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Experimental evidence for long-distance electrodynamic intermolecular forces

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Both Classical and Quantum Electrodynamics predict the existence of dipole-dipole long-range electrodynamic intermolecular forces, however these have never been hitherto experimentally observed. The discovery of completely new and unanticipated forces acting between biomolecules could have considerable impact on our understanding of the dynamics and functioning of the molecular machines at work in living organisms. Here, using two independent approaches, we demonstrate experimentally for the first time the activation

of resonant electrodynamic intermolecular forces. We characterize clustering transitions induced by these forces by fluorescence correlation spectroscopy when out-of-equilibrium conditions induce collective molecular oscillation observed by Terahertz (THz) spectroscopy. This is an unprecedented experimental *proof of principle* of a physical phenomenon that, having been observed for bio-macromolecules and with a long-range of action (up to 1000 Å), could be of importance for biology. Therefore, in addition to thermal fluctuations that drive molecular motion randomly, these resonant (and thus selective) electrodynamic forces may contribute to molecular encounters in the crowded cellular space. We anticipate our findings will provide a basis for future systematic deepening of physical aspects of the reported phenomena and for future systematic assessment of the relevance of electrodynamic forces in shaping the dynamics of biomolecular encounters and recognition in biology.

Introduction

Beyond the strong interest for fundamental physics of observing intermolecular dipole-dipole electrodynamic (ED) forces, this experimental study to detect these forces was highly motivated by their possible role at the molecular level in biology. Indeed, from a physicist's point of view, living matter offers a wealth of fascinating dynamic phenomena involving biomolecules (proteins and nucleic acids) organized in an intricate and complex network of biochemical interactions providing astonishing efficiency. In numbers, a single cell presents at any given time about 130,000 binary interactions between proteins (1, 2). The forces hitherto considered in biological contexts are of (quasi-) electrostatic nature (chemical-, and hydrogen-bonds, bare Coulomb, Van-der-Waals London, Hamaker-forces) and are limited to a range of action shorter than 10 Å due to Debye screening by small freely moving ions in the intracellular water. Such

interactions are relevant for stereo-specific, "key-lock" and "induced-fit" interactions at short distances but hardly effective to recruit distant molecules. Thus, understanding how the right molecule gets to the right place, at the right moment, in the right cascade of events of any biological action is one of the most striking challenges. Fundamentally, it is assumed that this network of interactions is dominated by random molecular diffusion throughout the cellular spaces in which, sooner or later, a molecule will encounter its cognate partners. However, free diffusion is considerably slowed down in a highly crowded environment (3) as in the case of the cell interior. Moreover, when diffusion measurements are performed in complex molecular organizations such as those of living cells, most of the biomolecules show anomalous rather than Brownian diffusion (4, 5). Furthermore, structuring of the cytosol into phase-separated domains (6, 7), substrate channeling of the metabolons (8), or long-distance interactions in DNA searching (9) and organization (10) have recently come to the forefront to question the discrepancy between the observed reaction rates in cells with the predictions of a strict random diffusion model (6, 11). Within this framework, dipole-dipole electrodynamic interactions are predicted to promote molecular attraction by being selective through resonance and to act over long distances (12). These forces can propagate without attenuation in electrolytes of ionic strength comparable to that in the cytoplasm, provided that their oscillation frequency exceeds few hundreds of MHz (13), since at such frequencies the Debye screening is ineffective (14). Therefore, we hypothesize that, in addition to random diffusion, selective long-range attractive electrodynamic interactions increase the encounter rates between A and B cognate partners through a mutual force field described by a potential $U(r)$ where r is the intermolecular distance. Then, after the Smoluchowski-Debye formula (15, 16), the association rate is given by $k_a^* = 4\pi R^*(D_A + D_B)$ where $D_{A,B}$ are their diffusion coefficients and R^* is given by

$$R^* = \left[\int_{R_A+R_B}^{\infty} \frac{e^{U(r)/kT}}{r^2} dr \right]^{-1} . \quad (1)$$

where R_A, R_B are the hydrodynamic radii of A and B , respectively; k is the Boltzmann constant and T the temperature. Remarkably, for an attractive interaction, $U(r) < 0$, Equation (1) implies $k_a^* > k_a = 4\pi(R_A + R_B)(D_A + D_B)$, that is, an increase of the association rate with respect to the purely diffusive k_a . However, electrodynamic macromolecular interactions have not previously been considered for several reasons, including: *i*) they have never been observed in any experimental context, though theoretically predicted by both Classical (12, 17) and Quantum Electrodynamics (18); *ii*) they require an out-of-equilibrium system, which though, of course, found in all living systems, is hard to organize in the laboratory *in vitro*, especially with molecules in metastable states with strongly excited giant dipole vibrations, as required for such interactions; *iii*) out-of-equilibrium collective vibrations of macromolecules are expected in the 0.1 – 1.0 THz domain, this is experimentally challenging to observe because of the strong absorption of water, and indeed such vibrations have only recently been detected for the first time (19). Interestingly, the coherence of these collective molecular vibrations is theoretically expected to be long-lived (20).

