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ABSTRACT

Understanding how proteins work requires a thorough understanding of their internal dynamics. Proteins support a wide range of motions, from the femtoseconds to seconds time scale, relevant to crucial biological functions. In this context, the term "protein collective dynamics" refers to the complex patterns of coordinated motions of numerous atoms throughout the protein in the sub-picosecond time scale (terahertz frequency region). It is hypothesized that these dynamics have a substantial impact on the regulation of functional dynamical mechanisms, including ligand binding and allosteric signalling, charge transport direction, and the regulation of thermodynamic and thermal transport properties. Using the theoretical framework of hydrodynamics, the collective dynamics of proteins had previously been described in a manner akin to that of simple liquids, i.e. in terms of a single acoustic-like excitation, related to intra-protein vibrational motions. Here, we employ an interacting-mode model to analyse the results from molecular dynamics simulations and we unveil that the vibrational landscape of proteins is populated by multiple acoustic-like and low-frequency optic-like modes, with mixed symmetry and interfering with each other. We propose an interpretation at the molecular level of the observed scenario that we relate to the side-chains and the hydrogen-bonded networks dynamics. The present insights provide a perspective for understanding the molecular mechanisms underlying the energy redistribution processes in the interior of proteins.

The detailed knowledge of internal dynamics of proteins is a prerequisite to understand their function. Due to their complex structure, proteins support a wide and varied spectrum of motions (in the femtoseconds to seconds time scale), related to essential biological functions that range from signal transduction[1,2] to enzymatic catalysis.[2] The sub-picosecond to picosecond time scale [i.e. terahertz (THz) frequency window] characterises the thermally excited low-frequency excitations, that can be divided into localised modes (e.g. fast vibrations of groups of side chain atoms such as methyl group librations), or collective modes (analogous to acoustic phonons in solids and collective dynamics in simple and complex liquids). The detailed description of these thermally excited modes is key, as they directly determine the vibrational partition function, and consequently the thermodynamic properties, of the system. Therefore, any change in the vibrational landscape of biomolecules, as in the case of interaction with ligands[3–5] or protein aggregation,[6] may have profound consequences on biological functional properties. As for the collective modes, they are describable as complex patterns of concerted motions of a large number of atoms throughout the protein,[7] and are suggested to play a significant role in controlling functional dynamical mechanisms, such as ligand binding and allosteric signalling, in directing charge transport and in influencing thermal transport properties.[4,7–12] Interestingly, collective vibrational modes are thought to largely contribute to the Boson Peak (BP) in proteins.[13,14] The BP is a widely debated spectral feature common to all disordered solids, describing an excess vibrational density of states located at ~2–4 meV, which has been related to acoustic dispersion curves[15] and their hybridization with modes localized around nano-heterogeneities.[16] In proteins the BP was found to be associated with the local rigidity and connected

with the size of the protein secondary structural motifs.[13] While short-wavelength collective dynamics are believed to play a crucial role, our understanding of their relationship with biological activity remains incomplete.

The key quantity for the characterization of the protein collective dynamics is the dynamical structure factor $S(Q,E)$, that can be measured as a function of the momentum and energy $(\boldsymbol{Q},E)$ transfer, using inelastic neutron or X-rays spectroscopies (INS and IXS). In $S(Q,E)$, the collective modes appear as inelastic features in the tails of the quasi-elastic peak. The high structural and dynamical complexity of biomolecules makes very challenging the exploitation of the experimental approaches. Indeed, inelastic spectroscopies have usually a finite energy resolution showing rather long tails (IXS) and a limited accessible dynamic range (INS), and in addition do not permit to easily single out the protein signal from that of its hydration water. Thus, these techniques have been employed only in a limited number of cases for proteins,[17–23] so that research in this field can be considered still in its early stage. In these cited works, the collective dynamics of proteins have been described in a similar way as those of simple liquids – that do not support transverse excitations-using the theoretical framework of hydrodynamics: the inelastic spectrum has been analysed using a single acoustic-like excitation, attributed to intra-protein longitudinal collective vibrational motions.

However, in contrast to this mainstream interpretation, INS[24] and MD simulations studies[25,26] suggest that the collective dynamics of proteins could significantly differ from the scenario outlined above, being characterized by the presence of additional modes. Notably, in a different biological system, namely phospholipid membranes, the first and oversimplified interpretation of the THz collective spectrum in terms of a single liquid-like acoustic mode has been revisited thanks to results from MD simulations[27] and spectroscopic measurements:[28,29,33] the proposed rich landscape of phonon excitations has been related to passive transport across membranes, thus providing a notable connection between collective dynamics and function.[28]

