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Contactless Interactions in the Cell by Exchange of Virtual Water Coherence Domains: A Hypothesis

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Abstract

Although the molecular biology of the cell recorded impressive success, a complementarily novel perspective still may come out. Noncontact interactions, different to the hand-glove contact forces between spatially fitting molecules, were evidenced between proteins in cytosol. By analogy to the atomic nucleus, where the exchange of virtual pions (pi mesons) explains the force between nucleons, we postulate an attractive force derived from a Yukawa potential; supposedly, the later is generated by exchange of virtual water coherence domains (CDs) between two proteins. The CDs are hypothetical spinless (S = 0) quasiparticles of ~13.6 eV effective mass (excitation energy), which can be roughly visualized as clusters of coherently oscillating water electric dipoles. With the CD exchange new features of the cell are explained. The CD effective mass defines an action range of 14.5 nm, which fits well to the mean distance of ~7 nm between proteins in cytosol (200 - 300 g/L density). Assuming a coupling constant of 3.5 eV·nm, the Yukawa potential prevails on the thermal agitation up to ~10.1 nm. Accordingly, the CD exchange shows saturation, being limited to first neighbor proteins. In cytosol, this may explain the liquid state of macromolecular condensates, the small variation of protein density in different cells, and the independence of protein-protein attractions on amino acid sequence in condensates. The additional cohesion energy due to the CD exchange stabilizes the cell only a little more than the classical hand-glove interactions. A simple model based on the Yukawa potential was proposed, showing that at high enough protein concentration, the total mean energy (in modulus) in condensate suspension may exceed that of an equivalent homogenous protein solution. Thus, for sufficiently short interprotein distances (5.6 - 7 nm inside condensates and >7 nm outside) and with a few hundred condensates per cell, the condensates form spontaneously and are stable, according to potential energy minimization. Finally, the CD exchange frequency is

consistent with intracellular communication channels of high speed and capacity. In brief, the postulated analogy of water CD exchange in cytosol to the atomic nucleus may open way to a better insight of certain cellular phenomena.

Keywords

Yukawa Potential, Exchange Force, Coherence Domains, Contactless Interactions, Cytosol, Living Cell, Meson Theory

1. Introduction

The molecular biology of the cell [1] recorded impressive success assuming specific interactions by hand-glove contact (short-range) forces between spatially fitting molecules. Still, a complementary perspective may come out, with a hypothetical new type of interaction. What if the classical and the new forces could account only together for the living state of matter? However, within the frame of Bohr's complementarity principle [2], the new interaction should have opposed properties with respect to the hand-glove mechanism—namely it should be long-range and contactless. Such interactions were shown to exist in cells and in model systems. Interfacial properties of molecular systems have been explained by noncontact potentials [3]-[5]. Solvent-mediated communication between non-contacting DNA and artificial polynucleotides has been evidenced in vitro [6]. Protein-protein potentials independent on the protein sequence have been demonstrated in concentrated solutions of lysozyme and other proteins [5] [7]. This behavior was pregnant especially in the so-called macromolecular condensates from cytoplasm ([8]-[10]; see [11] for a brief overview), where molecular crowding drives liquid-liquid phase separation and involves contactless interactions [11] [12]. Also, previous biophysical models of cytoplasm assume long-range interactions in water between cellular interfaces (e.g., [13]-[15]). Remarkably, the molecular dynamics in condensates are relatively independent on spatial structure of proteins and thus does not imply directly hand-glove interactions.

A note about nomenclature: we used above the more popular term "cytoplasm" which includes also, together with the cytosol, the membrane-covered cellular organelles. Without the later structures, one speaks about cytoplasmic ground substance [16], cytomatrix or cytoplasmic matrix [17], or cytosol [18]. The "cytosol" term is preferred throughout this paper, although the alternative names are equally valuable.

Because proteins are macro- and mesoscopic objects, the physical meaning of the above phenomena in biological systems can be understood mainly in terms of (semi)classical physics. But is the concept of hand-glove contact-specific interactions enough for understanding the whole molecular dynamics in the cell? An alternative approach of this question could explore the use of the concepts and

methods of quantum mechanics. Even Schrödinger, many years ago (1944-1969) in his famous book *What is Life*? [19], asked whether life could be a quantum phenomenon or at least undergo quantum influences. In fact, quantum biology [20] [21] goes beyond "trivial" calculations of molecular structure, reactivity and dynamics; perhaps, it may account also for the wholeness and oneness of the living cell, by assuming non-local quantum correlations among molecules [22]. Most important, there is a large variety of biological phenomena that make the object of quantum biology and have already found direct and indirect experimental evidence. They include photosynthesis in plants, algae and bacteria, magnetoreception in birds, olfaction, vision, long-range electron transfer and enzyme catalysis. To mention a more general attempt, the concept of "quantum metabolism" connects Planck's quantization rule with the metabolic energy per biological cycle [23].

Some of the models referred above [3]-[5] make use—without any fundamental physical assumption on particular systems, either biological or not—of so-called Yukawa potentials. The latter describes protein-protein potentials independent on the protein sequence, which have been demonstrated in concentrated solutions of lysozyme and other proteins [5] [7]. Finally, the latter looks like a screened electrostatic potential, irrespective of system. At the same time, the Yukawa potential proved itself to be of high physical significance in the quantum theory of strong nuclear force, which keeps together nucleons in the atomic nucleus. The theory was developed by Hideki Yukawa in 1935 [24] and explains the nuclear force by exchange of virtual bosons (spinless particles) called mesons or pions. The exchange force can exist only in condensed quantum systems like the atomic nucleus. Could a similar quantum phenomenon exist also in highly concentrated aqueous protein solutions? And, by extension, in the cytosol of the living cell?

In this conceptual paper we consider an affirmative answer to these questions. Our option is based on an analogy that we could evidence between the noncontact protein-protein interactions and the nucleon-nucleon exchange force. The model proposed here makes use of boson quasiparticles called coherence domains or CDs, a hypothesis proposed by Giuliano Preparata (1995) [25] and Emilio Del Giudice *et al.* (1982-2013) [26]-[31]. They are postulated to form spontaneously in water, especially in aqueous liquid hyperconcentrated protein solutions. With the further assumption of CD exchange between proteins, we examine in the following the plausible physical characteristics of a new type of contactless interaction. Possible biological consequences are discussed and simple theoretical predictions will be compared with cell biology data. Discussions of this approach may reveal new correlations of interest in the frame of biological physics and contribute to an emerging picture of the living cell.

2. Coherence Domains in Water

The concept of coherence domains (CDs) in water was postulated in the frame of

quantum electrodynamics (QED) [25]-[31] on the background of the Herbert Fröhlich's theory [32]-[34] of long-range coherent dynamics of dipolar molecules in non-equilibrium biological systems at room-temperature. Emergence of self-organization and hierarchies of collective order may occur involving Bose-Einstein condensation [35] [36] of quasiparticles. Non-linear interaction between longitudinal acoustic phonon vibrations and electric polarization fields, when pumped by metabolic (chemical) energy above a critical threshold, results in a single coherent electric oscillation in the THz (10^{11} - 10^{12} Hz) band, which generates intense long range dipolar electric fields and interactions. The system reaches a relative minimum of energy, a metastable state considered a general characteristic of living matter. Experimental proofs of Fröhlich's theory have been claimed in the last years [37] [38]. Some basic ideas in the present article, such as those about e.g. the living state of matter, were inspired from Fröhlich's picture.

The Preparata-Del Giudice QED theoretical model [25]-[31] describes the CDs to be quasiparticles created as collective self-organized dynamic structures of water dipoles and performing coherent oscillations. They are created from the "vacuum" of surrounding incoherent ("free" or "disordered") water; the later, however, contains to a large extent dynamic ice-like structures and clusters [39], transient on a nano-to-femtosecond scale [40] [41]. As compared to pions, the CDs have low effective mass (excitation energy) and thus relatively long action range. They are Goldstone (pseudo)scalar ($S = 0$ and negative parity) bosons generated by the restructuration or symmetry breaking (phase transition) of the "vacuum" [42]. Different types of CDs were predicted in very diluted polar liquids [43]; but here we deal with highly concentrated solutions. The above mechanism is postulated to occur also in the cytosol between the "hydration shells" of two interacting macromolecules. The present author and colleagues used this and related models [44]-[48]; other authors developed models based on QED and quantum coherence of water [49]-[52]. It was shown that ordered electromagnetic field coherent states could exist in microscopic, mesoscopic and macroscopic systems [53]. Therefore, the above restriction implied from the macroscopic nature of proteins is relaxed. Some of the QED models predict super-radiance [29] [53]-[55] and show that a periodic structure favors coherence [56] [57]. The periodic structure of tubulin in microtubules may provide a lattice with such role [22]. Attempts have been made to connect the thermodynamics of far from equilibrium systems [58] to the Fröhlich condensate concept [59].

In addition to the Fröhlich-Preparata-Del Giudice [25]-[34] and other theoretical models [44]-[52] [56]-[61], there are many experimental and computational proofs consistent to coherence phenomena and CDs in water and in concentrated protein systems [37]-[41] [43] [59]-[71].

Collective excitations were evidenced in heavy water by coherent inelastic neutron scattering, in agreement to the hypothetical CDs [60]. Also, the CD concept is consistent with evidence of clusters of molecules predicted by thermodynamic

models [61] and by theoretical chemistry calculations [62]. The results of the latter are in agreement with THz [63] and Raman [64] spectroscopy studies. As expected from the CD theory, long-range orientation correlation in water has been detected by hyper-Rayleigh scattering [65]. Ice-like transient structures in liquid water have been evidenced by X-ray diffraction many years ago [39]; these structures and clusters are short-lived as showed by nonlinear optical Kerr effect [41]. Most remarkable, studies by deep inelastic neutron scattering and X-ray Compton scattering evidenced quantum coherence in an anomalous quantum state of nanoconfined water [60] [66]-[71]; apparently, this confirms the defining hypothetical characteristics of the CD concept [44]-[48].

The incidence of CDs in liquid water as well as their characteristics are not unambiguously accepted. However, the present paper is based on the assumption of affirmative answers to these fundamental questions, and aims to analyze the dynamics of CDs from the perspective of biological physics. Here we follow the Preparata-Del Giudice CD model, because it is most appropriate both for bulk liquid water and for aqueous solutions. The milieu where the dynamics of CDs takes place is not "pure bulk" water but the incoherent water ("vacuum"), probably structured between two noncontact "hydrated" proteins in the cytosol. Previously we used the CD hypothesis and related concepts in models of biological relevance [44]-[48].

