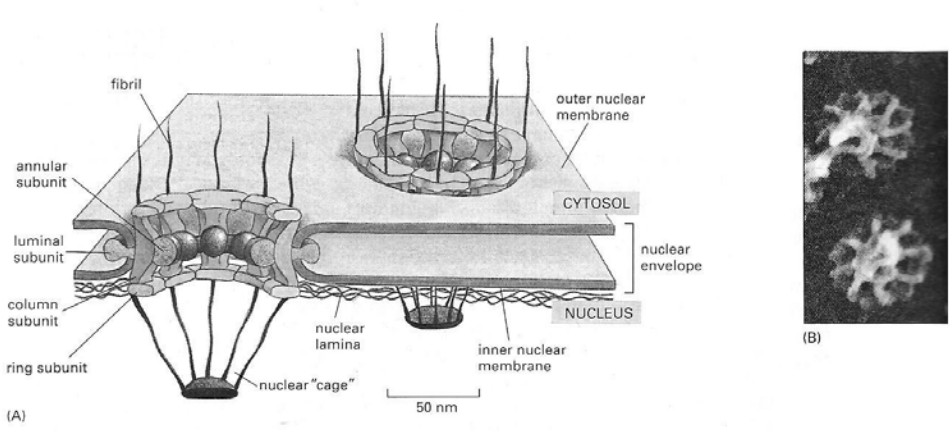

Fig. 3. The nuclear pore complex about 100 nm in diameter in the nuclear envelope's double membrane: a structural model (A) based on computer reconstruction of electron micrographs as illustrated in (B) [43]. Modified from [3].

Molecular morphogenesis of central symmetric structures in membranes and long-range forces

As we noticed earlier [42], an intriguing association seems to occur between multimembrane systems and well-defined central symmetric arrangements up to ~100 nm in diameter of membrane-bound globular particles (integral proteins and ribosomes). Examples may include the supermolecular morphology and genesis of nuclear envelope pores, of cellular gap junctions, of mitochondria multienzyme complexes, and of chloroplasts and chromatophores light reaction centers; the multi-stage "signal-sequence" polypeptide translocation from ribosomes through the rough endoplasmic reticulum; and the apoptosis cascade taking place in most of the above membranes. The functions of such systems are connected to metabolic energy conversion, and ATPases and similar bioenergetic enzymes, as well as receptor and translocator proteins of their membranes may represent electric activity centers, leading to the spontaneous self-organization of macromolecules in quasi-regular patterns. All of them show structures with central symmetries formed of up to ~100 or more distinct biopolymers; for instance, the nuclear envelope pores with C_8 symmetry are formed by 56 protein units disposed in a perfectly ordered molecular architecture (Fig. 3). Looking at such illustrations of complex local order, one may doubt whether their molecular morphogenesis could be merely the result of Brownian diffusion coupled to sequential interactions by short-range specific recognition. Rather, such order may be expected to emerge or to be assisted by a selective arrangement at the right places and times due to long-range resonant forces of the form of eq. (1) involving coherent domains of water, possibly characterized by polarization modes similar to a circular membrane oscillations.

Polyribosomes on the rough endoplasmic reticulum membrane and membrane proteins involved in apoptosis: long-range forces and solitons

The polypeptide translocation from ribosomes through the endoplasmic reticulum membrane as described by the signal peptide hypothesis is a complex multisequential process still

not completely understood ("correct in the outline but requiring additional components" [3]). One striking aspect is that a polyribosome (usually ~7-20 ribosomes bound to a mRNA macromolecule) forms a random coil when free in cytoplasm and displays a C_7 to C_9 or spiral symmetry (known as a "rosette" in cellular biology) when attached to the receptor proteins of the membrane (Fig. 4). Interesting to note, the long polyribosome from Fig. 4B do not form a C_{22} regulated polygon, but a spiral with 9 ribosomes on the first loop; thus the $2\pi/9 - 2\pi/7$ angles appear to be privileged. The spirals show also the interesting property that on rotation by a sufficient angle one finds m ribosomes on the first loop and approximately $2m$ on the same angle of the second loop. This observation suggests that the ribosomes follow the maxima or the knots of two stationary waves of the form $\sin m\phi$ and its harmonic $\sin 2m\phi$. Therefore, it sustains the conjecture that the globular particles (ribosomes or their underlying membrane receptor proteins) would be disposed in spirals or point symmetric arrangements under the action of a circularly polarized mode of the electric field given by a sinusoidal angular dependence with $m = 9 - 7$ and by Bessel polynomials radial functions, and associated to coherence domains of water corresponding to certain selected oscillation modes.

