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Chapter 11

Investigating encounter dynamics of biomolecular reactions: long-range resonant interactions *versus* Brownian collisions

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Abstract. Self-organization of living organisms is of an astonishing complexity and efficiency. More specifically, biological systems are the site of a huge number of very specific reactions that require the right biomolecule to be at the right place, at the right time. From a dynamical point of view, this raises the fundamental question of how biomolecules effectively find their target(s); in other words, what forces bring all these specific cognate partners together in an environment as dense and ionized as cellular micro-environments. Here, we investigate the possibility that biomolecules, besides traditional Brownian motion, interact through long-range electromagnetic interactions as predicted from first principles of physics; long-range meaning that the mentioned interactions are effective over distances much larger than the typical dimensions of the molecules involved.

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Introduction

Progress in molecular and cellular biology is consistently linked to a better knowledge of the structure of, and functional interplay between, biomolecules such as DNA, RNA and proteins. Even though these building blocks of the living matter display no apparent systematic order, it is well known that all the relevant biochemical processes follow a precise time schedule, in other words display a dynamical order. Far from having anything to do with a chemical reactor, living cells host chemical reactions catalyzed by enzymes whose critical action accelerates by orders of magnitude the reactions rates of biomolecules via lowering of the free energy barrier (*i.e.* making them realistically feasible) (Garcia-Viloca et al., 2004). Likewise, DNA/RNA-interacting proteins (*e.g.*, helicases, polymerases, nucleases, recombinases) modulate essential transaction processes involving nucleic acids to achieve DNA duplication and repair, gene expression and recombination, with an astonishing efficiency. Such an astonishing efficiency raises a fundamental question from a physical point of view. With biochemical reactions mostly being stereospecific, two (or more) reacting partners have to come in close contact and exhibit a definite spatial orientation to initiate particular reactions. Then, how do the various actors in a given biochemical process efficiently find each other (*i.e.*, how does a protein effectively *recruits* the appropriate co-effector partner(s) or selectively connects with its DNA/RNA target(s) in a crowded cyto/nucleoplasm environment)? In other words, what kind of *physical forces* bring all these players at the right place, in the right order and in a reasonably short time to sustain cellular function and ultimately cellular life? The classical way to tackle these issues invokes Brownian motion. At physiological temperature, ubiquitously distributed water molecules undergo chaotic motion, colliding with larger/heavier fluid components. On the latter, the neat outcome from simultaneous hits is a force of both random intensity and direction. Hence, large molecules move in a diffusive way throughout the cellular spaces and sooner or later shall encounter their cognate partners. Is this truly a good answer to the problem formulated here? Many doubts arise when one tries to estimate diffusion driven activation for some of the biochemical processes mentioned above. In particular, it turns out that proteins are capable of finding their cognate partner 10 and even 100 times faster than predicted by Brownian diffusion rates (Stroppolo et al., 2001). On the basis of these results, many authors surmised that electrostatic effects could critically affect the time needed by two biomolecular partners to meet each other. Yet, while electrostatic effects are dominant only over very short distances, this is not the case for time varying fields; they might have (regarding typical molecular dimensions)

influence over very long distances. Let us sketchily discuss below why this is so.

1. Electrostatic and electrodynamic intermolecular interactions

Typical biomolecules (*e.g.*, proteins, nucleic acids) are electrically charged and have non-vanishing dipole moments [1]. So it is natural to consider the possible role that might be played in the above-mentioned dynamical organization by *electrostatic* intermolecular interactions. On this point, it should be stressed that significant progress has been made understanding interactions acting at a *short* distance, *i.e.* at a distance comparable with the typical size of bio-macromolecules (around 50 Å for typical proteins) or shorter (Cherstvy et al., 2008). But electrostatic interactions can principally also act at a long distance like in dipole-dipole or Coulomb interactions and, hence could *a-priori* play a role in the dynamical organization of biomolecular reactions in living matter. However, freely moving ions in intracellular water (cytoplasm) make the Debye length [2] smaller than 10 Å, shortening the action range of Coulomb and dipole interactions too. Moreover, the static dielectric constant of water, which is ubiquitous in living matter, is very large (~80) at room temperature implying a further reduction of the strength of electrostatic interactions. These are perhaps the reasons why intermolecular interactions acting at a long distance have been hitherto poorly investigated in biology. Nevertheless, though electrostatic interactions between charges/dipoles in the electrolyte of cell cytoplasm are exponentially damped with distance, Debye screening proves generally inefficient for interactions involving oscillating electric fields. In particular, it was experimentally shown that, when acted upon by an electric field oscillating at a frequency larger than ~250 MHz, an electrolyte in physiological-like conditions behaves like a pure dielectric (Fig. 1) (*i.e,* without conducting properties so that Debye screening – or more specifically skin effects – is no longer effective) (de Xammar Oro et al., 1992; de Xammar Oro et al., 2008).