Caution is needed to avoid confusion between the macromolecular condensates of cytosol, which are biological macro- and mesoscopic objects (proteins), and the Bose-Einstein and Fröhlich condensates of water CDs, which are physical (quantum) objects. Both undergo condensation defined as hyperconcentration of components, but this process follows different laws and roles in the two systems. Thus, macromolecular condensates obey classical statistics, while water CDs condensates are of quantum nature. In the present approximation, the difference between the two kinds of condensates comes from the orders-of-magnitude difference between the molecular mass of proteins (57 kDa) and the effective mass (excitation energy) of 13.6 eV (2.42×10^{-35} kg) of the CDs. Thus, $M_{protein}/m_{CD} = 9.5 \times 10^{-26}$ kg/2.4×10^{-35} kg = 4×10^{9}. Nevertheless, there is a degree of interdependence between these two levels of organization, which will be discussed later. Indeed, the protein mass imposes a limit to the mean free path of proteins in water, which must not surpass the action radius (R_a) of the CD field.

3. The Basic Analogy between Water Coherence Domains and Pions

The aforementioned view of contactless interactions between proteins in cytosol is sustained by a number of experimental facts [5]-[7] [11]-[15] and by theoretical models which use the Yukawa potential [3]-[5], but is not fully understood in its details. Accordingly, we propose to examine this novel hypothesis and its biological consequences. By this—based on a striking analogy with interactions in the atomic nucleus—an interaction between proteins mediated by exchange of virtual

water CD quasiparticle is assumed.

The model of an exchange force mediated by virtual particles is one of the fundamental ideas of physics and of quantum mechanics in particular [72] [73] and it will serve as a foundation for our hypothesis of protein-CD-protein non-contact interaction. To this end, the protein-CD-protein system of the cytosol is treated in analogy with the nucleon-pion-nucleon interaction in the atomic nucleus. The notion of exchange force between particles begins with Yukawa's postulate [24] that inside the atomic nucleus the strong nuclear force between nucleons is caused by the exchange of the virtual bosons called π mesons or pions [35].

Two important cases in the nucleon-nucleon interaction should be envisaged. Consider two interacting protons or neutrons in the nucleus; one of the two may release a virtual neutral pion towards its pair, namely $p^+ \leftrightarrows p^+ + \pi^o$ or $n^o \leftrightarrows n^o + \pi^o$, respectively. In these processes, the state of the nucleon (charge, spin, parity, etc.) is unchanged: the proton state remains a proton and the neutron state remains a neutron. On the other hand, within the nucleus the nucleons may undergo interactions which are forbidden for free nucleons (because they would break energy and momentum conservation), by which a nucleon changes its state by emission of a virtual charged $\pi^{\pm}$ pion, hereby exchanged between a proton and a neutron—for instance $p^+ \leftrightarrows n^o + \pi^+$ and $n^o \leftrightarrows p^+ + \pi^-$. Thus, nucleons may undergo two types of transformations during the pion exchange—without or with change of state (charge, spin, parity).

In cells also, two types of changes—reversible and irreversible—may affect proteins. Consider now two "hydrated" protein molecules in cytosol interacting by exchange of virtual CDs. The first case (corresponding to the π^o meson exchange) may involve mild and reversible conformational changes in the protein and its "hydration shell". We may suppose that such a process takes place in the normal cell and it represents the main object of interest in this paper. The second case (corresponding to the $\pi^{\pm}$ exchange) has to be mentioned in order to evidence the parallelism between the protein's interactions and the strong nuclear force. The structured water shell and even the protein may undergo more drastic and irreversible changes, which may alter the "hydration shell" and the spatial structure of the polypeptide, impairing dramatically the CD exchange and the protein function. This may presumably happen especially in various proteinopathies, which generate much public concern: Creutzfeldt-Jakob disease and other prion diseases, Alzheimer's disease, Parkinson's disease, amyloidosis, multiple system atrophy, cancer, etc. In the following, attention is given primarily to the healthy cell case; and, for the sake of simplicity, a single type of CDs (with zero electric charge) is considered.

Thus, in the present approximation the virtual CD-mediated protein-protein exchange interaction is represented as follows:

$$P_{aq} \leftrightarrows P'_{aq} + \mathrm{CD} \tag{1}$$

where a "hydrated" protein in state P_{aq} releases a virtual water CD quasiparticle and undergoes a transition to the state P'_{aq}. As mentioned, this exchange occurs

only at the high protein concentration of cytosol.

To resume, several similarities are evidenced in the frame of the present hypothesis, when comparing the interactions between proteins in the cytoplasm of the living cell and those between nucleons in the atomic nucleus. 1) Both the cytosol and the nuclear matter are very crowded environments with complex interactions between components. 2) Both the mesons exchanged between nucleons and the water CDs between proteins are pseudoscalar bosons ($S = 0$) of finite nonzero mass. 3) Both the CD and the pion are composite particles. 4) There are two types of both protein-CD-protein exchange and of nucleon-pion-nucleon exchange (one of them neglected in the following). The formal physical analogy allows the postulation of a Yukawa potential between the "hydrated" proteins, just like between nucleons. This, as shown later, is consistent to a number of biological data and hypotheses (like the presumed existence of an intracellular communication network throughout the cytosol in the whole cell).

4. The Foundations of the Yukawa Theory

In his original argument Yukawa [24] started from a partial analogy of the nuclear interaction field and the electromagnetic field. While in the e.m. interaction the exchange of a massless photon is the cause of the force, he postulated that the nuclear force between nucleons is caused by the exchange of virtual spinless ($S = 0$) massive particles, namely the pions [35]. A brief presentation of Yukawa theory of nuclear forces, representing also a conceptual framework in general, is necessary to substantiate our hypothesis of CD exchange interactions between proteins in water.

Yukawa introduced a scalar potential with central symmetry $U(x, y, z, t) = U(\boldsymbol{r}, t)$ assumed to satisfy an equation similar to the wave equation for the e.m. potential. However, such an equation should not be identical to the e.m. wave equation, $\left(\Delta - 1/c^2\, \partial^2/\partial t^2\right)U = 0$, because the only time-independent solution of the later has central symmetry in $1/r$, while the potential of nuclear force—according to the experimental data available in the 1935s—should decrease more rapidly with the distance. Thus, a modified wave equation—containing an additional term μ^2 for a field of massive virtual bosons instead of the massless photons—was assumed to be the correct equation for U in vacuum:

$$\left(\Delta - \frac{1}{c^2}\frac{\partial^2}{\partial t^2} - \mu^2\right)U = 0 \tag{2}$$

where Δ is the Laplacean operator. This equation written for spinless ($S = 0$) massive particles by Yukawa in his 1935 article [24] and by Proca in 1936 (quoted in [35]) is formally identical to the time-dependent Klein-Gordon equation [74] [75], which describes spinless particles with positive, negative, and zero charge, with negative parity, and with nonzero mass; here μ^2 accounts for the mass of the exchanged boson. The time-dependent solution of Equation (2) is assumed to be separable and may be written:

$$U(\mathbf{r},t) = A(r,\theta,\varphi)B(t) = \chi(r)\exp(\mathrm{i}\omega t - \mathrm{i}\mathbf{kr}) \tag{3}$$

where the radial factor $\chi(r)$ has central symmetry. The time-dependent factor $\exp(\mathrm{i}\omega t - \mathrm{i}\mathbf{kr})$ evidences the oscillations of the virtual boson field, with angular frequency ω of the boson exchange and with corresponding wavenumber $\mathbf{k}$.

The time-independent Yukawa (Klein-Gordon) equation is a homogeneous screened Poisson equation, having the central symmetric factor $\chi(r)$ as a solution. In its turn, the latter will contain as a factor the Yukawa potential $V(r)$, namely $\chi(r) \sim V(r)$. Therefore, the $V(r)$ potential is a time-independent solution of the wave equation with central symmetry. The Yukawa (or Yukawa-like) potential has the form of a screened Coulomb potential around an electric negative charge [24] [35] [74] [75]:

$$V(r) = -g^2 \frac{\mathrm{e}^{-\mu r}}{r} \tag{4}$$

where μ depends on the effective mass of the virtual boson and r is the radial distance between the two interacting particles. The exponential factor, due to the nonzero mass m of the meson or of the CD, respectively, restricts the significant potential to a finite range. The minus sign and the squared g show that the potential $V(r)$ is always attractive.

In the Yukawa potential, the $1/r$ factor results from the "dilution" of the field line flux in space; further reduction of the flux through the surface is due to the "disappearance" of CDs similarly to the radioactive decay and results in the exponential factor $\exp(-r/R_a)$. Besides nuclear strong forces, the K-G equation can be used for approximations of various quasi-particles without spin [75] [76], as the CDs are.