Alternatively, we may assume the statement of Del Giudice [28] that as far as quasi-unidimensional structures are concerned, another non-linear, collective, but energy-conservative excitation – the Davydov soliton [44] – plays also a role. Thus one may suggest that a soliton is triggered in the mRNA chain by a ATPase-driven metabolic energy burst on binding of the 5' mRNA end to a first endoplasmic reticulum receptor protein. Then, by propagating along the mRNA chain, the latter bends under a definite angle at each ribosome, due to the coupling between the vibrational displacement of monomers and the chain deformation. At the same time, the two mechanisms – the dissipative coherent oscillations and the conservative soliton – may co-operate. And the role of the soliton concerted to that of the coherent oscillation modes, together with the coupling with radiation of local electric activity centres, is claimed essential in the feed-back control of such membrane- and combined membrane-biopolymer processes. In fact it was demonstrated that in general, once a critical level of pumping of metabolic energy is achieved and the emergence of a self-organized dissipative structure ressembling a nonequilibrium Bose-Einstein condensation (the Frohlich condensation) takes place, signals propagate into the system in the form of Davydov-like solitons with enormously enhanced lifetime and for very long range [45]. Note in this context the remarkable medium offered for signal propagation by the cytoskeleton network shown in Fig. 1.

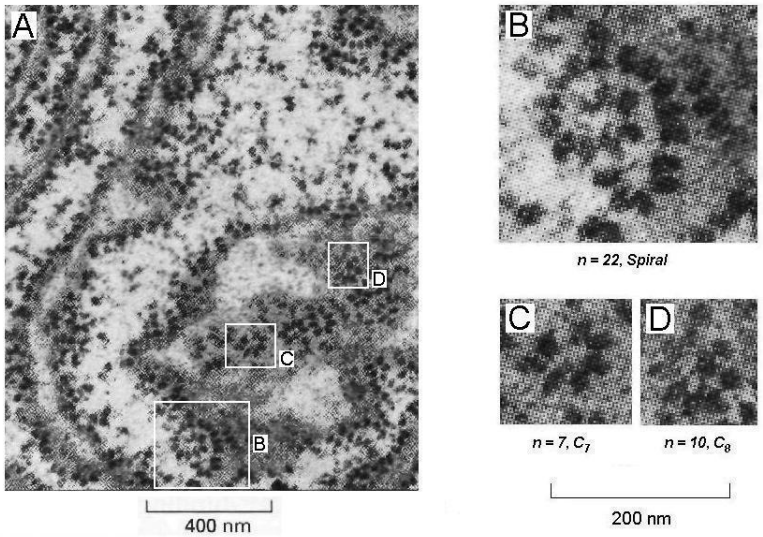

Fig. 4. Polyribosomes forming point symmetry and spiral patterns on the surface of the rough endolasmic reticulum in a section roughly parallel to the membrane. The mRNA biopolymer connecting the ribosomes is not visualized. Electron micrograph by George Palade. Modified from [3].

Finally, we suggest that solitons and long-range resonant forces may be involved as well in apoptosis, *i.e.* programmed cell death [3, 46]. Here a number of proteins (*Bcl-2* and *Bax* subfamilies)

are membrane-localized, while the *Bim* and *Bmf* proteins are associated with the filamentous intracellular network. With the synchronous oscillations of water in microtubules as a cell clock [47], it may happen that cytoskeleton-bound proteins initiate the apoptosis following a soliton signal, and subsequently long-range forces activate specifically membrane proteins which complete the apoptosis cascade leading to the cell death.

5. Conclusions

A critical analysis of the conceptual situation in molecular biology unveils many limitations of the current mainstream analytical-descriptive approach in promoting a physical theory of the cellular dynamics able to account for the unparalleled emergence of self-organization and hierarchies of collective order which characterize the living state. Pregnant patterns of order and symmetry in subcellular structures spanning a range of up to tens and hundreds of nanometers, well-beyond the specific interactions below one nanometer, point to the necessity of long-range correlations in the cell. A brief review of the theoretical attempts initiated in this direction by Frohlich, Preparata, Del Giudice and their groups as well as by other investigators, with a special emphasis on the collective dynamics of water, evidences the spectacular possibilities opened from this perspective in understanding a large diversity of integrative phenomena in the cell.

Our further suggestions for the involvement of water collective dynamics in long-range correlations inside the living cell included possible roles in ultrastructure-dependent eigenfrequencies inside multimembrane organelles, in non-diffusive wave-form propagation of heath and in the structural stabilization of these wide-spread subcellular assemblies, as well as in the molecular morphogenesis of membrane-bound central symmetric protein arrangements such as the nuclear pore. Also, long-range resonant forces associated to water coherent oscillations and soliton propagation in mRNA and in cytoskeleton proteins were proposed to underlie the formation of spiral and point group symmetric structures of polyribosomes on the surface of the rough endoplasmic reticulum membrane and the control of membrane-associated proteins involved in apoptosis.

Although the above suggestions are predominantly speculative, our heuristic approach showed that different mechanisms of collective excitations evidence a still unexploited potential for significant insight of the membrane- and membrane-biopolymer chain-associated cellular processes. They foreshadow a simple general principle often neglected in molecular biology, but which apparently weigh heavy in the cell on a nanometer scale, namely, that not only the parts shape the whole, but also that the whole acts significantly upon its components. Moreover, such exercises of imagination may be multiplicated to a great diversity of (sub)cellular structures and processes may put forward further studies for theoretical elaboration and experimental verification.

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