In other words, charges/dipoles oscillating faster than a suitable frequency are not screened by any static electric charges and are thus able to exert long distance forces.

In this context, it should be also remarked that high-frequency electric fields are neither shielded by free ions nor weakened by the dielectric constant of water, which, beyond a few hundred of GHz, drops from the value of ~ 80 to about 4 (Ellison, 2007).

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[1] For example, the dipole moments of protein molecules such as hemoglobin, albumin, myoglobin and lactoglobulin were found to be very large, of the order of 200−1000 Debye units. These values should be compared with the dipole moments of small organic compounds, i.e., 3−5 D.

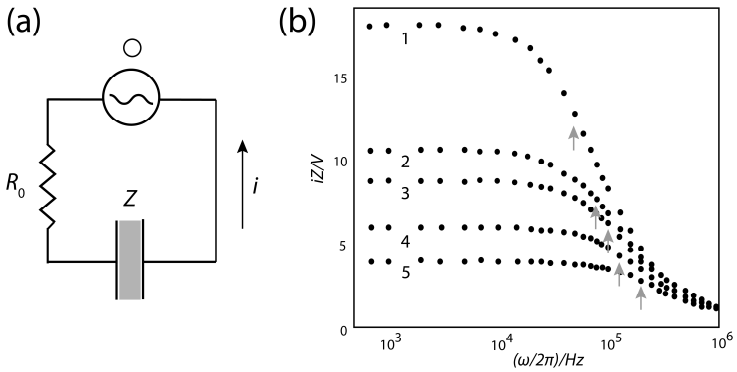

Figure 1. (a) Scheme of the experimental device to measure the frequency response of an electrolyte (Z) contained between the plates of a capacitor and (b) the impedance Z of the electrolytein experimental setting as a function of the frequency of the applied electric field according to (de Xammar Oro et al., 1992; de Xammar Oro et al., 2008).

All in all, one may legitimately inquire whether *electrodynamic* interactions do play a sizable role in the organization of biomolecular reactions, for example, as far as attractive interactions (negative potential) are concerned, by facilitating encounters of biomolecular cognate partners over long distances. In this case, this would imply that electrodynamic forces might have resonant properties so that a particular biomolecule would be only attracted by its specific target, and not by other neighbouring biomolecules. At this stage, we should remark that electrodynamic interactions are especially well known in quantum electrodynamics (QED) when occurring between two neutral atoms – or small molecules. In this case, *long-range* interactions have been shown to arise when one of the atoms is in an excited state, and the transition energies of both atoms are roughly similar, *i.e.*, at resonance (Stephen, 1964; McLachlan, 1964) (off-resonance conditions would lead to *short-range* interactions). This is the condition of exchange degeneracy implying that the atoms are in a quantum entangled state (Stephen, 1964; McLachlan, 1964). However, as entangled states are fragile (with lifetimes estimated around 10^{-10} s) their persistence over long distances (*i.e.,* larger than 50 Å) in the noisy environment of living matter could be questioned. Therefore, long-range quantum interactions between biomolecules are not very probable. On the other hand, electrodynamic interactions can be well derived classically (Preto, 2012; Preto et al., 2013). In this case, it can be shown, similarly to QED, that electrodynamic interactions are effective at a long-range only in resonant conditions. Here resonance means that the *dipole moments* of the two

molecules – due to conformational vibrations rather than electronic motions – oscillate with a common frequency.

2. Physical picture behind long-range resonant interactions

For the sake of clarity and to give the reader a rough picture about why frequency resonance can lead to dipolar interactions of a much longer range than off-resonance ones, it is worth recalling that the motion of two interacting molecules with oscillating dipole moments can be generally decomposed as the sum of two uncoupled motions of the interacting system. These collective motions, usually referred to as normal modes, are characterized by their own frequency (normal frequency) whose value, of course, strongly depends on the frequencies of each dipole taken separately. For a system of two dipoles exhibiting the same frequency, it can be shown (Preto et al., 2013) that normal modes correspond exactly to situations where dipoles oscillate in phase (attraction) and out of phase (repulsion) respectively (see Fig. 2).