5. The Origin of the Action Range in the Yukawa Potential

5.1. Energy-Momentum Derivation of Action Range

The physical meaning of the μ^2 additional term in the Yukawa's interpretation of the Klein-Gordon equation is evidenced by an approach of a different kind with respect to the above. The Equation (2) is written in the position space form, in terms of separated space and time components (t, $\mathbf{x}$) or by combining them into a four-vector $x = (ct, \mathbf{x})$. By Fourier transform of the field into momentum space $p = (E/c, \mathbf{p})$, the solution obeys the energy-momentum relation from special relativity.

$$E^2 = p^2c^2 + m^2c^4 \tag{5}$$

here m is the effective mass of the virtual boson and p its momentum. By inserting in this equation the quantum-mechanical operators for momentum and energy

$$\mathbf{p} = -\mathrm{i}\hbar\nabla \tag{6}$$

$$E = \mathrm{i}\hbar\frac{\partial}{\partial t} \tag{7}$$

and by rearranging terms, the result yields immediately the Equation (2) but with a definite, $\hbar$-containing expression for the additional term μ^2 describing the field of massive virtual bosons

$$\mu^2 = \frac{m^2c^2}{\hbar^2} \tag{8}$$

so that:

$$\left(\Delta - \frac{1}{c^2}\frac{\partial^2}{\partial t^2} - \frac{m^2c^2}{\hbar^2}\right)\psi(\mathbf{r},t) \tag{9}$$

here the term $\mu^2 = m^2c^2/\hbar^2$ of above introduces the action radius R_a as the reciprocal of μ:

$$R_a = \frac{1}{\mu} = \frac{\hbar}{mc} \tag{10}$$

The action range R_a (known also as the Compton length) shows how far can the two particles feel a mutual attraction, and it is inversely proportional to the effective mass of the exchanged boson. As shown by the Yukawa potential (Equation (4)), with each increase by a R_a step of the distance between the interacting particles, the potential energy decreases in magnitude by 1/e. With the above notations, the Yukawa potential (4) takes the form [24] [35] [74]:

$$V(r) = -g^2\frac{\mathrm{e}^{-\frac{mc}{\hbar}r}}{r} = -\frac{f^2}{4\pi}\frac{\mathrm{e}^{-\frac{r}{R_a}}}{r} \tag{11}$$

where, by analogy to the e.m. potential, f^2 corresponds to some kind of "boson charge" (carried by the nucleons in atomic nucleus, or by the hydrated proteins in cytosol, respectively). In fact, the factor

$$g = \frac{f}{(4\pi)^{1/2}} \tag{12}$$

is related to the coupling constant between the boson field and the field of interacting particles. In the case of CD exchange between proteins, by analogy to the e.m. and pion fields, each protein—and more precisely their "structured water layer"—caries a "boson charge" f which generates the water CD field.

Moreover, the protein mass and size imposes a limit to the mean free path of proteins in water, which must not surpass the action radius (R_a) of the CD field of effective mass m_{eff}.

5.2. The Action Range Is an Exclusive Property of the CD Boson Exchange Field

There are important properties of the action radius (Equation (10)) with immediate biological consequences. In general, to the first approximation of the exchange force, both in Yukawa meson theory and in the present CD exchange model, the action range $R_a = \hbar/mc$ is an exclusive property of the exchanged boson. It is depending only on the boson's (pion or CD) effective mass m_{eff}, being independent

on any other parameter of the system (e.g., interprotein distance, boson lifetime, exchange frequency, possible additional freedom degrees, etc.). In particular, the action radius is independent on the characteristics of proteins (molecular volume, size, shape, spatial structure, electronic charge distribution, etc., which all depend on amino acid sequence). The invariance of the action radius ħ/mc is explained by the fact that the latter comes from the invariant effective mass (excitation energy) term mc^2 of the CD in the relativistic expression (Equation (5)) of the energy. For the present study we keep in mind that the action radius R_a in the Yukawa potential does not depend on the structural characteristics of the two interacting proteins but only on the effective mass of the exchanged CD.

6. The Coupling Constant and the Yukawa Potential

6.1. The Effective Coupling Constant

A numerical evaluation of the coupling constant f^2 is needed for some of the applications, but the above theory is incomplete as it could not predict *ab initio* a value for f^2. This parameter has to be chosen such as to fit reasonably with the available experimental data. An effective f^2 value should be defined within reasonable upper and lower limits. The first one is obvious: because the center-to-center distance between proteins should always be greater than the diameter $2R_p$ of a protein ($r > 2R_p$). At this distance the potential energy of the CD-mediated interaction $|V(r)|$ should be higher than the thermal energy $k_BT/2$, and hence a lower limit for f^2 can be evaluated. The second assumption is aimed to evaluate an upper limit for f^2 but a somewhat arbitrary postulate has to be made. We assume that the energy of thermal agitation $k_BT/2$ will exceed the energy of the exchange interaction potential $|V(r)|$ at a center-to-center distance between proteins equal to or longer than the action range ($r > R_a$). Taken together, the two conditions for the potential energy writes

$$\left|V_{CD}\left(r > 2R_p\right)\right| > k_BT/2 > \left|V_{CD}\left(r > R_a\right)\right| \tag{13}$$

and, after simple operations, the expressions of the lower and upper limits of f^2 are obtained.

$$\frac{k_BT}{2}4\pi\frac{2R_p}{\exp\left(-\frac{2R_p}{R_a}\right)} < f^2 < \frac{k_BT}{2}4\pi\frac{R_a}{\exp\left(-\frac{R_a}{R_a}\right)} \tag{14}$$

For $r = 2R_p = 5.62$ nm and $r = R_a = 14.5$ nm, one gets 1.4 eV·nm < f^2 < 6.5 eV·nm, respectively. Although the two limits of f^2 diverge substantially, they are of the same order of magnitude. Therefore, within the above interval we assume—somewhat arbitrarily—a distance—and temperature-independent coupling constant, e.g. f^2 = 3.5 eV·nm = const. (at 310 K/37˚C). This value of the coupling constant f^2 is reasonable, but correct only as order of magnitude. With definite values of f^2 and R_a, some consequences can be discussed. The selected coupling constant of 3.5 eV·nm should be considered as a model input rather than a vali-

dation parameter. In a more precise approximation f^2 may take other values, to account e.g. for the dissolved ions. Within the allowable range of 5.62 - 14.5 nm, the potential $|V_{CD}|$ decreases monotously, implying that the main conclusions persist, at least qualitatively.

6.2. The Hard Sphere Yukawa Potential

Given that the Yukawa potential between point-like, dimensionless particles scales with the factor ~1/r, a plot would show a singularity at $r = 0$. However, this is of no consequence in our case, because proteins are approximated as hard spheres of finite R_p radius. The Yukawa potential is always attractive (negative) and the two proteins will tend to approach, up to a limit imposed at $r = 2R_p$ when they "touch each other" and they meet repulsive forces. Due to the finite size of impenetrable proteins, a modified form of the expression (11) obtained for CD exchange between point particles can be implicit for a hard sphere Yukawa potential:

$$V(r) = \begin{cases} +\infty & \text{for } r < 2R_p \\ -\dfrac{f^2}{4\pi}\dfrac{\exp\left(-\dfrac{r}{R_a}\right)}{r} & \text{for } r \geq 2R_p \end{cases} \tag{15}$$

The distance $r = 2R_p$ is approached in highly concentrated (saturated) solution or in a crystal when all proteins are in surface-to-surface contact and further shrinkage is no more possible. This is equivalent to an infinite repulsive (positive) potential term at $r < 2R_p$. The Yukawa potential reaches its lowest value at $r = 2R_p$. With the above "hard sphere" simplified model of the Yukawa potential, $V(r)$ and $\mathrm{d}V/\mathrm{d}r$ are finite and nonzero at $r = 2R_p$, and there is no singularity at this point. Then $V(r)$ increases asymptotically to zero for longer distances ($r > 2R_p$). Although the Yukawa potential without a repulsive term is only an approximation, it is satisfactory for our present goals. (Adding a positive term results in a minimum at a distance r_o somewhat longer than $2R_p$).

6.3. The Yukawa Potential vs. Thermal Agitation

The interprotein distance r_T where the attractive Yukawa potential prevails over the thermal agitation energy is the solution of the transcendental equation:

$$\frac{f^2}{4\pi}\frac{\exp\left(-\dfrac{r_T}{R_a}\right)}{r_T} = \frac{k_B T}{2} \quad \text{with } r_T > 2R_p \tag{16}$$

where $k_BT/2 = 0.0134$ eV at 310 K and r_T is given in nm. This equation is biologically significant because it evidences a maximum distance beyond which the CD exchange force is annihilated by the thermal agitation. The numerical solution is $r_T = 10.1$ nm.

The above model assumes a certain physical structure of cytosol and definite properties of cytoplasm (review in [18]). Accordingly, the cytosol is approximated to a homogeneous colloidal solution with equal center-to-center interprotein dis-

tances (if not specified otherwise, e.g. when macromolecular condensates are present). Also, all proteins are considered identical spheres; the protein-protein mean distance r is considered inversely proportional to the cubic root of the mean concentration. The protein size is evaluated by assuming a density equal to the water's one. The mentioned assumptions emphasize the limitations introduced by the neglect of protein size and shape diversity, molecular crowding, hydration layers, and nonuniform cytosolic composition. These are neglected because in the present approximation the action radius $R_a = h/mc$ depends only on a single parameter, the effective mass, irrespective of the other ones. In the action radius formula $R_a = \hbar/m_{eff}c$ the effective excitation energy (effective mass) may take various values according to the mass of various cytosolic proteins and to their specific (local) concentrations. Thus, a mean action radius would correspond to a correct mean mass of the CD exchange field, defined as the mean mass of proteins weighted with their specific concentrations. However, in most cells the individual values of proteins' mass and concentrations are not known extensively [18]. Instead, the mean of the masses is approximated to the mass of the mean which can be measured experimentally and can be used in the definition of a mean effective energy. Although this approximate calculation is affected by errors, it allows a significant and unique evaluation of R_a as a fundamental parameter. Thus the relevant distances where the virtual water CD exchange force acts between proteins of 5.62 nm diameter are restricted to the range 5.62 nm < r < 10.1 nm. The corresponding mean protein concentrations range is 520 g/L > $conc$ > 90 g/L. Thus, a minimal protein concentration c_{min} = 90 g/L, and a range of concentrations able to maintain interprotein CD-mediated interactions in the cytosol, are predicted. The theoretical estimate includes well the 200 - 300 g/L range of experimental values of protein concentrations in the cytosol of various cells [18], which corresponds to a range of about 6.8 - 7.7 nm mean interprotein distances. Other (semi)quantitative developments are discussed in following sections.

7. More Physical Aspects of the CD Exchange Interaction

7.1. The CD Exchange Field Is of Quantum Nature

The occurrence of the $\hbar$ constant in Equation (9) and afterwards emphasizes the quantum nature of the boson exchange field both for π mesons and for water CD quasiparticles. This is because the exchange interaction is essentially a quantum phenomenon, as shown by Heisenberg and Majorana in nuclear physics. By contrast, the Planck constant is absent in classical theories, like the Debye-Hückel theory of dilute electrolyte solutions in water [77]. Below, various arguments show the physical difference between two formally similar theories (of whom only one is a = of quantum nature).