Here we demonstrate experimentally the activation of long-range attractive electrodynamic forces between proteins. This was made possible through the study of R-Phycoerythrin (R-PE), a protein that can be excited naturally by an external energy supply, a light source. Then, by working at different concentrations (i.e. intermolecular distances) and excitation power of a laser as the light source, we have achieved what follows: *i*) observation of the activation of collective intramolecular oscillation of the proteins, a necessary pre-requisite to activate the physical mechanism pictorially outlined in Figure 1a; *ii*) observation of a distributed-clustering transition dependent on activation of these collective molecular oscillations, as expected after a

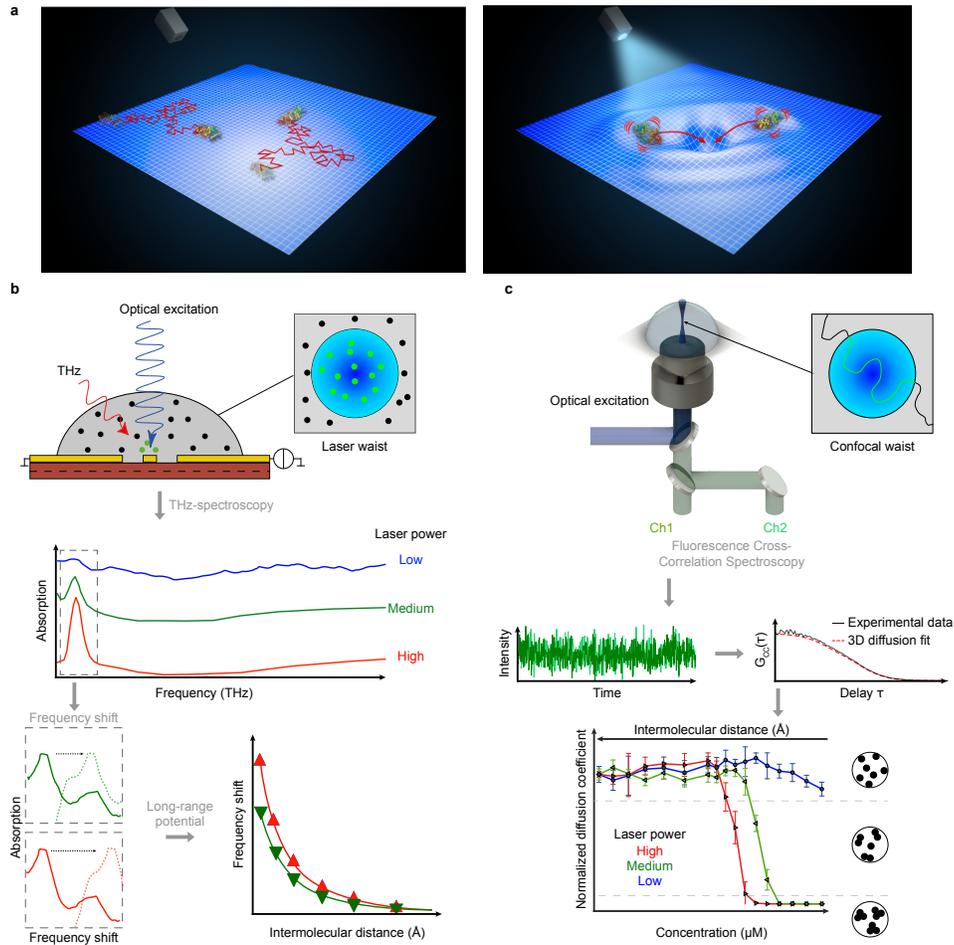


Figure 1: Long-range electrodynamic interactions - Principle and experimental approaches (a) At thermal equilibrium, macromolecules show a Brownian diffusive motion in solution (left panel). By switching-on an external energy source, molecules are in an out-of-thermal equilibrium collective vibrational state that can generate ED forces through associated large dipolar resonant oscillations (right panel). (b) In THz spectroscopy, the frequency of the collective vibration varies as a function of the average intermolecular distance (determined by the protein concentration). With respect to the reference frequency at "infinite" dilution, a frequency-shift inversely proportional to the cubic power of the average intermolecular distance is theoretically expected if the proteins interact through ED forces. (c) In FCS, the transit times of the proteins across the volume of observation are measured, hence the protein diffusion coefficients. Under out-of-thermal equilibrium conditions, the theory predicts a phase transition due to ED forces clustering proteins. This should be observed at a given protein concentration by a sudden drop in the diffusion coefficient from its Brownian value. In both (b) and (c), out-of-thermal equilibrium is activated by optical excitation.