In this case, by favoring one normal mode with respect to the other one, attraction or repulsion (according to which mode has been excited) can be expected to remain between both dipoles during a time much longer than the characteristic period of dipole oscillations. Thus, averaging the interaction energy over this period will eventually result in a net attracting or repulsing long-distance force between the two molecules. Of course, this result is mainly because dipoles oscillate with the same frequency.

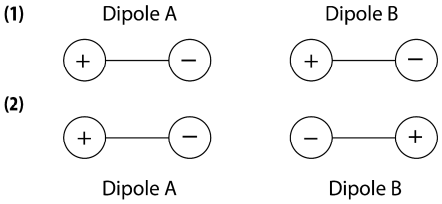

Figure 2. *Two normal modes of a system of two interacting dipoles A and B oscillating at the same frequency;* (1) symmetric mode characterized by attraction between the dipoles (in-phase oscillations), (2) antisymmetric mode characterized by repulsion (out of phase oscillations).

In the case of two molecules with notably different frequencies, in-phase and out-of-phase motions cannot bemaintained indefinitely. More specifically, it can be shown, when averaging over a period of dipole oscillations, that attractive and repulsive contributions balance exactly at first order, leading to second-order *short-range* interactions between molecules with amplitude comparable to standard van der Waals interactions of quantum electrodynamics (Preto, 2012; Preto et al., 2013). Coming back to dipolar interactions at resonance, it should be again emphasized that long-range interactions (strong attraction or repulsion) take place only if one normal mode is strongly excited (in other words, the interacting system should be in a quasi-stationary state characterized by phase locking). If not, this might lead to a situation similar to off-resonance where long-range attractive and repulsive contributions balance one another. From a biological point of view, it is thus of particular importance to investigate whether interactions between molecules of living cells can lead to the excitation of a particular collective mode of vibration. This point is discussed in details in the two upcoming sections.

3. Coherent collective excitation in biological systems

Long-range interactions between molecules and their possible role in a biological context were originally investigated by Fröhlich (Fröhlich, 1968; Fröhlich, 1977; Fröhlich, 1980). Herbert Fröhlich (1905-1991) was a distinguished theoretical physicist who started his research right after the formulation of quantum mechanics. He made important contributions to many fields of physics but he is mostly famous for providing the first successful explanation of superconductivity as the result of electron-phonon interaction. In the last 24 years of his life he turned to fundamental problems in biophysics developing a new fundamental idea known as "Fröhlich coherence". Fröhlich considered the extraordinary dielectric and polarization properties at the microscopic level of living matter, noting, for example, that the electric field of a cell membrane is in the order of 10^5 V/cm (very high indeed; and this value can even grow in proximity of proteins, nucleic acids, etc.). A major consequence is that non-linear effects may occur under such physical conditions of the cell membrane. Thus he developed a theory that took into account non-linearity, in particular, he considered that vibrations in polar systems – here the cell membrane – are accompanied by polarization waves generating an electromagnetic field that could mediate a long-range interaction and play the role of an ordering agent. The main idea is as follows: random vibrations are obviously an omnipresent kinetic property of matter, but order can emerge out of disorder if non-linearity is considered. In fact, non-linearity in a system of oscillators enables energy transfer between different normal modes of vibration. Energy may be

channelled from the high-frequency oscillators downward to the low-frequency oscillators. Energy supplied to a nonlinear open system is not immediately thermalized, but condenses in certain modes. Typical examples of strong excitation of particular normal modes in open systems are given by the Laser or by the Rayleigh-Bénard convective instability (where only a few degrees of freedom are excited that give rise to macroscopic collective behaviours). On the basis of general principles Fröhlich derived a system of rate equations that describe the time evolution of average occupation numbers in a collection of vibrational modes of model structures such as proteins or membranes. He considered mode-mode coupling, *e.g.*, of two molecules through the individual interaction of each mode with a heat bath. This interaction enables energy transfer between two normal (vibration) modes with different frequencies and the heat bath balances the difference in energy quanta. In that sense, a Fröhlich system displays the (open system) analogue of a Bose-Einstein condensation; since if the energy supply rate (coming from the environment) exceeds some threshold value then almost all the energy is concentrated in the lowest frequency mode of a vibration. In other words, it can be considered that almost all the components of the system *synchronize, i.e.* oscillate in a collective way, at the lowest frequency of the system's spectrum.