The Debye-Hückel theory uses a very similar formalism as in Yukawa theory, but the former does not have implications for the later. It is also based on a time-independent Poisson-Boltzmann equation formally similar to the Klein-Gordon equation. However, the Yukawa and Debye-Hückel theories refer to phenomena

physically different on all accounts (e.g. energies, scale, nature and interactions). Our present Yukawa-type CD exchange model is conceptually much closer to the virtual pion exchange between nucleons than to the ionic atmosphere in diluted aqueous solutions, where no exchange takes place.

The CD exchange is not an "epiphenomenon" of some ionic atmosphere occurring in water A qualitative comparison of the CD exchange and the screened electrostatic potential appears significant. Thus, the CD exchange between two proteins has axial symmetry, while the Debye-Hückel screened e.s. potential has spherical symmetry. Also, a possible experimental observation of each interaction's specific symmetry might distinguish CD exchange from other effective interactions occurring in aqueous environment.

Moreover, a Yukawa-shaped fitted potential does not by itself establish virtual-particle exchange. Although both theories use formally similar potentials, only the occurrence of boson exchange can be attributed to a quantum phenomenon. These two amounts have completely different definitions and physical meanings. The former is microscopic and quantum, while the latter is macroscopic and classical.

A plausible argument sustaining the quantum nature of concerns the Bose-Einstein condensation of quasiparticles, which occurs below a critical temperature T_c; here the individual wavefunctions collapse together in an unique wavefunction with a single phase, as the momentum of the particles falls down and their de Broglie wavelength increases above the average distance between them. Could this phenomenon involve CDs in the cell, at relatively high temperatures and in the highly dissipative water environment? Macroscopic and mesoscopic size of cell (~10 μm) and of protein-protein distances (~10 nm) should not be an impediment, as suggested by various examples. In the particular case of lasers, they show the characteristic behavior at room temperature and in spite of being macroscopic devices. Thus, while pumped with energy from outside, condensation of photons in the resonant cavity occurs at normal densities. This was due to the low effective mass of photons; but the CDs also have a low effective mass. Note that the same phenomenon takes place in the dye lasers, which contains a dye aqueous solution as a liquid active medium. Moreover, lasing effects have been claimed in water [29]. Although the above argument is rather flexible, it suggests that the condensation of the Yukawa exchange field could be also a reasonable hypothesis supporting the quantum nature of CDs.

7.2. Electromagnetic Origin of the CD Exchange Force

Substitution of the above numerical values of f^2 and R_a in Equation (11) for $r > 2R_p$ allows the examination of specific aspects of the Yukawa potential. To begin with, note that the CDs can be pictured by assuming to be self-organized clusters of water dipoles connected by electric dipole fields and performing coherent oscillations [62]. Obviously, one can expect the CD-exchange mediated protein-protein interactions to be of electromagnetic nature, too.

This assumption is supported by an order of magnitude comparison between the energy of the Yukawa potential $V_{CD}(r)$ and the electrostatic potential of two elementary point charges at the center-to-center interprotein distance r. Within the distance of 5.62 - 14.5 nm (between the protein diameter and the action radius), the CD exchange force is rather close to the e.m. force or one order of magnitude lower, which means that the former is of the same nature as the latter.

7.3. Is There Any Spin Problem in the Yukawa CD Exchange Force?

Another aspect concerns the spin of the hydrated proteins involved in the CD exchange. In the general frame of the Yukawa theory, a spinless boson is exchanged between two fermions. While the water CD is a boson by definition ($S = 0$), a "hydrated" protein can change its total spin (electronic + nuclear) by binding or releasing a proton ($^1H^+$, $I = 1/2$), and thus might behave like a fermion in some of its ionization states. On the other hand, in his original article, Yukawa states that

> [a] "simple non-relativistic wave equation *neglecting spin* [my Italics] will be used for the heavy particle"

(*i.e.* for the π meson, cf. [24], or the CD, respectively). Thus, in either case a spin problem for the hydrated protein, if any, can be circumvented or ignored.

7.4. THz Vibrations in Water and "Water Buckyballs"

The energy of the Yukawa potential estimated for CD exchange at the mean protein-protein distance of ~7.0 nm is 0.0241 eV; a corresponding e.m. frequency is 5.8 10^{12} Hz, *i.e.* in the THz domain (47 μm wavelength). This frequency fits very well to the 6.0 - 15 THz vibration eigenfrequencies found by electronic structure calculations for a cluster model [62] of 12 and 21 water molecules—forming a dodecahedron and an icosahedron, respectively—connected by hydrogen bonds in polyhedric clusters ("water buckyballs", of 0.7 - 0.9 nm diameter). Accordingly, a representation of the water CD molecular geometry is given, which proves useful in the following. However, note that this representation is very approximate, because the CD is a QED concept and clouds of probability density should be used instead of definite positions.

Surface vibrations of large water clusters have been detected by He atom scattering [78]. In the ~6 THz domain, intermolecular electron density modulations in water with effects on the far-infrared spectral profiles [79] and vibrational signatures of hydrated ions with low-frequency motions in aqueous solutions [63] have been detected. In agreement with Fröhlich's theory, Bose-Einstein condensates of molecular vibrations [59] and of exciton-polaritons [37] in non-biological systems and in protein crystals [38] have been observed experimentally. Further support came from Raman spectroscopy [64], while long-range orientation correlations were detected in water by hyper-Rayleigh light scattering [65].

The THz frequencies associated to the energy of Yukawa potential describing the CD exchange and to the "water buckyballs" vibrations, may have implications

for a possible intracellular communication network. Moreover, it seems plausible that the present model could be tested experimentally in the THz and far IR region, both *in vitro* (on highly concentrated protein solutions) and *in vivo* and *in situ* (on living cells and on purified cytosol preparations, respectively).

7.5. Clathrate "Water Cages"?

Water around proteins is expected to be different from the bulk liquid and form a structured layer or cluster, which may show appreciable variability. This has been referred to as "hydration" water, without making any supposition on its structural details. Because of having in common aspects with the water buckyballs (CD molecular structure), we discuss here the subject of clathrate water cage. This is one of the two general cases that can be distinguished in the water-protein interactions, depending on the local order in protein structure.

1) Around proteins with ordered p*olar* regions and having definite tertiary structure, water is bound by electrostatic forces and hydrogen bonds to polar groups of the protein. By such forces water molecules may form layer(s) around proteins; they would be involved in the classical, specific, hand-glove, short range, contact interactions.

2) On the other hand, we assume that around *apolar* groups and disordered regions of proteins [11] water may form transient clathrate-like cages; these are a particular case of ice-like crystalline structures and clusters [39]. Typical water clathrates were first observed around argonides like Xe and simple hydrocarbons like CH_4, these examples just illustrate the structural concept. Around the central atom or molecule, the water is forming a cage (a polyhedron with pentagonal and hexagonal faces) with each H_2O molecule coupled by O-H…O bonds to other 4 molecules at 2.76 Å, like in ice. In the particular case of Xe, the elementary cell of the crystalline structure is formed by 6 merged polyhedra, containing 46 water molecules [39].

Attempts to visualize the clathrate water cages around hydrophobic side-chains of proteins and the CDs themselves in the form of dodecahedric and ikosahedric water clusters [62] evidenced similar local point (crystalline) symmetries. Accordingly, the former and the latter seems to have common structural elements.

The similar structure would facilitate the interaction between CDs and the clathrate cages around protein hydrophobic groups ("absorption" and "emission" of CDs near the protein surface), and thus the CD exchange between two contactless proteins. Although the details are hypothetical, the emerging picture is proposing a plausible mechanism occurring as an essential part of the long range, non-contact, CD exchange interaction. Imagine a protein exposing on its surface a row or an area of hydrophobic side chains, like e.g. …-Lys-Lys-Lys-… Such a row or area will form local quasi-crystalline (quasiperiodic) 1D and 2D water structures at the level of the water geodesic domes. The periodicity enhances coherence in general [56] [57]; in our case, it enhances the coherence of water dipole oscillations, and thus of the CD's dynamics, including exchange. In further dis-

cussions about CD exchange, the term "hydration layer" of proteins will refer primarily to the transient water "cages" or clusters (clathrate water cages around hydrophobic groups of proteins), and not to the classical "bound water" near charged or dipolar protein groups.

7.6. Fluctuations, Percolation, Hydrophobicity and Coherence

In the interactions of water with hydrophobic groups of proteins, percolation processes [80] and local water density fluctuations could also play some roles. It was shown that a percolation transition generates the formation of a "spanning hydrogen-bonded 2D water network on protein surface" and that strong fluctuations of the surface water network occur close to the percolation threshold [81]. Also, water density fluctuations are enhanced near hydrophobic surfaces and, in their turn, the former enhance cavity formation and water-water correlations [82] [83]. We previously published a model of density oscillations in pure water [44].

Hydrophobic groups of proteins may favor in their proximity relatively stable H-bonded structures of water with coherent dynamics—like the clathrate cages and the water buckyballs—as shown by studies of water in solutions of a prototypical hydrophobic amino acid, performed by quasi-elastic neutron scattering (QENS) and molecular dynamics (MD) simulation [83]. Thus, at high concentrations, suppression of translational and rotational water dynamics was evidenced near the hydrophobic side chain. Moreover, evidence of de Gennes narrowing, was an indication of coherent structural relaxation dynamics. The architecture with water bucky domes on the protein surface is only hypothetical, but it can't be excluded. Note that the studies referred above [81]-[83] provide experimental and computational support for coherence in water and for water-water correlations around hydrophobic side chains of proteins.

7.7. Brief Review of the CD Picture

A picture consistent to the above hypotheses emerges and a summary is useful. By analogy with the nucleon-pion-nucleon exchange force in the atomic nucleus, an attractive Yukawa-type non-contact potential of quantum nature is postulated between two proteins in water. The derived force is due to the exchange of virtual water CDs. The later are pseudoscalar ($S = 0$, positive parity) quasiparticles with non-zero effective mass, which at the classical limit may be visualized as polyhedric cages ("water buckyballs"). In this view, the CDs are exchanged between proteins' structured water, probably between the clathrate-like "water cages" around hydrophobic side chains. The action range of the Yukawa potential depends only on CD effective mass and does not depend on other factors like the protein size and shape, interprotein distance, frequency of exchange, etc. It is plausible that around proteins with internally disordered regions and around intrinsically disordered proteins, the "water cages" around hydrophobic groups may favor the CD exchange. This view is consistent to the contactless long-range protein-protein attractive force, which is essentially different from the classical hand-glove contact

interactions, and which may support a communication network in the cell.