thorough preparatory work (3, 21–23), and *iii*) the consequent expected change of the frequency of the collective oscillation (24). For this, two experimental techniques were used, THz spectroscopy and fluorescence fluctuation spectroscopy (Figure 1b,c). Overall, our experimental work supports a *proof-of-principle* that out-of-equilibrium collective oscillations are capable of activating dipole-dipole electrodynamic intermolecular forces, thus paving the way to explore the potential role of ED intermolecular forces in living matter.

Results

This first experimental study has been performed with a natural light-harvesting protein derived from red algae, the R-PE (see Figure S2 in (25)). This protein naturally contains a total of 38 fluorochromes, phycoerythrobilin and phycourobilin (the terminal acceptor of energy).

These pigments are highly sensitive to the $\lambda = 488$ nm light used in these experiments. By illuminating the R-PE molecules in saline solution each molecule can enter a coherent vibrational state (Figure 2) displaying similar phenomena to those reported for Bovine Serum Albumin (BSA) protein in (19): the existence of a threshold for the energy input rate to activate the collective mode, and a saturation of the oscillation amplitude at high values of the energy input rate. Two collective oscillation frequencies for R-PE are found. One at 0.071 THz (= 2.4 cm^{-1}) and another at 0.096 THz (= 3.2 cm^{-1}) (see Figure 3 (25)). Let us schematize the R-PE protein as a doughnut-shaped object of $M = 240$ kDalton, with a larger midline radius $R = 37.5 \text{ \AA}$, a minor radius $r = 30 \text{ \AA}$ (26), density ρ (the ratio between M and the volume of the torus), and Young elastic modulus E . The frequencies of the collective extension modes (those corresponding to oscillating larger radius R) are given by (27)

$$\nu_n = \frac{(1 + n^2)^{1/2}}{2\pi R} \left(\frac{E}{\rho} \right)^{1/2}, \quad (2)$$

whence the ratio $\nu_1/\nu_0 = \sqrt{2} \simeq 1.41$ which approximates within a 4% the ratio between

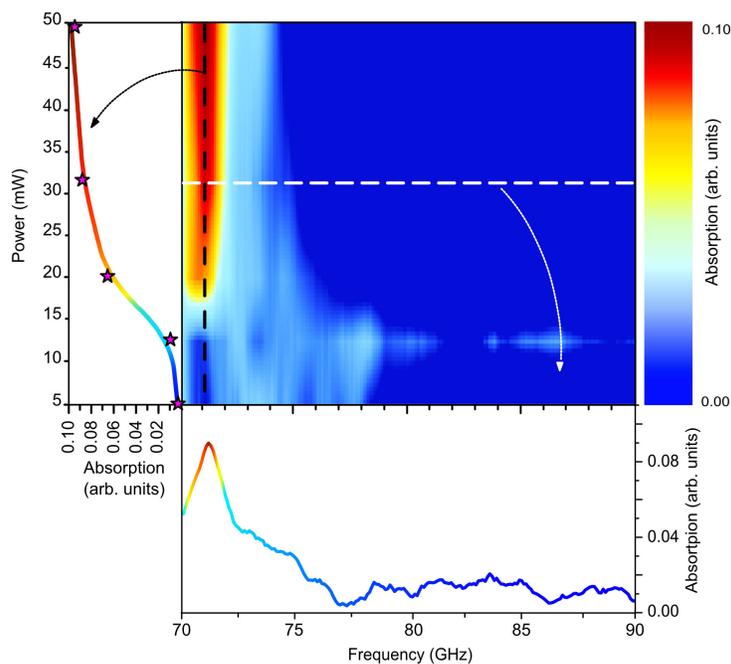


Figure 2: Collective oscillation of the R-PE measured by THz-Spectroscopy. Absorption strength of the R-PE (1 mg/mL in 200 mM NaCl) as a function of detection frequency and the laser power activating the molecular collective oscillation at a frequency of 71 GHz (2.4 cm^{-1}). The absorption line profile (bottom) indicated by the horizontal white dashed line was measured at an optical power of 31.5 mW, while the laser power threshold (left) behaviour is indicated by the black dashed line. Stars stand for experimental data.

the observed frequencies, that is $0.096/0.071 = 1.35$. The Young modulus of R-PE is not known in the literature, but by inverting the above formula we obtain $E \simeq 5.3 \text{ GPa}$ which seems reasonable knowing that at 300 K for Myoglobin $E \simeq 3.5 \text{ GPa}$, and for BSA $E \simeq 6.75 \text{ GPa}$ (28) (both proteins being mostly made of α -helices like R-PE).