4. Coherent collective excitations and their relevance to long-range resonant interactions between biomolecules

Experimental evidence for the existence of collective excitations within macromolecules of biological relevance is available for proteins (Painter et al., 1982; Chou, 1985; Xie et al., 2002) and for polynucleotides (DNA and RNA) (Painter et al., 1981; Painter et al., 1982; Chou, 1984; Powell et al., 1987; Fischer et al., 2002) through the observation of low-frequency oscillations modes in the Raman and far-infrared spectra of polar proteins. These spectral features are commonly attributed to coherent collective oscillation modes of the whole molecule (protein or DNA) or of a substantial fraction of its atoms, which could be strong enough to be "felt" by other macromolecules from far away despite thermal noise. Applied to biomolecular dynamics, such coherent excitation could give rise to strong dipolar interactions between biomolecules that would be still active well-beyond Debye length provided that the dipole moments of molecules oscillate with the same frequency, as mentioned above. Moreover, let us remark that Fröhlich estimated on the basis of theoretical arguments (Fröhlich, 1968; Fröhlich, 1977; Fröhlich, 1980) collective vibrational modes of metabolically active biological systems in the frequency range of 0.1–10 THz. This is in line with spectral features of standard biomolecules

(Markelz Et al., 2002). In particular, it is seen that the range of relevant frequencies is larger than hundred of GHz, so that corresponding electric fields are hardly affected by the surrounding medium (Debye length and dielectric dispersion, see above).

Coming back to the theory of electrodynamic interactions, it should be stressed that Fröhlich emphasized, *inter alia*, that long-range interactions may occur at resonance even if the system of interacting dipoles is close to thermal equilibrium. Yet, after theoretical investigations and numerical estimates of electrodynamic interactions, we found the above statement to be incorrect: besides resonance, oscillating dipoles must be out of thermal equilibrium to interact effectively over long-distances (Preto, 2012; Preto et al., 2013). More explicitly, using elements introduced in section 2, it turned out that a system of interacting dipoles in thermal equilibrium gives rise to a situation where normal modes of the interacting system, characterized by in-phase and out-of-phase oscillations respectively, contribute the same way to the overall dynamics, hence cancelling out any long-range average effect of dipolar nature. Thus, an out-of-thermal-equilibrium condition, characterized by the strong excitation of a particular normal mode of the interacting system, is required so that net long-range attraction or repulsion can emerge between dipoles. From a biological point of view, the above-mentioned result raises a new question; namely, can biomolecules of living cells be subject of such energy redistribution in the space of modes? A possible answer is again provided by Fröhlich's theory (Fröhlich, 1968). In fact, the above reported condensation phenomenon, which is characterized by the emerging of the lowest frequency mode that contains nearly all the energy supply from the environment, can also be seen as an out of equilibrium energy distribution among normal modes of two interacting molecules. In biological systems, the environmental energy supply could be attributed to metabolic energy stemming, for example, from the hydrolysis of adenosine triphosphate (ATP) or guanosine triphosphate (GTP) as well as from ion collisions. In fact, recent works show that the presence of certain ions can enhance the rate of some biomolecular reactions, thus suggesting that these ions – through their collisions on specific sites of the concerned biomolecules – transfer external energy (Pingoud et al., 2009). On the other hand, it goes without saying that the mode of lowest frequency always corresponds to a configuration of *least energy*, which, in the case of two interacting polar molecules, is the mode characterized by a *strong attraction* (in-phase oscillations) as mentioned in section 2.

Thus, if a mechanism such as Fröhlich condensation (or more generally dynamic synchronizations) between molecules turns out to be effectively active in biological systems, this could imply long-range attractive interactions between biomolecules provided that the latter share common frequencies in their vibration spectra (Fig. 3).

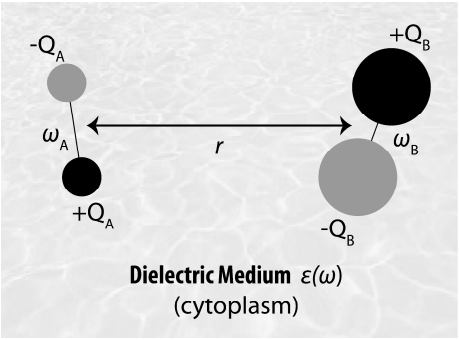

Figure 3. Scheme of two oscillating dipoles A and B in water. When both dipoles oscillate with a same frequency $\omega_A \approx \omega_B$, attractive or repulsive long-range interactions may set in provided that a normal (collective) mode of vibration of the interacting system is strongly excited; see Refs. (Preto, 2012; Fröhlich, 1977).