8. Experimental Support: Straightforward Consequences and Biological Implications

Ideally, the validation of the theory would require direct comparison of theoretical predictions with specifically designed biophysical experiments or with other biological facts still to be discovered. So far, both our predictions and our biological observations are not precise enough for this. However, some of the available biological facts already known could be related to, and (partly) explained by the predictions of the theory. Some consequences of this approach are straightforward and are discussed below, as illustrated with respect to the action range of the CD field.

8.1. Theory and Facts: The Predicted CD Action Range and the Mean Interprotein Distance in Cytosol Fit with Each Other Better than Order of Magnitude

The action radius is the most important predicted physical parameter of the CD boson field connecting two proteins, while the mean protein-protein distance in cytosol is the main and experimentally measurable biological parameter of cytoplasm [18]. A comparison of the two amounts is necessary. To a first approximation, the condensates in cytosol are ignored; the cytosol is described as a homogeneous, hyperconcentrated, true solution (or colloidal suspension) of proteins.

As mentioned, the action radius $R_a = \hbar/mc$ depends only on the effective mass of the exchanged boson, and does not depend on any characteristics of the interacting proteins, in particular on their amino acid sequence. Based on the postulated analogy between the CD-mediated protein-protein interaction in cytosol and the pion-mediated nucleon-nucleon strong nuclear force, we can use the eq. (10) to evaluate the action range of the former. In the case of the protein-CD-protein force, the effective mass m_{eff} of the water CD boson was estimated to 2.4 10^{-35} kg (13.6 eV) [28]. Substitution of this numerical value defines an action range R_a of the Yukawa potential around 14.5 nm.

In various publications of the Milano group [25] a slightly different—12.06 eV—excitation energy is used, which corresponds to one higher excitation level of water near its ionization energy. We preferred an excitation energy of 13.6 eV equal to the Rydberg constant because of the more universal character of the latter. This yields an action range larger than ours by only 13%, but this numeric difference is of no relevance for the present semiquantitative evaluations. However, we keep in mind the 12.06 eV—or an energy close to it—because it allows a direct physical justification for the 13.6 eV excitation of CDs in terms of energy levels and ionization energy of water.

The composition of the hypothetically homogeneous cytosol as an equivalent protein solution corresponds to a concentration of 200 - 300 g/L [18]. Assuming a globular shape and a mean molecular mass of 57 kDa for all proteins, the mean center-to-center distance between the macromolecules falls in the range of 6.8 -

7.7 nm. These distances are around half of the ~14.5 nm action range estimated for the Yukawa potential action range. Given the many approximations involved, this fit can be considered surprisingly good (up to a ~2 factor!). It evidences as a major result of our model the correspondence between the (physical) action range of CD exchange and the (biological) mean distance between proteins in cytosol.

The results suggest some biologically relevant conclusions. First, that in cytosol the proteins are close enough of each other to be connected by exchange of virtual water CDs. Second, that the CD-coupled proteins are far enough to interact by long range forces of a completely different nature than the usual hand-glove contact interactions between biomolecules. Third, as a corollary of the above, that the relatively narrow range of high protein concentrations compatible with cellular life has been selected in the process of evolution, so as to allow optimal distances for CD exchange interactions. Fourth, that outside these interprotein distances (*i.e.* concentrations), alterations of cellular functions are to be expected.

In brief, the predicted 14.5 nm value of R_a compares better than order of magnitude with the ultrastructure associated to the known composition of cytosol (~7 nm mean interprotein distance). This provides strong experimental confirmation for the postulated CD exchange. The connection between the action range and the interprotein distance may also play biologically relevant roles in the living cell and its evolution.

8.2. Theory and Facts: The Size and Shape of Proteins Do Not Influence the CD Action Radius

In the Yukawa meson theory, the interacting nucleons are point-like, dimensionless particles. The same prerequisite is used in the CD exchange model, where the finite radius R_p of the "hydrated" proteins was ignored. However, by the above argument, even if accounting for the finite size of proteins and their shape, the action radius $R_a = \hbar/m_{eff}c$ (Equation (10)) would not change, because it depends only on the CD effective mass m_{eff} and on no other characteristic of the CD, the protein and the environment. More explicitly, the action radius R_a in the Yukawa potential is independent on factors which could influence R_p (like protein's size and its irregular shape, temperature, ionic strength, pH, microviscosity, etc.). This property is particularly relevant for protein dynamics in condensates.

8.3. Theory and Facts: The Invariance of the CD Action Range Parallels the Independence of Proteins' Behavior on Their Structure and Size

One can observe a notable parallel between the behavior of proteins in condensates and in other hyperconcentrated aqueous solutions and the invariant action radius predicted by the Yukawa model: both are approximately independent on the amino acid sequence of the proteins. Accordingly, at high concentrations, the postulated Yukawa attraction between the hydration (clathrate-like) water shells of two proteins by CD exchange, may plausibly explain the independence of pro-

teins' dynamics on the amino acid sequence, as observed experimentally.

8.4. Non-Contact CD Exchange-Forces vs. Hand-Glove Interactions

It is useful to outline the fundamentally new characteristics of the novel type of protein-protein interactions based on the CD exchange postulate. The new concept of CD-mediated interactions in biomolecular condensates (and in the surrounding liquid phase of cytosol) is fundamentally different on the current concept of specific hand-glove contact interactions; instead, it is fully consistent to the picture of long-range non-contact interactions. While the hand-glove picture is based on spatial folding and contact of complementary regions, being strictly dependent on the primary amino acid sequence of the protein, the postulated CD exchange mechanism is practically independent on the latter. The non-contact CD exchange interactions may explain the formation and stability of condensates, while the contact hand-glove interactions seem to play no essential role in the energy balance of condensates. In contrast to the hand-glove interaction, the CD-mediated coupling implies longer action range, quasi-independence on diffusion and shorter time resolution (see below).

9. Saturation of Cd Exchange Interactions

9.1. The CD Exchange Couples Only Nearest Neighbor Proteins

Note that r_T is of the same order of magnitude as the action range R_a although somewhat shorter; it depends on the thermal agitation of H_2O molecules in the incoherent water "vacuum". At the same time, r_T falls between the mean interprotein distance and its double, which implies that the CD exchange interaction couples directly only a few proteins of the nearest neighbor sphere. Most remarkably, the upper interaction distance r_T of CD exchange, limited only to the separation between the water cages' of the nearest neighbors, is similar to the saturation phenomenon from atomic nucleus; there a nucleon interacts only with a few other ones and additional nucleons have only small effects [35]. Saturation occurs also in the chemical bond, where only strictly limited and characteristic numbers of atoms can bind with each other (valence). In general, the saturation property results from the exchange nature of the forces involved and from their relatively short action radius, as shown by Heisenberg. Thus, its occurrence in cytosol would provide new validation for our hypothesis of the Yukawa forces' quantum nature.

9.2. Theory and Facts: Biological Implications of CD Exchange Field Saturation

The prediction of a saturation effect in cytosol suggests possible explanations to biological facts (or to possible observables relevant to the latter). First, the maximum experimental concentration of 300 g/L (r = 6.8 nm) in cytosol is lower than the predicted maximum of 520 g/L (r = 5.62 nm); the latter corresponds to a solid state crystal packing, and does not occur as such in the living cell. This shows that

while supporting protein-CD-protein interactions, the cytosol is not solid and remains normally in a liquid state both inside and outside the macromolecular condensates, in agreement with biological and biophysical data [11] [18]. The cytosol is similar to the substance of the atomic nucleus, which is closest to a liquid where the nucleons are able to move, in contrast to a solid where they would only vibrate around fixed positions, as specified by N. Bohr [35].

Second, the range of mean protein concentrations in cytosol, namely 200 - 300 g/L [18] is relatively narrow according to biological standards, and it includes data from a very large variety of cells. The data reveal that the density of proteins in cytosol shows little variation, or that each protein occupies approximately the same volume when passing from a given cell to another one. A similar situation occurs in the atomic nucleus, where due to saturation the density of nuclear substance is approximately constant for all chemical elements and each nucleon occupies approximately the same space [35]. Implicitly, the cytosol from different cells would have similar ultrastructure, biochemical composition and biophysical properties.

Third, the range of mean interprotein distances (6.8 - 7.7 nm) corresponding to the above concentrations (200 - 300 g/L) shows an even smaller variability. This suggests that in cytosol the hydrated proteins pass most of the time at distances where they are connected by the exchange force and only "tumble around one another", while they "touch briefly and move on" [11]. This behavior has been evidenced in condensates. Therefore, between proteins in cytosol the postulated Yukawa force should play a different role as compared to the classical hand-glove interaction. In fact independence of interactions on primary protein sequence has been evidenced both in condensates (see [8]-[11] and in model systems [7]).

Fourth, restricting the interprotein interactions to the first neighbors, saturation favors a molecular organization of the cytosol which is adequate for percolation [80]. Such a structure could play an important role in the formation of "water networks" on protein surfaces and around hydrophobic side chains [81]-[83], and thus in a hypothetical intracellular communication network [84].

In brief, with the assumption of 3.5 eV·nm for an effective coupling constant, a maximum distance of 10.1 nm within which the CD exchange force overcomes the thermal agitation (at 310 K) is evaluated. Therefore, only proteins of the nearest neighbor sphere are coupled by the CD exchange interaction, a property similar to the saturation in the atomic nucleus and with high biological relevance. By analogy, the saturation in cytosol explains, or is consistent with, a number of biological properties, including: the liquid state of the macromolecular condensates; the comparatively small variation of protein density in the cytosol from different cells; the amino acid sequence-independent exchange force, prevalent over the classical hand-glove interaction; and a characteristic molecular organization which may favor percolation. Thus, the saturation may provide the cytosol with some of the prerequisites needed for an intracellular communication network.