A theoretically expected signature of attractive electrodynamic forces among macromolecules vibrating at the same frequency is a phase transition between a dispersed phase of rapidly diffusing molecules, and a clustered phase of very slowly moving aggregates of molecules (22) (see Supplementary Information). The control parameter of this transition is the average intermolecular distance, which is set by adjusting the molecular concentration.

In the fluorescence correlation spectroscopy (FCS) experiments, the protein concentrations

C have been varied in the interval between $0.1 \mu\text{M}$ and $10 \mu\text{M}$ to make the average intermolecular distance $\langle r \rangle = C^{-1/3}$ vary in the interval $550 - 1950 \text{ \AA}$.

The ionic strength of the protein solution is kept at 200 mM by means of suitable concentrations of NaCl in water. This ensures a good shielding of electrostatic interactions. Moreover, the laser power ($\lambda = 488 \text{ nm}$) has been varied between 50 and $150 \mu\text{W}$. Typical fluorescence traces are reported for different laser powers and protein concentrations in (25) (Figures 6 and 7).

The diffusion times τ_D determined from the Cross Correlation Functions (CCFs) of fluorescence traces, and the measured waist of the confocal volume where the molecules are both excited and observed, allow estimation of the diffusion coefficients D . The use of CCFs is motivated in sections Methods and in Additional Data by Figures 4 and 5 of Ref. (25). The values of the diffusion coefficient D are normalized with respect to the Brownian values D_0 of each data series recorded at a given laser power (Figure 3). At low laser power the measured value of D_0 matches the expected theoretical one $D_0 = k_B T / (6\pi\eta R_H)$, with η the viscosity of the solution, and R_H the hydrodynamic radius of the protein. At laser power of $50 \mu\text{W}$, the observed values of D (blue circles) do not change with the intermolecular distance. The diffusion of the R-PE molecules is Brownian for all the concentrations considered. This means that the energy input rate is either below the threshold value required to excite molecular collective vibrations, or the intermolecular ED forces are very weak because of the small amplitude of the collective vibrations of the R-PE proteins. The mismatch between the laser power values mentioned in Figure 2 for THz experiments and those reported above for diffusion experiments is due to the different volumes illuminated (see Methods in (25)).

At higher laser power, $100 \mu\text{W}$, obviously and consistently with a thermal effect, the measured value of D_0 at low concentration is larger than in the preceding case. However it cannot explain, in the interval of inter-molecular distances $700 - 750 \text{ \AA}$ (green triangles), the steep drop

of D/D_0 that correlates with the increase of the fluorescence fluctuations and a sudden increase of the diffusion time τ_D .

At the highest laser power considered, $150 \mu W$, again the steep drop of D/D_0 is observed but now in the interval of inter-molecular distances $900 - 950 \text{ \AA}$ (red triangles). In both cases, the steep drop of D/D_0 correlates with a strong increase of the fluorescence fluctuations and a sudden and huge increase by several orders of magnitude of the diffusion time τ_D .

The steep drop of D/D_0 and the increased amplitude of fluorescence fluctuations are the observable effects of a clustering phase transition stemming from the competition between the electrodynamic intermolecular attractive forces and thermal fluctuations. This is confirmed theoretically by a semi-analytical model, by Molecular Dynamics simulations and by Monte Carlo computations (see Supplementary Materials (25)). In Figure 3b two snapshots are shown of numerical Monte Carlo computations performed by considering long-range electrodynamic interparticle forces. Thus, the appearance of clusters predicted theoretically has been experimentally observed through the sudden enhancement of fluorescence fluctuation amplitudes and long transit times across the confocal volume of the FCS setup. Clusters of R-PE were visually evidenced by fluorescence microscopy (Figure 11 of Additional Data in Ref. (25) and Video in online Supplementary Material).

Increasing the laser power, the higher the power the stronger the collective oscillation of R-PE molecules and the larger the associated oscillating dipole moment. Hence the displacement of the clustering transition to a greater average intermolecular distance for the stronger molecular oscillations. Consistently, by suddenly lowering the power of the laser light supply in the clustered phase a rapid disaggregation of the clusters is observed, as shown in Figures 10 of Additional Data in Ref. (25).

All these results are a clearcut proof of the activation of electrodynamic intermolecular attractive forces due to the collective vibrations of the R-PE molecules.

