The long reach of dipoles

In 1950, the German physicist Herbert Fröhlich published a paper arguing that the phenomenon of superconductivity rested on the interaction between electrons and lattice vibrations. His analysis correctly predicted the so-called isotope effect — the inverse variation of the superconducting critical temperature and the isotopic mass of nuclei in the crystal. Fröhlich nearly arrived at the fundamental explanation for superconductivity, but fell just short, having never envisioned the curious process of Cooper pairing of electrons, which helped complete the BCS theory published in 1957.

Over several decades, Fröhlich's research explored the consequences of quantum coherence in many settings, including biology. In several speculative papers in the 1970s, he noted that biological cells and tissues have remarkable dielectric properties, sustaining strong electric fields, in particular, across cell membranes. In principle, he suggested, a cell driven away from equilibrium by some continuous source of energy would likely contain coherent electric fields able to support the existence of long-range order. Formally, he demonstrated how a collection of vibrational oscillators, driven away from thermal equilibrium, could enter a state possessing coherent order not completely unlike that of a Bose–Einstein condensate.

Fröhlich's idea has long been neglected in biology, in part because he put his argument in quantum terms, and simple arguments suggest scepticism about the relevance of quantum coherence in biological systems at room temperature. Moreover, traditional molecular biology emphasizes short-range interactions among molecules moving about mostly through diffusion — and long-range interactions have never been observed experimentally. This has now changed, however, after a twenty-year effort to observe effects of the kind Fröhlich envisioned.

In particular, researchers in a series of recent experiments have shown convincing evidence for long-range dipole–dipole attractive forces acting between proteins. Although not yet observed in a realistic biological setting, this confirmation of a 50-year-old conjecture could transform our view of the dynamics and control mechanisms available within living cells.

For the most part, the forces that biologists and chemists think about in biology issue from electrostatic forces, and lie behind things like chemical reactions, hydrogen bonds and van der Waals forces. They act only over short distances less than 10 Å or so, and get washed out over longer distances by Debye screening due to the rapid movement of ions in the water of the intracellular matrix. These kinds of interactions support much of ordinary molecular biology as we understand it, operating through binding and reaction between suitably matching molecular pairs.

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Pairwise interactions among particles over long distances are generally considered non-existent. Biomolecules move about in the cell mostly due to random diffusion, constrained of course by the boundaries of biological organelles and membranes. As a result, the crucial reactions supporting life come about in large part by chance, rather than because any long-range action brings them together. In principle, this may actually be the case. Yet Fröhlich's work of long ago suggests some other possibilities.

In several papers over the past decade, physicist Marco Pettini of the CNRS Centre of Theoretical Physics in Marseille and colleagues have developed a classical analogue of Fröhlich's original argument. They consider a classical system with many modes in contact with both a thermal bath and an external energy source. What their analysis shows is that, for sufficiently strong forcing, there is an effective condensation of the energy into the lowest frequency mode of the system. In effect, the source injects a flow of energy into the system, which eventually flows out into the thermal bath. Because the lowest frequency mode gives up its energy to the bath more slowly than higher frequency modes, energy should pile up (or 'condense') into the lowest frequency mode. The stronger the forcing, the stronger the condensation. (For this analysis and its experimental confirmation, see I. Nardecchia et al., *Phys. Rev. X* **8**, 031061; 2018.)

This general analysis has established the plausibility of Fröhlich-like long-range modes acting in bio-matter, and having nothing to do with quantum dynamics. Further recent work has established one likely manifestation of such general low-frequency modes to be long-range dipole–dipole interactions — attractions and repulsions are both possible — among specific biomolecules (see, for example, J. Preto et al., *Phys. Rev. E* **91**, 052710; 2015). Such interactions would arise under non-equilibrium conditions created by some energy source. Now, in a new paper, many of the same researchers have taken another step through observation of clear experimental evidence of such long-range electrodynamic interactions in a real system (see M. Lechelon et al., *Sci. Adv.* **8**, eabl5855; 2022).

Here the researchers report on experiments with photosensitive proteins in solution. With sufficiently strong laser light, they could excite dipole modes of the proteins, thereby pumping energy into the system, energy which should — according to the prior analysis — condense into a low-frequency collective mode. Spectroscopically, the team was able to detect these modes at 71 and 96 GHz — frequencies high enough not to be screened out in the solution. Adjusting the density of the proteins — and thereby, the typical intermolecular distance between them — Lechelon and colleagues then observed a dramatic transition. With large intermolecular distances (1,500 Å), the individual proteins followed ordinary diffusive motion. For distances smaller than about 900 Å, however, the long-range attractive dipole–dipole interactions instead triggered a more cohesive or 'clustered' dynamics tending to bring the proteins together. Here, finally, direct evidence of long-range attractive forces in an out-of-equilibrium system.

After a wait of some fifty years, this is the first solid evidence of Fröhlich's conjectured long-range forces in a biological setting. The setup is of course cleaner and simpler than the real biological world. But it seems hard to believe similar fundamental new forces won't be acting in messier and realistic settings. Through evolution, of course, biological organisms make use of any mechanism they can to gain an edge. It may only be a matter of time before we find ways in which biology has made use of this fundamentally new organizing force. ❐

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