10. Exchange Frequency and Communication in the Cell

10.1. Dispersion Relation and Exchange Frequency: Communication in Cell by CD "Spikes"?

The relatively long-range, CD-mediated exchange interaction can be visualized in various ways: as a CD field of high frequency linear oscillators; as a self-consistent mean field of bosons where each CD "feels" the influence of each other; or as a transient CD "network". In the essence, this defines a CD field, and by substituting in Equation (9) a solution of the form $\phi = \phi_0 \exp(\mathrm{i}\omega t - \mathrm{i}\boldsymbol{kr})$ given before (Equation (3)), one obtains the dispersion relation [35] [72]:

$$\omega^2/c^2 - k^2 - 1/R_a^2 = 0 \tag{17}$$

which gives the exchange frequency. Here $k = 2\pi/\lambda = \pi/r$; $r = \lambda/2$ is the center-to-center distance between point-like proteins, and R_a is the Yukawa potential action radius for CDs of effective mass m_{eff}. For $r \sim 7.0$ nm and $R_a \sim 14.5$ nm, the above approximation of the dispersion relation gives $\nu \sim 10^{16}$ Hz for the CD exchange frequency. This defines an upper limit of the frequency. Alternatively, the upper frequency may be evaluated with the basic relation

$$\nu = m_{eff} c^2/h \tag{18}$$

which, for the effective mass of 13.6 eV, gives $\nu \sim 3.3 \times 10^{15}$ Hz. Thus, the upper limit of the frequency obtained with the two methods converges surprisingly well.

A lower limit may be defined by the reciprocal of the H-bond lifetime, *i.e.* $\sim 10^{11}$ Hz. The CD exchange frequency may be located somewhere between these two values. Therefore, at a certain moment and at a given point in a macromolecular condensate (or in the whole cytoplasm), the field of CD exchange—or its absence—may define a "spike" with a binary value of 1 or 0 [84]. Such modulation mechanisms might provide the cell with communication channels of very high capacity and speed.

10.2. Theory and Facts: Biological Implications of Communication and Complexity

One may speculate that in this way proteins could exchange information on position, orientation, conformation, reactivity, etc. It is plausible to assume that during the evolution of life on Earth, the cells have learned at a certain moment to transfer sequences of spike signals between remote proteins. This was probably done by use of the CD exchange interaction, and could have represented a considerable adaptive advantage. The sequences of spikes may be extremely diverse and thus might connect a given emitter protein with a unique receiver individual protein out of many other potential receivers. Accordingly, each chemical reaction and conformational transition would occur at the right place and moment, in agreement to the current view of cell biochemistry.

This picture contrasts to the hand-glove mechanism which, due to the spatial folding specificity, is strictly limited in space to only one emitter-receiver couple. The hand-glove mechanism is also limited in time, by the comparatively much slower diffusion process. Thus, a CD exchange-based intracellular communica-

tion would have the advantages of a fast "digital" system, comparatively to the slow "analogic" hand-glove mechanism. Multiplexation may expand even more the capacity of interprotein communication by sequences of spike signals.

11. Yukawa Attractions vs. Other Protein-Protein Interactions

A comparison of the Yukawa-like force and some of the noncovalent forces (Coulomb, dipolar, van der Waals, H-bond) [85]-[87] at mean interprotein distances in cytosol [84] [85] may be relevant for further insight on the protein-CD-protein interactions.

11.1. Coulombian Interactions

The most important implication of the Coulombian interaction $V_C = e^2/4\pi\varepsilon\varepsilon_r$ concerns the possibility of estimating—by comparison—the magnitude of the Yukawa interaction $V_Y = f^2\exp(-r/R_a)/r$. For R_a = 14.5 nm and f^2 = 3.5 eV·nm, at center-to-center protein-protein distances increasing from 5.62 = to 10.1 nm distances, the ratio |Yukawa/Coulomb| decreases from 0.132 to 0.097, respectively. This shows that the CD interaction is about ten times weaker than the e.s. one, which is a reasonable result based on the assumption that the Yukawa interaction is a residual one of electromagnetic origin, as implied by the QED definition of the water CDs. Of course, the result would change if a different value is selected for the coupling constant f^2, which is a model parameter. Also, the relative electric permittivity ε_r, which is 70 in water, is defined for the electrostatic potential energy V_C but not for the CD exchange interaction V_Y, as the Yukawa potential in the present approximation does not contain ε_r. Thus, the Yukawa/Coulomb ~ 1/10 rule should be considered only as an order of magnitude indication.

Moreover, both the Coulomb and the Yukawa potentials do not take into account the influence of dissolved cations and anions and the ionic atmosphere around charged groups of proteins. The ionized groups with opposed charges on proteins' surfaces will almost neutralize each other and neat charges will be low. The conditions in the cytoplasm are typically close to the isoelectric point. The mean isoelectric point of proteins (from mammals) is usually slightly acidic, pI = 6.8 - 6.9 [88] while the intracellular pH is neutral or slightly basic, pH_i = 7.0 - 7.4 [89]. Thus, there is only a small prevalence of ionized acidic over basic groups and of cytoplasmic proteins with neat negative charge. Therefore, the contribution of interactions between proteins at ~7 nm mean distance by Coulombian ion-ion forces appear to be of little consequence for the stability of cytosol. Even if the effect of counterions is ignored, repulsions between proteins carrying neat charges of the same sign will not prevent the participation of "hydrated" proteins in a possible intracellular dynamic protein-CD-protein network based on the attractive Yukawa potential.

One can see that the Yukawa potential may be lower than the electrostatic one—but not more than ~10 times lower, and attractive. In absolute value, the potential energy of the CD exchange is apparently small (0.014 - 0.034 eV), and the CD

exchange field can contribute to the stability of the cytosol as a correction to the Coulombian interaction. In the presence of dissolved ions, with the ionized groups surrounded by an ionic atmosphere, the dielectric constant of water decreases when the distance decreases [77] and some more corrections may be made, but the picture remains the same.

11.2. Dipolar Interactions

The contribution of the long-range r^{-3} dipolar interaction between high dipole moment CDs and dipolar proteins, or between two dipolar proteins in water, is given (in kcal/mol) by the well-known formula [85] [86]:

$$E_{dipole\text{-}dipole} = -10.8\frac{\mu_{CD}\mu_{protein}}{r^3\varepsilon_r} \tag{19}$$

where the original notations were used. Here μ_{CD}, $\mu_{protein}$ are the dipole moments of the CD and protein, respectively (in Debye units D), r is the distance (in Å), and ε_r is the relative permittivity. For the $(H_2O)_{21}H^+$ water nanoclusters assumed as a CDs structural model, the calculated ground-state dipole moment is approximately10 D [62]. With a similar dipole moment for the hydrated proteins, after substitution of numbers ($\mu_{CD} = \mu_{protein}$ = 10 D, r = 70 Å and ε_r = 80) one obtains for the dipole-dipole CD-protein and protein-protein interaction energy $E_{dipole\text{-}dipole}$ = 0.008 eV. As expected, the dipolar interactions are generally comparable to the ion-ion Coulombian ones, but weaker. Also, when compared to the CD-mediated exchange interactions between proteins, the dipole-dipole interactions are close as order of magnitude but weaker.

11.3. Van der Waals Interactions

For two ideal spheric proteins with smooth surface and radius σ = 5.6/2 = 2.8 nm situated at a distance a [86] [87] [90], the interaction energy is given approximately by the formula:

$$E_{VdW} \approx A\sigma/12a\,, \tag{20}$$

which gives ~10^{-1} - 10^{-2} eV; here A~(10^{-19} - 10^{-20}) J is the Hamaker coefficient. The strengths of the Van der Waals attractions between proteins at ~7 nm center-to-center distance are similar to (or slightly higher than) the potential energy of CD exchange.

11.4. Hydrogen Bonds

Hydrogen bonds contribute most to the stability of cytosol, not due to proteins but to water. Precisely, the bond strength of a water-water O-H…O hydrogen bond is 0.22 eV [39]. A single H-bond ~0.28 nm long does not form between the two proteins because of the large mean distance of ~1.4 nm between their surfaces. Also strings of some five H-bonded water molecules each connecting the proteins at this distance are rather improbable. Thus H-bonds between hydrated proteins may form only by occasional neighborhood of macromolecules or by collisions

between them.

The contribution to the stability of the cytosol due to H-bonds, which is larger as compared to the Coulombian, dipole-dipole and Van der Waals interactions, and also larger than the CD exchange interaction, is due to several factors: 1) the energy of the H-bond itself in water [39], is higher as compared to all above interactions; 2) the other interactions involve proteins at ~ 7 nm mean center-to center distance, while the H-bond oxygen-H-oxygen length between two water molecules is about 0.29 nm and thus is stronger; 3) the H-bond also manifests the saturation property, and each water molecule participates in average to between 2 - 4 hydrogen bonds [90]; 4) H bonds between water molecules involve up to 95% of them [91]; and 5) the number of proteins of 5.62 nm diameter in a spherical cell with a radius of ~5000 nm is only around 1.9×10^9, while the number of water molecules occupying 70% of the cell volume is as high as 1.5×10^{13}. This example shows that there are 8×10^3 times more H-bonds (O_2 molecules) than proteins, each involved in around 3 H-bonds, overwhelming by far the contribution to the total energy of interaction associated to the classical weak forces and to the Yukawa exchange force.

11.5. Overview of CD Exchange vs. Other Specific Interactions

In brief, the H-bonds between water molecules are practically the main force responsive for the stability of the cytosol, while the other interactions are expected to play another role in the cell. In reality, a homogeneous structure of the cytosol has been tacitly assumed, neglecting thus the condensates. Also, the Coulombian, dipole-dipole and Van der Waals forces may have a more substantial contribution when considering their involvement in hand-glove specific interactions, where they act at (sub-)nanometer distances. This leaves open the way for the hypothesis that the Yukawa long-range forces may support interactions supposedly independent on the sequence and spatial structure of proteins; also they may involve less energy than the hand-glove ones. Such interactions are consistent to a possible role in intracellular communication, as suggested before.

12. A Model of Condensates' Formation and Stability: Application of Yukawa Potential

In condensates the interprotein distances are shorter than the mean distance in an equivalent homogeneous solution. Thus, the exchange interactions in condensates are stronger and the Yukawa potential may contribute more to the formation and stability of these membraneless organelles. For instance, the ratio between the potential energy per CD at 5.5 nm (in condensates) and at 7.0 nm (in homogeneous solution) is $1.4 = \varepsilon_{cond}/\varepsilon_s = \varepsilon(5.5\text{ nm})/\varepsilon(7\text{ nm}) = 35\text{ meV}/25\text{ meV}$.