Here we present an extensive MD-based investigation of the collective dynamics of the Maltose Binding Protein (MBP), a two-domains protein (370 aminoacids), chosen as a model for globular proteins. Unlike the inelastic scattering spectroscopy investigations based on the $S(Q,E)$,[17–22] here we investigate the behaviour of the longitudinal $C_L(\boldsymbol{Q},E)$ and transverse $C_T(\boldsymbol{Q},E)$ current correlation spectra. In particular, calculation of $C_T(\boldsymbol{Q},E)$ allows us to reliably ascertain whether the system supports transverse dynamics, a quantity not experimentally accessible. By jointly analysing these spectra in terms of an interacting phonon model, we propose a consistent picture of the short-wavelength collective dynamics of MBP, that accounts for the presence of multiple and possibly coupled excitations. This picture, which significantly differs from previous research and can be representative of the behaviour of other globular proteins, is expected to impact our understanding of the dynamical mechanisms in the THz region at the basis of the biological activity.

We have carried out herein simulations of a crystal-like sample of MBP in its ligand-free conformation at a hydration level of $h = 0.42$ (g of water/g of MBP), close to that often used in inelastic scattering experiments,[30] and at 150 K. This low temperature has been chosen in order to reduce the protein and solvent molecular mobility and to limit the high-temperature-induced broadening of the linewidth of the modes. However, we note that in the low Q limit ($Q < 1$ Å^{-1}), the results of the present study can be reasonably extended to physiological conditions, as the collective vibrational properties of proteins are not expected to change significantly as temperature increases.[20,22] In particular, the vibrational density of states of MBP at low and room temperatures are practically coincident for $E > 3$ meV,[14] i.e. the range relevant to present investigation. According to molecular dynamics simulations, it has been suggested that at 300 K, ~99.5% of the modes in a protein behave harmonically.[3,31] If this assumption holds true, the collective dynamics of the protein will remain unchanged at 150 K as it is at 300 K.

To specifically probe the intra-protein collective dynamics, we have singled out the contributions to the $C_\alpha(Q,E)$ $(\alpha = L,T)$ spectra from the protein in the $0 < E < 50$ meV and 0.2 Å^{-1} $< Q <$ 1.9 Å^{-1} range. This is one of the main advantages of simulations compared to experiments for which separating the signal of the solute from that of the solvent is a challenge that requires complex data analyses and assumptions and, in the case of INS, measurements performed on completely deuterated protein samples. $C_\alpha(Q,E)$ can be defined through their associated current functions $\boldsymbol{J}_\alpha(Q,t)$ as $C_\alpha(\boldsymbol{Q},E) \equiv \langle \boldsymbol{J}^*_\alpha(\boldsymbol{Q},t)\cdot\boldsymbol{J}_\alpha(\boldsymbol{Q},t)\rangle$, where $\boldsymbol{J}_L(\boldsymbol{Q},t) \equiv N^{-1/2}\sum_i \hat{\boldsymbol{Q}}\big(\hat{\boldsymbol{Q}}\cdot\boldsymbol{v}_i(t)\big)\exp\left[-j\boldsymbol{Q}\cdot\boldsymbol{r}_i(t)\right]$ and $\boldsymbol{J}_T(\boldsymbol{Q},t) \equiv N^{-1/2}\sum_i \hat{\boldsymbol{Q}} \times \boldsymbol{v}_i(t)\exp\left[-j\boldsymbol{Q}\cdot\boldsymbol{r}_i(t)\right]$, where $\hat{\boldsymbol{Q}}$ is the unit vector along $\boldsymbol{Q}$, $\boldsymbol{r}_i(t)$ and $\boldsymbol{v}_i(t)$ are the positions of atom i and N is the total number of atoms. A collective mode appears as a peak in the $C_\alpha(Q,E)$ spectra and its dispersion curve can be determined by reporting the energy of this peak as a function of Q. $C_\alpha(Q,E)$ were calculated for each given Q, considering an isotropic average (see supplementary material).

In Fig. 1 we report the $C_L(Q,E)$ and $C_T(Q,E)$ spectra for the carbon atoms, monitored as reporters of the protein dynamics. Such a description aims at achieving a reduction of the complexity in the interpretation of correlated motions while capturing the relevant motions. Figure 1(a) shows that in the low Q region, both $C_L(Q,E)$ and $C_T(Q,E)$ exhibit a distinct peak, with its center converging toward $E = 0$ as Q approaches zero. This characteristic behavior is indicative of a propagating mode. This result unambiguously indicates that proteins support both longitudinal and transverse acoustic-like collective excitations. For $C_L(Q,E)$ the low-Q peak is very broad and, from inspection of the spectra at higher Q, it is clear that at least two collective excitations – well separated in energy-contribute to it. At higher Q, $C_T(Q,E)$ atypically broadens out too, again pointing to a scenario where more than a single mode characterises the collective dynamics. By focussing on the high (Q,E) range ($Q = 1.2 - 1.9$ Å^{-1}, $E = 20 - 50$ meV) additional longitudinal and transverse collective optical excitations are clearly observed (at ~30 and ~ 40 meV), despite their low intensity. Thus, a first purely qualitative inspection of the spectra reveals a high complexity in the protein collective dynamics. The most prominent excitations at each Q can be detected by normalizing each spectrum to its maximum [Fig. 1(b)]. Such a representation highlights indeed the fact that at low Q (below ~0.6 Å^{-1}) both $C_\alpha(Q,E)$ are dominated by a sharp acoustic excitation, while at higher Q optical-like branches prevail.