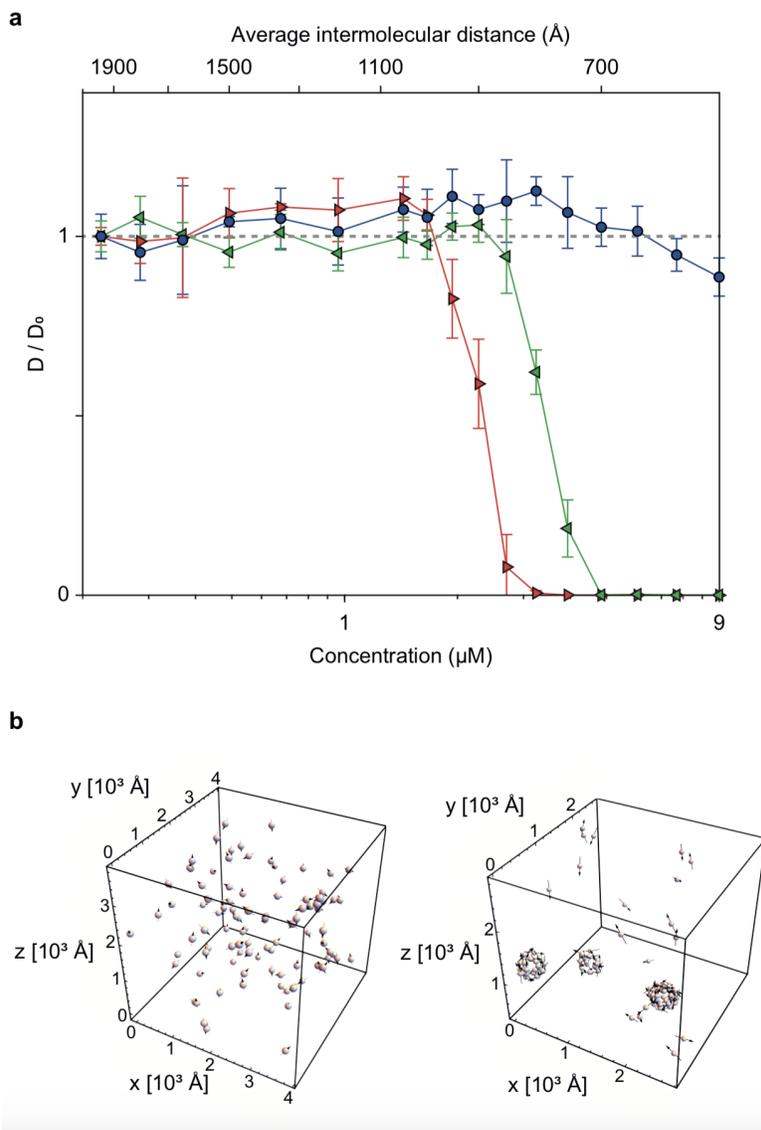


Figure 3: Effect of protein concentration and laser power illumination on R-PE diffusion: Clustering phase transition. (a) Diffusion coefficients normalized to the Brownian D_0 values measured for each data series at $0.223 \mu M$ ($\langle r \rangle \simeq 1950 \text{ \AA}$) and recorded at $50 \mu W$ (blue circles), $100 \mu W$ (green triangles), and $150 \mu W$ (red triangles). Each point corresponds to the average of 5 independent experiments. (b) Snapshots of numerical Monte Carlo computations involving long-range electrodynamic inter-particle forces obtained with different initial values of $\langle r \rangle$. With $\langle r \rangle_{initial} \simeq 1000 \text{ \AA}$ the system remains in the dispersed phase (lower left box) where $D/D_0 = 1$ (Brownian diffusion); with $\langle r \rangle_{initial} \simeq 950 \text{ \AA}$ the system switches to the clustered phase with D/D_0 very small (lower right box).