12.1. Macromolecular Condensates, Coacervates and the Origin of Life

The cytosol is a stable colloidal protein-water system, heterogeneous on a scale of

nanometers (proteins) and of microns (condensates), and homogeneous on average on a scale of microns to tens of microns (cells). How does it form? What explains the non-uniform structure and stability of cytosol? The hypothesis of a relatively long-range interaction—the water CD exchange force between proteins, active up to ~10 nm—may inspire an intuitive picture. The condensates show characteristics highly similar to the coacervates postulated in the Oparin-Haldane hypothesis on the origin of life [92]-[94]. Coacervates are supposed to be almost identical to the primordial "droplets" able to sustain a rudimentary form of metabolism [92]-[94] in theories which assume that metabolism preceded the genetic functions based on the nucleic acids apparatus. Just like condensates, the coacervates are dispersed droplets of hyperconcentrated solutions of macromolecules, in equilibrium with the more dilute aqueous environment [94]-[96]; they form spontaneously, are stable, and do not aggregate.

In our picture, the formation and stability of coacervates seems to involve molecular crowding driven by CD exchange attraction between proteins with hydrophobic regions and clathrate-like organizing of water around them. This hypothetical mechanism appears to be different on the interaction between charged polymers known to occur in coacervates [95] [96]. The latter has been shown experimentally to be driven by entropy variation associated to biopolymer dehydration [12]; In particular, liquid-liquid phase separation was enhanced by polyethylene glycol, a molecular crowder polar polyether. One can assume that the two competing phase-separation mechanisms concur in hyperconcentrated protein aqueous environment. When both are present (as expected in cytosol), the weight of each one will depend on the specific protein composition; but the later parameter was not accounted for explicitly in the present study. In the following, a very simple model is presented.

12.2. A Simple Model for Condensates' Formation and Stability

The model aims to evidence some qualitative trends in the condensate suspension. To illustrate the role of Yukawa potential in the stability of condensates, the following approximations are assumed: 1) condensates are made by a single type of ‚hydrated' protein molecules exchanging CDs between each other's water cage; 2) the proteins in the condensates and in the surrounding liquid are immersed in water at the isoelectric point (*pI*) and, therefore, no major Coulombian intermolecular interactions occur in the mean; 3) the charged groups of proteins, when they exist, are screened; 4) dehydration of proteins, if occurs, is neglected; 5) only Yukawa exchange forces are supposed to exist between proteins at distances of 5.6 - 8.4 nm; and 6) the CD exchange action radius R_a is the same in condensates, their environment and equivalent homogeneous solution.

The main parameters of the CD-mediated Yukawa interactions in cytosol are the mean center-to-center distances x_c, x_l and x_s between proteins—in condensates, in the surrounding liquid phase and in an equivalent homogeneous solution (of the same volume and containing the same number of protein molecules).

Equally important in the model is the number n_c of condensates in the cell. Any admissible configuration of the above distances must obey the relations $x_c < x_s < x_l$. Making use of the Yukawa potential [11] and looking to the balance of interaction energy in the cytosol and in a genuine protein solution, simple relationships may be established. That is, in order to explain the stability of cytosol, the heterogeneous condensate + liquid suspension must be energetically more advantageous as compared to a homogeneous protein solution with the same mean number of proteins and volume, namely:

$$\frac{E_H}{E_s} = \frac{E_c + E_l}{E_s} = \frac{-|E_c| - |E_l|}{-|E_s|} \geq 1 \tag{21}$$

where E_H is the total CD exchange energy of the heterogeneous cytosol suspension, equal to the sum between the energy E_c in the condensates and the energy E_l in the liquid environment ($E_H = E_c + E_l$); and E_s is the energy of the equivalent homogeneous true solution. (Here the minus sign of the attraction energies is of no explicit consequence in the E_H/E_s ratio.) In the heterogeneous cytosol, the total number of proteins, N_H, is the sum of the total number of proteins in the condensates, N_c, and their total number in the liquid environmental solution, N_l:

$$N_H = N_s = N_c + N_l . \tag{22}$$

here also N_H is the same as the number N_s of proteins in the equivalent homogeneous solution. Note that $N_H = N_s$, while $E_c + E_l = E_H \neq E_s$ by hypothesis. Thus, the interaction energies due to the Yukawa potentials with action radius R_a write:

$$E_H = E_c + E_l \sim N_c \frac{e^{-x_c/R_a}}{x_c} + (N_s - N_c)\frac{e^{-x_l/R_a}}{x_l} \tag{23}$$

$$E_s \sim N_s \frac{e^{-x_s/R_a}}{x_s} \tag{24}$$

Note that the above energies depend on N's to the power of one, which is an effect of the saturation as discussed previously: only proteins in the first neighboring sphere (at ~ 5.6 - 8.4 nm of each other) interact, and at ~ 10 nm the CD exchange is annihilated by the thermal agitation. Further we take advantage of the fact that N_c and N_s are given by simple expressions:

$$N_c = n_c \frac{v_c}{x_c^3} \tag{25}$$

$$N_s = \frac{V_{cell}}{x_s^3} \tag{26}$$

where n_c is the number of condensates per cell, v_c is the volume of a condensate, and V_{cell} is the cell volume. After substitution above, the following expression is obtained for the ratio of energies due to the Yukawa potential in the heterogeneous cytosol and in the equivalent homogeneous solution:

$$\frac{E_H}{E_s} = \frac{E_c + E_l}{E_s} = n_c \frac{v_c}{V_{cell}} \left(\frac{x_s}{x_c}\right)^3 \left[e^{-\frac{(x_c - x_s)}{R_a}} \frac{x_s}{x_c} - e^{-\frac{(x_l - x_s)}{R_a}} \frac{x_s}{x_l} \right] + e^{-\frac{(x_l - x_s)}{R_a}} \frac{x_s}{x_l} \tag{27}$$

The present model is phenomenological, because the interprotein distances x_c, x_s, x_l are reasonable given amounts consistent with the cytosol composition; *i.e.*, they are not calculated from physical or physical-chemical amounts depending on parameters like temperature, pressure, pH, ionic strength, etc. Also, the x's are not calculated *ab initio*, e.g. from molecular structure of proteins and water.

12.3. Results and Biological Implications

A relevant particular case of Equation (27) arises when $x_c \cong x_s \cong x_l$. This corresponds to a dispersed protein system situated near the critical point between homogeneous solution and incipient condensate formation. Because phases are not separated, the mean intermolecular distances can be considered the same everywhere, just like in a homogeneous solution. Therefore, the particular value of the ratio E_H/E_s reduces to one, $E_H/E_s = 1$. However, in general $x_c \neq x_s \neq x_l$ and implicitly $E_H/E_s \neq 1$, the ratio being either an improper fraction (>1) or a proper one (<1), depending on the values of the x's and of the parameters. Thus, the E_H/E_s ratio divides the "energy landscape" based on the Yukawa potential into two distinct regions. In the improper fraction region ($E_H/E_s > 1$), condensates form spontaneously and are energetically stable, in agreement to the principle of potential energy minimization. By the contrary, in the proper fraction region ($E_H/E_s < 1$) they do not form at all or form only as brief fluctuations and vanish immediately. However, one Although the phenomena are probably more complex, one may expect at least order of magnitude predictions from the above calculation. In brief, our simple model shows that the Yukawa potential associated to CD exchange may explain the formation and stability of condensates in highly concentrated protein solutions and, by extension, in cytosol.

Equation (27) shows that the ratio E_H/E_s depends on three independent variables: the number n_c of condensates per cell and any two of the three interprotein distances x_c, x_s, x_l. Thus, the function $E_H/E_s = f(n_c, x_i, x_j)$, $(i, j = c, s, l)$ is 4D (defined on a 3D space) and is difficult to visualize.

However, one can get an intuitive and qualitative idea on the behavior of the E_H/E_s function, by reducing its definition space to only two independent variables in particular cases. To this purpose, in agreement to the inequality $x_c > x_s > x_l$, we assume a constant value for x_s, (in particular $x_s \cong 7.0$ = const., which is consistent to the protein concentration in cytosol within the experimental limits.). Also, symmetrical for x_c and x_l, namely $|x_c - x_s| = |x_s - x_l|$, are postulated. Moreover, it is assumed that 5.6 nm < x_c < 7.0 nm and 7.0 nm < x_l < 8.4 nm. Thus we get a two variable function $E_H/E_s = f(x_c, n_c)$ which generates an "energy landscape" (a "state diagram") defined on a 2D space, and which can be represented in a plane projection (**Figure 1**).

The chart of E_H/E_s evidences a certain domain with specific values for x_c and n_c where the condition $E_H/E_s > 1$ is fulfilled, and another domain where $E_H/E_s < 1$ (**Figure 1**). In the former domain, condensates form spontaneously and are more or less stable due to the Yukawa attractive, non-contact, long-range potential, and

to potential energy minimization. In the later domain, the modulus of the attraction energy in the condensate suspension is lower than in the homogeneous solution; therefore, the condensates do not form at all or are unstable and disintegrate.