It is speculated that a variety of biomolecules share similar frequencies with their specific cognate partner (due to specific conformational analogies or complementarities that are crucial so that the chemical reaction actually takes place), which would result in lowering the encounter times between such molecules and thus in increasing the efficiency of particular biochemical reactions.

Table I presents a list of observed low-frequency modes in Raman spectra of different proteins. Characteristic features are also present in cells: some studies on Raman spectra of bacterial and mammalian cells revealed that metabolically active systems exhibit many Raman lines in the range of 0.1–10 THz, whereas these resonances were not observed in resting cells (Webb et al., 1977).

Since a large range of chemical reactions of biological relevance are to be expected for metabolically active cells in comparison to resting ones, such a result might be consistent with the presence of resonance effects influencing the encounter dynamics of biological cognate partners [3]. Rowlands reported of effects possibly coming from long-range interactions of the Fröhlich type. In particular, he reported that red blood cells, *i.e.,* erythrocytes (Rowlands et al., 1981; Rowlands et al., 1982) tend to array themselves in stacks, called rouleaux. Rowlands (Rowlands, 1983) found attractive forces to become apparent when red cells were at a mutual distance of about 4 μm apart or less.

[3] Note that these finding are also supported by the measured value of the ratio between the intensities of Stokes and anti-Stokes lines ($R \approx 1$) very different from the value which should be observed in oscillating systems in thermal equilibrium ($R \approx 0.55$) (Webb, 1980).

Protein	Molecular weight	Observed raman line (cm^{-1})
Insulin	5800 (monomer)	22
	11600 (dimer)	22
Ribonuclease A	13700	Not observed
Lysozyme	14000	25
β-Lactoglobulin	18000 (monomer)	25
	36000 (dimer)	25
α-Chymotrypsin	22600	29
Pepsin	35000	20
Ovalbumin	44000	22
Concanavalin A	55000	20

Table I. Observed Raman low-frequency mode in Raman spectra of standard biomolecules (Painter et al., 1981; Painter et al., 1982; Chou, 1984; Powell et al., 1987; Fischer et al., 2002).

Interestingly, the interaction between the cells is weakened or disappears, either when the cells are deprived of metabolic energy stores, or when their membrane is disorganized, or even when the quasi-static membrane potential is considerably lowered.

Another possibly relevant consequence of Fröhlich's coherence theory concerns (the still open) topic of interacting weak electromagnetic fields (EMF) within biological systems. In fact, Fröhlich's work inspired some experiments on the influence of millimeter waves EMF (10–100 GHz) on biological systems. We cite the works of Grundler and Keilmann (Grundler et al., 1977; Grundler et al., 1983) on growth of yeast cells irradiated with an EMF of 42 GHz with effects on cell division rates and compared to the non-irradiated control as well as the work of Belyaev et al. (Belyaev et al., 2000) on a resonant like dependence of chromatin conformational state of *E. coli* irradiated with a weak EMF with a frequency around 52 GHz. Possible explanations of these resonant-like effects of external EMF concern conformational effects on biomolecules which, in turn, would modify the endogenous fields generated by their low-frequency vibrations in the cellular environment.

5. Experimental feasibility of a direct detection of intermolecular long-range interactions

In spite of the above mentioned results, Fröhlich's ideas as well as the hypothesis that electrodynamic long-range interactions could be relevant to understand the complex organization of living matter at the molecular level