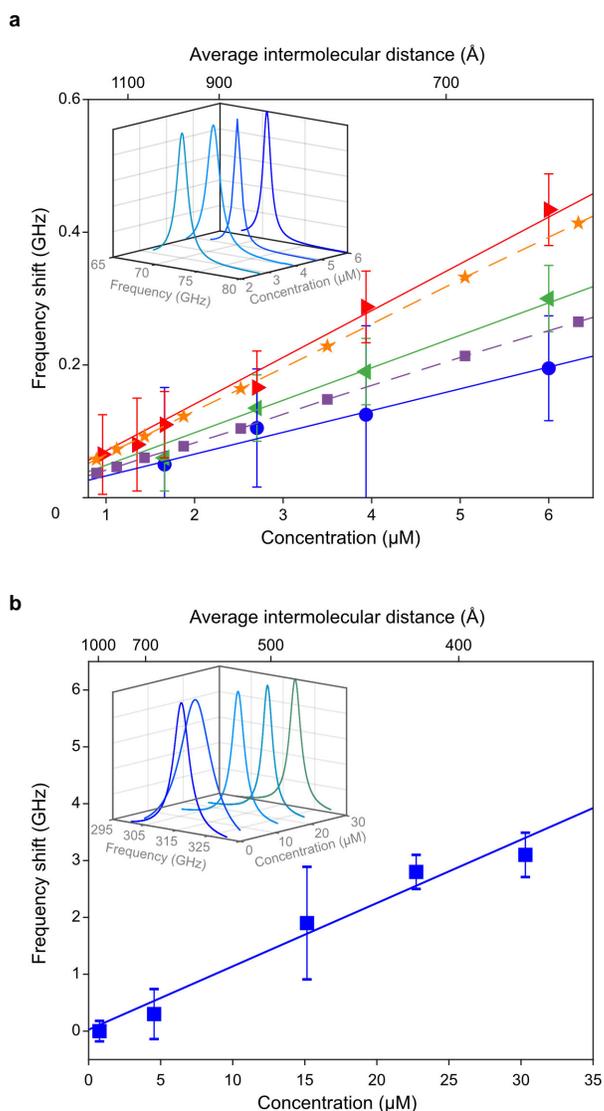


Figure 4: Frequency shifts of the intramolecular collective vibrations of R-PE and BSA at different concentrations. (a) Measurements for R-PE were performed at 30°C in 200 mM of NaCl. The shift is relative to the reference frequency measured at the lowest protein concentration. Measurements have been performed at different powers of the laser: 31.5 mW (blue circles), 39.5 mW (green triangles), 50 mW (red triangles). Purple squares and orange stars refer to theoretical outcomes worked out with different values of molecular dipole moments (see Supplementary Materials). (b) Measurements for BSA were performed at 30°C in 200 mM of NaCl at a laser power of 40 mW. Insets: Lorentz fits of the resonances as a function of concentration and for maximal optical power.

An independent confirmation of the activation of electrodynamic intermolecular attractive forces is obtained by measuring the shift of the collective vibrational frequency as a function of the concentration of molecules. Once again the proteins were observed in aqueous solution with the addition of 200 mM of NaCl to screen electrostatic interactions. In fact, theory predicts that electrodynamic dipole-dipole interaction between two molecules results in a shift $\Delta\nu$ of their vibration frequency from the unperturbed frequency ν_0 , shift proportional to $1/r^3$ with r the intermolecular distance (12). Remarkably, this law is preserved also for a large number of interacting molecules, that is, the frequency shift is proportional to $1/\langle r \rangle^3$ where $\langle r \rangle$ is the average intermolecular distance given by $\langle r \rangle = C^{-1/3}$ (see Supplementary Materials for the theoretical explanation (25)). The unperturbed vibration frequency ν_0 is operationally measured at very low molecular concentration. The shifts $\Delta\nu$ are then measured with respect to this value of ν_0 .

The collective oscillation frequency of the R-PE at 0.071 THz (i.e. 2.4 cm^{-1}) allowed to use as THz detector an electronic nano-device, namely a bow-tie antenna on the 2D electron gas layer of a FET transistor called a rectenna (29–33) (see Figure 1a of Methods in (25)). The measured frequency shift is found to follow a linear dependence on the protein concentration, that is, the experimental outcomes are in excellent agreement with the theoretical predictions (Figure 4a). The steepening of the fitted lines in Figure 4a as laser power is increased is also in agreement with expectations. This is because the increasing oscillation amplitude (entailing a larger oscillating dipole moment), results in stronger intermolecular electrodynamic interaction and hence a larger frequency shift (for theoretical details see Supplementary Materials (25)). The case of R-PE is especially important because two independent experimental approaches lead to the same physical conclusion: the activation of intermolecular electrodynamic forces acting at a long distance. Thus the possibility of artefacts or misinterpretations is ruled out. Importantly, these forces are not peculiar of the R-PE since they are also observed by making

measurements with another protein, BSA. BSA molecules were labeled with an average number of 5 fluorochromes AF488 5-TFP, covalently bonded to the Lysine residues, excitable by the light emitted by a diode laser at 488 nm. The reason for considering the BSA is twofold: first, the labeled BSA molecules, when continuously supplied by laser light at $\lambda = 488$ nm, are driven in a collective vibration mode at 0.314 THz (i.e. 10 cm^{-1}) (19); second, R-PE and BSA both have a structure composed largely of alpha-helices (Figure 2 in (25)), a property supposed to facilitate the activation of collective vibrational modes.