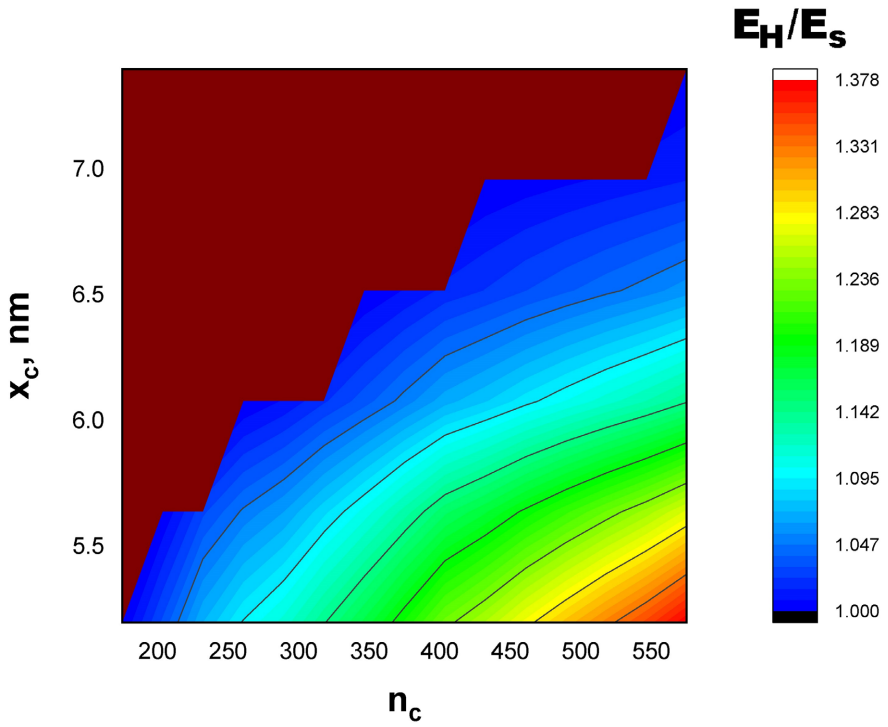


Figure 1. Simplified map illustrating qualitatively the dependence of E_H/E_s ratio predicted on the basis of the Yukawa potential model, on the condensate number per cell n_c and on the interprotein center-to-center distance in condensates x_c. Here R_a = 14.5 nm according to CD's effective mass; the domains' values of n_c and x_c are consistent to experimental biological data. The landscape of E_H/E_s has been reduced to a 2D projection by the particular assumptions $|x_c - x_s| = |x_s - x_l|$ and x_s = 7 nm. The two domains are revealed. In the $E_H/E_s > 1$ domain, the condensates form spontaneously and the heterogeneous structure of the cytosol is stable. In the domain with $E_H/E_s < 1$ the condensates do not form. Along the boundary between the two domains (with $E_H/E_s = 1$), the liquid-liquid phase transition between hyperconcentrated solution and condensate suspension occurs.

Along the boundary between the two domains ($E_H/E_s = 1$), the phase transition between hyperconcentrated solution and condensate suspension takes place. The plot evidences the relationship between the energy ratio predictions of the Yukawa model and the state of the system, which can be characterized experimentally.

The sharp discontinuity in the phase diagram between the condensate-containing phase and the homogeneous solution phase are typical for a first-order phase transition. Thus, during the transition, the system is in a "mixed-phase regime" in which some parts of the system have completed the transition forming condensates and other have not, like in the freezing of water. Also, the system probably releases a measurable latent heat during the phase transition of condensates' formation.

The curves of constant energy ratio (E_H/E_s = const), expressing x_c vs. n_c, may be approximated roughly with Freundlich power functions; up to a constant term, they scale like:

$$\left(x_c\right)_{E_H/E_s} \sim n_c^{\alpha} \quad \text{with} \quad 0<\alpha<1 \quad \text{and} \quad \alpha \neq 1. \tag{28}$$

As expected for the Yukawa potential between any two proteins, it shows that the condensate formation is due to a single and unitary mechanism (associated to potential energy minimization).

A similar image is valid in many biological and model systems. For instance, a similar graph describes the bacterial growth rate as a function of available substrate concentration and enzyme expression level. In the end, as both need high levels of amino acids building blocks and ATP and intense protein synthesis, growth would stop because making the enzyme itself takes resources (fig. 140 p. 223 in [84]).

Some qualitative conclusions evidenced from **Figure 1** are straightforward. The formation and stability of the condensates in cytosol requires a minimal number of condensates per cell and a minimal density of proteins in the condensates. In particular, according to Equation (25) and with the optional approximations assumed in **Figure 1**, it appears that n_c should be in the range of e.g. hundreds of condensates per cell, and x_c should fall in the range of ~5.62 - 6.8 nm. But these two high density requirements are competing. If the resources are not enough, increase of proteins in condensate above a critical number may hamper the number of condensates below their critical number per cell or vice versa, and thus E_H/E_s may fall in the <1 domain where the condensates will disintegrate. Thus, there are optimal values of both the above competing parameters, which are needed for the energy balance of Yukawa potential in the living state of the cell. Although the graphs in **Figure 1** are based on an indirect argument and were obtained with particular assumptions, it is highly plausible that the same qualitative trends were valid also in the general case with E_i/E_s defined on a 3D space.

The present model is also consistent with theories on the origins of life, which already assume the fundamental role of metabolism and thresholds of protein concentrations in the primitive protocells [92]-[94]. Semiquantitative tests of the model may also be feasible.

13. Conclusions

The present picture integrates distinct hypotheses and simple models, which converge in sustaining the postulate of contactless interaction between proteins in cell water. The basic concept used throughout is the CD. As mentioned extensively, it is currently referred to as a hypothetical spinless (S = 0) quasiparticle, namely a pseudoscalar boson of nonzero effective mass (excitation energy), made by coherently oscillating water dipoles. On this basis, the exchange of virtual CDs between protein-influenced transient water structures is our main hypothesis. Thereby, a new protein-protein attractive force—derived from a Yukawa potential—is gen-

erated. This mechanism is supposed to occur especially in hyperconcentrated environments, like the macromolecular condensates from cytosol. By these characteristics and by their dynamics, the CDs are strikingly similar to the pion bosons, which mediate the attractive nucleon-nucleon force in the atomic nucleus. Also, there is a similarly crowded environment in the macromolecular condensates of cytosol and in the atomic nucleus. However, in contrast to the pion from the atomic nucleus, the effective mass of the water CDs' is small (~13.6 eV). With the CD exchange a new picture of the cell emerges, which leads to qualitative and (semi)quantitative predictions, confirmed by molecular and cell biology data. The main results include:

1) The most important example is the action range of the Yukawa potential—a measure of the CD exchange interaction—which is estimated to ~14.5 nm by use of a CD effective mass as the only numerical model input. Remarkably, this result fits better than order of magnitude to the ~7 nm mean distance between proteins in cytosol, as determined by cell biophysics measurements. Thus, the theoretical prediction is only about twice the experimental value.

2) The independence of the Yukawa action radius on any molecular characteristics of the proteins, evidences a new type of protein-protein interaction. In the molecular biology of the cell, proteins couple by the classical hand-glove, short-range, contact, specific interactions between 3D fitting molecules, depending strictly on the amino-acid sequence. In the presence of the CD exchange force, there is a different, complementary, relatively long-range, contactless interaction, independent on the primary protein sequence and thus on its spatial folding. More generally, the invariance of the action range parallels the relative independence of protein interactions on their structure and size: both evidenced similar patterns.

3) Although the details of water dipoles organization in CDs and around proteins are not yet known, structural models may play at least a heuristic role. In the new type of interaction, water around hydrophobic side chains of proteins seem to form clathrate-like clusters ("water cages") or at least partial (hemispherical) geodesical domes, in contrast to the classical case where hydration is determined only by polar protein groups. At the same time, CDs may be formally described as polyhedric "water buckyballs", structurally related to the "water cages". This may facilitate the exchange of CDs between proteins. Though the similar polyhedral clathrate-like structure is more or less hypothetical, it is consistent with biological data which show that the formation of condensates is favored around intrinsically disordered proteins and around proteins with disordered regions.

4) Assuming a (somewhat arbitrary) value of 3.5 eV.nm for the coupling constant in the Yukawa potential, the property of saturation was evidenced in the interaction between proteins coupled by CD exchange. Their behavior was similar to the saturation of nucleons in the atomic nucleus. At ~ 7 nm mean protein-protein distances, the CD exchange interaction couples only few neighboring proteins, all from the nearest neighbor sphere. Saturation supports a number of hypotheses consistent to selected biological observations. The latter includes: the liq-

uid state of macromolecular condensates; the comparatively small variation of protein density in the cytosol from different cells (density conservation); and the amino acid sequence's relative independence (sequence independence). Other hypotheses from the same category are derived from our simple model of condensate formation and stability driven by CD exchange attractions; from an important role of coacervates in the protocellular evolution; and from a possible role of intracellular communication by high capacity channels (see below).

5) The frequency of the CD exchange was estimated somewhere in a wide range of values. This was located between the THz band or far UV band as an upper limit given by the dispersion relation, and the reciprocal of the H-bond lifetime as a lower limit given by the dispersion relation. The high CD exchange frequency may be used as a carrier of messages in the form of sequences of signals ("spikes") for information transfer. Thus, the CD exchange field may support an intracellular communication network, able to connect remote proteins in cytosol.

6) With the numeric values of the action range and the coupling constant, the Yukawa potential energy in condensates and surrounding solution could be evaluated. Thus, in the energy balance of the cell, the additional cohesion energy due to the non-contact CD exchange force appeared to be close to or below the weak specific interactions (Coulombian, dipolar, Van der Waals, etc.) involved in the classical hand-glove mechanism. Only H-bonds contribute significantly more to cytosol stability, because the number of water molecules involved in such bonds is much larger than proteins' number per cell.

7) The hypothesis of Yukawa CD exchange makes possible a model of condensates' spontaneous formation and stability in cytosol, based on the evolution towards the lowest potential energy of the whole system of protein-CD-protein links. The model estimates the ratio between the total potential energy of the heterogeneous system formed by condensates and surrounding liquid, and of the equivalent homogeneous solution. The model is consistent to interprotein distances close to 5.6 - 7 nm inside, and to 7 - 10 nm outside condensates. The energy map reveals two different domains—one with a ratio below unity where the condensates do not form, and another with a ratio above unity where the condensates form spontaneously. Along the boundary between the two domains, where the ratio is one, the liquid-liquid phase transition occurs. The boundary evidenced critical values of interprotein distance (concentration) in condensates, and of condensate number in cells. For sufficiently short interprotein distances and sufficiently large condensate numbers, the heterogeneous structure of the cytosol was stable.

The emerging picture expands the image of the living cell by a complementary phenomenology. Although it may appear sketchy with respect to the complexity of the cell, it showed that the postulate of CD exchange may lead to a better understanding of cytosol structure, properties and functions. Also our model may remain open for quantum extensions about entanglement and decoherence [97]. With a few exceptions, the present picture is mainly phenomenological and sem-

iquantitative. Because, to quote von Neumann, "truth is much too complicated to allow anything but approximations". The Yukawa model of CD exchange between hydrated proteins is of genuine quantum nature (having some possible similarities to dye lasers); it is not an "epiphenomenon", and extends our understanding of the living cell by a novel perspective. At the same time, the results rise new questions, which open way for a more quantitative approach. Linking together the living state of matter and the water CD quasiparticles—if they exist—may bring deeper insight on a few more, but relevant, aspects in the foundations of life.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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