In such a multicomponent vibrational landscape, the most general description has to carefully consider the total number of excitations and their coupling. Actually, anharmonic interactions and/or structural disorder, universal features of disorder systems

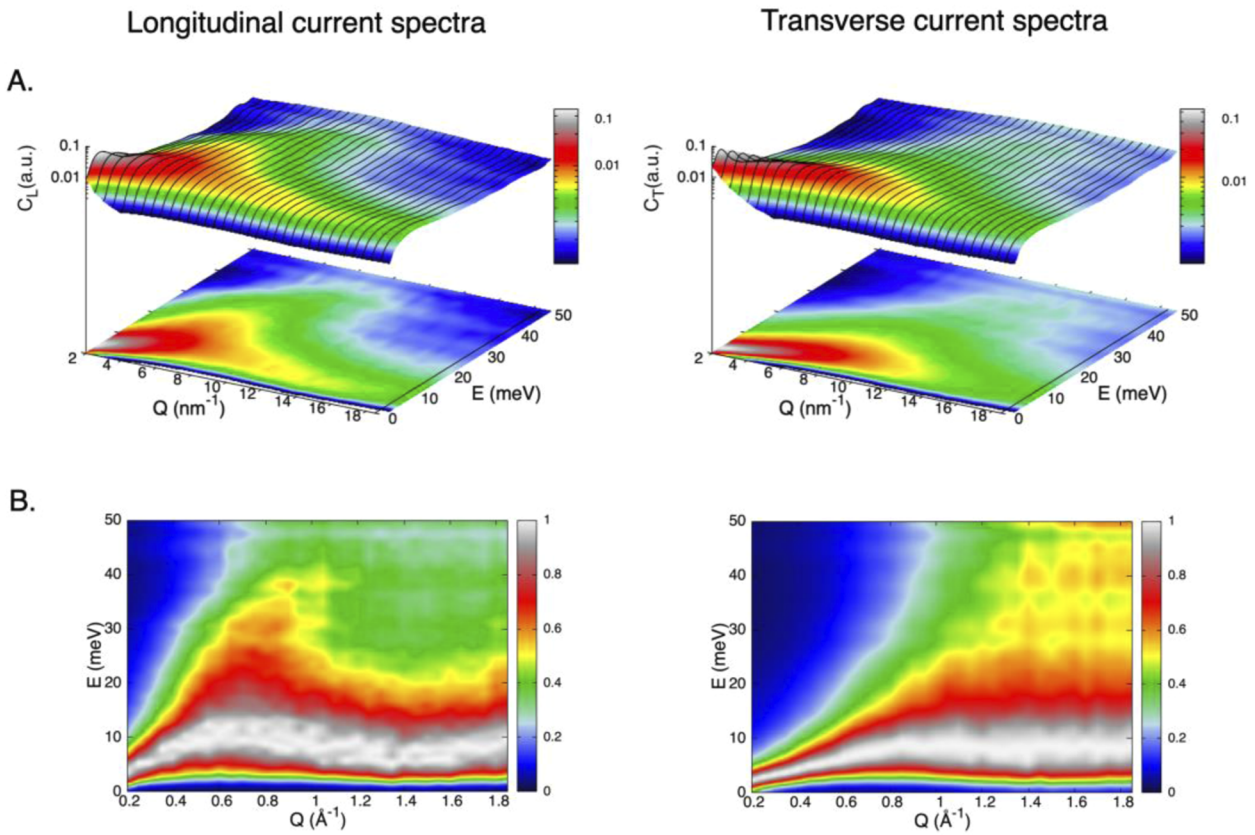

FIG. 1. $C_L(Q,E)$ (left) and $C_T(Q,E)$ spectra (right) of the protein C-atoms [panel (a), top] are projected in 2D contour plots [panel (a), bottom], also shown in a normalised representation [panel (b)], as detailed in the text.

such as proteins, are expected to play a defining role in determining their collective dynamics, causing – inter alia - a strong damping and a large mixing of the longitudinal and transverse symmetry of the modes.[32,33] Then, the interaction between optic-like and dispersive modes with mixed character is expected to give rise to an avoided crossing of the dispersion relations, with an oscillator strength transfer between the two modes and an exchange of their character.