The collective oscillation frequency of the BSA at 0.314 THz required the use of a near-field microwire-based probe coupled with a wave-guide (see Figure 1b of Methods in (25)). Again, the measured frequency shift is found to follow a linear dependence on the protein concentration as expected (Figure 4b). This provides a remarkable confirmation of the activation of long distance electrodynamic interactions also for BSA.

It is worth pointing out that the two THz experimental setups have been operated at a different spatial density of the laser light, with respect to diffusion experiments, to prevent a clustering transition during the frequency shift measurements (see Methods in (25)).

Discussion

In the work presented here, we have experimentally shown, for the first time, that the excitation of out-of-equilibrium collective oscillations is capable of driving molecular association through the activation of electrodynamic intermolecular forces. R-PE provides convincing evidence for these forces using a pair of complementary experimental approaches. Thus, R-PE represents the “*Rosetta stone*” allowing us to identify attractive intermolecular forces through two completely different physical effects.

Long-range electrodynamic interactions have also been activated using a second protein, fluorescent dye-labeled BSA. These results confirm the generality of this phenomenon thus

paving the way for the experimental searching of ED forces in the more complex environment encountered in cell biology.

A central feature of the ED forces activated by collective molecular vibrations is their long-range property, that is, they stem from an interaction potential decreasing as the third inverse power of the intermolecular distance. This generates first-order phase transitions with the formation of molecular condensates. A thorough theoretical analysis of this transitional behavior, and of the frequency shift of the collective vibrations of the proteins, caused by their interaction through ED forces, can be found in Supplementary Materials.

By being dynamic and reversible, ED forces can be instrumental in structuring the mesoscale molecular organization through the formation of biomolecular condensates and thus provide a rationale to explain the speed of many cellular processes. While we have evidence of the association of biological macromolecules driven by ED forces *in vitro*, the conditions are far from the ones found *in cellulo*. Here, the energy sources necessary to maintain the molecules out-of-equilibrium need to be characterized. Among the potential candidates, there are: adenosine triphosphate (ATP) as a universal biological fuel, ionic currents such as those used to drive ATP synthesis, ionic collisions, photons produced by mitochondria, or external light. The notion of selectivity of ED forces will also need to be explored in a crowded environment composed of a vast diversity of molecular components. More specifically, it will be important to consider the possible role of ED forces between different molecular species (ligand-receptor, DNA-protein) co-resonating at one or more collective oscillation frequencies.

Moreover, our findings could be of general interest for methodological applications requiring a tight control in space and time of molecular interactions in living cells to decipher cellular functions. As an example, in the developing field of optogenetics where molecular interactions are switched on/off by engineered proteins controlled by light (34).

Further, ED forces could also be exploited in the domain of drug design. It has been hy-

pothesized that combining steric complementarity with “long-range complementarity” could improve therapeutic efficiency. Thus, ED forces could allow recognition at a distance and drive an efficient mutual approach between a drug and its therapeutic target before their final chemical binding (35).

Finally, throughout evolution, life has exploited all the available physical laws, processes, and phenomena. It is thus exciting to speculate how the new phenomenon reported here for the first time has been used to gain adaptive advantage and possibly overcome some of the adverse effects of molecular crowding in cells.

References

1. L. Bonetta, *Nature* **468**, 851 (2010).
2. K. Venkatesan, et al., *Nature Methods* **6**, 83 (2009).
3. M. Gori, I. Donato, E. Floriani, I. Nardecchia, M. Pettini, *Theoretical Biology and Medical Modelling* **13**, 13 (2016).
4. D. S. Banks, C. Fradin, *Biophysical Journal* **89**, 2960 (2005).
5. Y. Golan, E. Sherman, *Nature Commun* **8**, 15851 (2017).
6. S. Banani, H. Lee, A. Hyman, M. Rosen, *Nature Rev. Mol. Cell Biol.* **18**, 285 (2017).
7. J. Berry, C. P. Brangwynne, M. Haataja, *Reports on Progress in Physics* **81**, 046601 (2018).
8. L. J. Sweetlove, A. R. Fernie, *Nature Communications* **9**, 2136 (2018).
9. O. I. Kulaeva, E. V. Nizovtseva, Y. S. Polikanov, S. V. Ulianov, V. M. Studitsky, *Molecular and Cellular Biology* **32**, 4892 (2012).