have, however, suffered from lack of clear-cut experimental evidence and, sometimes, from contradictory results. As a consequence, the approach has lost its attractiveness and sometimes has even been discredited. Moreover, the idea of a simple co-resonance on a single common frequency in the vibrational spectra of interacting molecules seems oversimplified, though justified for a preliminary investigation. Thus, what is the reason to put it forward again? First of all, long-range electrodynamic interactions have been experimentally induced between microscopic dielectric objects (plastic spheres of 1.43 μm diameter suspended in water) by means of intense optical fields (Burns et al., 1989) to excite their dipole oscillations. So, why dipole oscillations due to conformational vibrations of macromolecules should not do the same job? Then, another reason for a renewal of interest in this topic is due to a recent assessment of the feasibility of a yet unexplored strategy to experimentally tackle the question of a possibly active recruitment at a large distance of cognate partners of biomolecular reactions (Preto et al., 2012). It turns out that the present availability of advanced experimental techniques allows coping with an almost direct detection of these putative long-range interactions. Likewise, a feasibility study was based on simplified one-dimensional models describing the dynamics of the approach of a molecule A to a molecule B either under the condition of a random force only or the condition of a random force plus a deterministic long-range attractive force. The aim was to work out the orders of magnitude of the relevant physical parameters of a basic experimental situation, with the latter referring to a solution where a biochemical reaction takes place (Fig. 4).

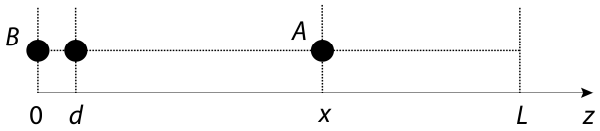

Figure 4. Molecules A and B are initially placed at a distance x. When they get closer than d they react together.

The results of the analytic computation of the average encounter time between A and B in the two mentioned conditions are given in Fig. 5, where the average encounter time is reported as a function of the initial distance *x*.

The physical values of *x* are considered in the interval 10–1000 nm corresponding to easily accessible concentrations C of molecules in laboratory experiments, that is, in the range 1 nM–1 mM (*x* is estimated as $C^{-1/3}$).

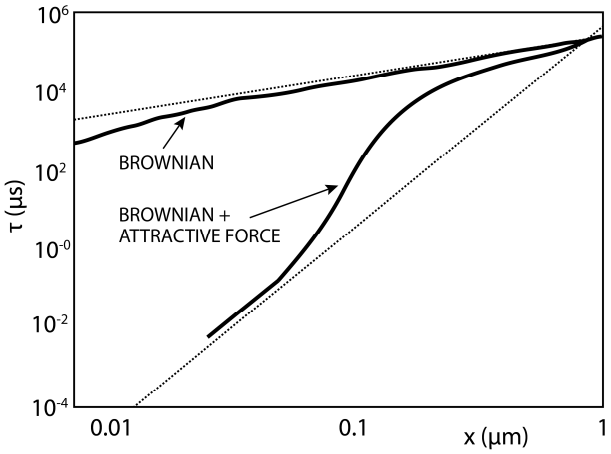

Figure 5. The average encounter time between molecules A and B is reported versus their initial speraration *x*. Dotted curves stand for asymptotic behaviours stemming from theoretical predictions (Preto et al., 2012).

The other physical parameters that enter the model (such as temperature, viscosity of the medium, hydrodynamic radii, molecular weights, and so on) are chosen as values typical for average sized proteins. The resulting mean encounter times – obtained with a given set of parameters – vary in the interval of hundred of milliseconds for $x \sim 1$ µm down to the microsecond for $x \sim 700$ Å. For the latter value of x, a purely random encounter time exceeds by four orders of magnitude the encounter time in presence of long-range attractive potential of the kind $U(r) \sim -1/r^3$.

The distance at which noticeable differences between encounter times of Brownian molecules and those of molecules driven by a long-range attractive force could be observed, may vary significantly depending on the actual value of a yet free parameter of the resonant potential.

6. Conclusions

We have addressed the longstanding problem of long-range recruitment of biomolecular reaction partners in living matter. The astonishingly efficient organization of the complex network of biochemical reactions inside the cell seems hardly understandable in terms of purely random encounters of biomolecules. On the other hand it seems unavoidable that the oscillating dipole moments of macromolecules activate (because of resonance) mutual and selective attraction forces as is predicted by the first principles of electrody-

namics. However, the lack of compelling experimental evidence has hitherto hindered substantial development of according ideas and intuitions that were put forward by Herbert Fröhlich more than forty years ago.

Thanks to powerful experimental techniques nowadays available, it becomes possible to investigate whether the encounters among interacting macromolecules are driven by Brownian diffusion or are accelerated by the presence of attracting forces: an ongoing collaboration between the Theoretical Physics Center (CPT) in Marseille and the Center of Immunology Marseille Luminy (CIML) is addressing this question thoroughly from both theoretical and experimental viewpoints. Preliminary experiments have already given very encouraging results.

Acknowledgements

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