10. J. Wang, *et al.*, *Briefings in Functional Genomics* **15**, 385 (2016).
11. I. Wheeldon, S. Minter, S. Banta, *et al.*, *Nature Chemistry* **8**, 299 (2016).
12. J. Preto, M. Pettini, J. A. Tuszynski, *Phys. Rev. E* **91**, 052710 (2015).
13. J. R. de Xammar Oro, G. Ruderman, J. R. Grigera, *Biophysics* **53**, 195 (2008).
14. J. C. Maxwell, *A Treatise on Electricity & Magnetism* (Dover Publications Inc., New-York, 1954).
15. P. Debye, *Transactions of The Electrochemical Society* **82**, 265 (1942).
16. R. M. Noyes, *Prog. React. Kinet.* **1**, 129 (1961).
17. H. Fröhlich, *Rivista Nuovo Cimento* **7**, 399 (1977).
18. A. Salam, *Molecular Quantum Electrodynamics* (John Wiley and Sons, Inc., New Jersey, 2010).
19. I. Nardecchia, J. Torres, J. Sturgis, M. Pettini, *et al.*, *Phys. Rev. X* **8**, 031061 (2018).
20. Z. Zhang, G. S. Agarwal, M. O. Scully, *Physical Review Letters* **122**, 158101 (2019).
21. J. Preto, E. Floriani, I. Nardecchia, P. Ferrier, M. Pettini, *Phys. Rev. E* **85**, 041904 (2012).
22. I. Nardecchia, M. Gori, E. Floriani, M. Pettini, *et al.*, *Phys. Rev. E* **90**, 022703 (2014).
23. I. Nardecchia, M. Lechelon, M. Gori, M. Pettini, *et al.*, *Phys. Rev. E* **96**, 022403 (2017).
24. S. Olmi, M. Gori, I. Donato, M. Pettini, *Scientific Reports* **8**, 15748 (2018).
25. See supplementary materials on science online.
26. W.-r. Chan, *et al.*, *Journal Molecular Biology* **262**, 721 (1996).

27. R. D. Blevins, *Formulas for natural frequency and mode shape* (Van Nostrand Reinhold Company, New-York, 1979).
28. S. Perticaroli, *et al.*, *Soft Matter* **9**, 9548 (2013).
29. M. Dyakonov, M. Shur, *Phys. Rev. Lett.* **71**, 2465 (1993).
30. W. Knap, *et al.*, *Journal of Applied Physics* **91**, 9346 (2002).
31. P. Nouvel, *et al.*, *Journal of Applied Physics* **106**, 013717 (2009).
32. M. I. Dyakonov, *Comptes Rendus Physique* **11**, 413 (2010).
33. F. Schuster, *et al.*, *Opt. Express* **19**, 7827 (2011).
34. D. Tischer, O. D. Weiner, *Nature Rev. Mol. Cell Bio.* **15**, 551 (2014).
35. N. Veljkovic, S. Glisic, V. Perovic, V. Veljkovic, *Expert Opinion Drug Discovery* **6**, 1263 (2011).

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Authors Contributions

M.L., Y.M., M.G. have been crucial for the success of the project. M.L. designed and performed all the experiments in Marseille regarding diffusion, he fixed the problem of operating the FCCS at high concentrations, and made the successful choice of the proteins to be studied. M.G. performed all the theoretical modelling and the related Molecular Dynamics and Monte Carlo numerical computations. Y.M., S.R. and A.K. carried out the experiments in Montpellier concerning THz-spectroscopy using the rectenna sensor and the micro-wire probe, both used for intramolecular collective vibration and frequency shift measurements. I.N. participated in the project from its very beginning many years ago paving the way to the present findings and suggested that ED forces could be detected through the frequency shift reported here. E.F. participated in the project from its very beginning and contributed the theoretical part of the paper. S.M. and D.M. gave fundamental support to perform the FCS and FCCS experiments. P.F., F.T. and L.V. participated in the project supporting it since its very beginning many years ago. J.S. contributed on the biophysical and biochemical aspects of the work. J.T., with the support of D.C. and S.R., conceived, designed and built the experimental setup in Montpellier and supervised the experiments. M.P., in quality of project leader, initiated this research many years ago and designed, supervised and intervened in all the theoretical and experimental aspects of the project. All the authors contributed to the discussion and to the analysis of the results. M.P. wrote the paper with the help of J.T., D.M., J.S., M.G., M.L., S.R., E.F., L.V..

Data Availability

The data that support the findings of this study are available from the corresponding authors upon request. Theoretical models to interpret the experimental outcomes, as well as videos showing the formation of clusters, are available in the online version of the paper.

Code Availability

The codes that are used in this study are available from the corresponding authors upon request.

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Competing interests

The authors declare no competing financial interests.

Supplementary Materials

Materials and Methods:

Theoretical Methods

Experimental Materials and Methods

Additional Experimental Data

Theoretical interpretation of the experimental results

Fig S1 - S22

Online also:

Movies S1 - S4