In our previous work, we have indeed shown that three excitations with a mixed symmetry character contribute to the $C_\alpha(Q,E)$ spectra in the low Q region: however, our analysis did not account for the interaction between these modes.[26] This interaction is, on the contrary, described by means of the interacting phonon model here applied,[34] that has been recently exploited to describe the vibrational landscape of biological and inorganic systems[33,35,36] and the heat capacity Boson peak (BP)-like anomaly.[37] The adopted model includes an elastic line plus a phonon-like contribution based on a Hamiltonian consisting of (i) a non-interacting term (N harmonic oscillators), (ii) a term representing the damping of modes due to disorder and/or anharmonic interactions and (iii) a term accounting for mode-mode interaction (see supplementary material for details). Thanks to the simultaneous analysis of the $C_\alpha(Q,E)$ spectra (with different amplitudes for the L,T symmetries), we could unravel the mixing of longitudinal and transverse dynamics. The model allows us to determine the energies of the non-interacting system (referred herein to as *bare* energies) and the energies of the effective collective excitations with the interaction term accounted for (referred to as *dressed* energies). The dressed energies are here defined as the modulus on the complex plane of the poles of the Green functions generating the dynamic structure factors.[34] The model response function produced overall a good and stable fit with four modes ($E < 25$ meV, $Q < 1$ Å^{-1}; Fig. S1 in the supplementary material).

In Fig. 2 the dispersion curves of the dressed and bare collective modes are reported. As for the bare energies [coloured lines in Fig. 2(a)], at low Q values, our analysis reveals (1) a linearly dispersive mode that describes the propagation of the longitudinal sound (j = 1, mode named LA); (2) a dispersive low-energy mode that can be related to a transverse acoustic branch (j = 2, referred to as TA); (3) two optic-like modes that take an energy value of about 10 and 14 meV when extrapolated to zero (j = 3, 4, named O-low and O-high). The mutual interaction has been included only for modes j = 1, 3, 4 to limit the number of fit parameters. The low-Q trend of the dressed modes has been obtained by a smooth extrapolation to $Q = 0$ of the bare frequencies. Most importantly, the applied

interacting model reveals two avoided-crossing events in the dressed modes [black lines in Fig. 2(a)]: (1) a strong anti-crossing between the LA branch and the O-low mode at $Q_I \approx 0.3$ Å^{-1} and (2) a weak anti-crossing between LA and the O-high mode at $Q_{II} \approx 0.7$ Å^{-1}. Importantly, in correspondence to both the avoided crossings a transfer of the intensity from the acoustic phonon to the optical phonon is observed, with the latter becoming much more visible in the spectra [Fig. 2(b)]. In particular, the symmetry-dependent amplitudes [Figs. 2(b), S1, and S3 in the supplementary material] show: (1) an abrupt increase (decrease) for the O-low mode (LA mode) in the 1 ⇔ 3 mode interaction; (2) an increase for the O-high mode in correspondence of the 1 ⇔ 4 mode interaction. At Q_I, a large gap between the dispersion curves opens, indicating a strong interaction between the modes while at Q_{II} the interaction is marginal; additionally, the phonon lifetime of the LA mode is reduced ($\tau = \hbar/\Gamma/2$, $\tau = 0.45$ ps at $Q = 0.24$ Å$^{-1} < Q_I$, $\tau = 0.29$ ps at $Q = 0.31$ Å$^{-1} > Q_I$, see supplementary material), suggesting a strong suppression of the thermal conductivity k.[38] Indeed, according to kinetic theory $k = C_V v_g l/3$, where C_V is the volumetric heat capacity, v_g is the phonon group velocity, and $l = v_g \tau$ is the phonon mean free path, τ being the phonon lifetime.[38] Notably, a very low value for the thermal conductivity (~0.2 W m^{-1} K^{-1}) is found experimentally[39,40] and theoretically[41–43] in proteins.

Interestingly, the TA branch shows a flattening at $Q \approx 0.5$ Å^{-1} and at $E \approx 4$ meV, and a considerable softening at higher Q, a behaviour that can be traced back to the interaction with the O-low mode [see Figs. 2(a) and 2(b)]. At approximately the same energy, a Boson peak (BP) emerges in the $S(Q,E)$ of hydrated MBP.[14] As a consequence, here the BP can be ascribed to the hybridization of localized low-energy optical modes and transverse acoustic phonons, similarly to what has been observed in inorganic crystals:[37] this avoided crossing mechanism generates a pseudo-van Hove singularity in the acoustic phonon branches, i.e. the energy at which band flattening, $dE/dQ = 0$, occurs. Although the excitations emerging from this hybridization have a diffusive or utmost ballistic character more than a propagating one, they are believed to contribute to biomolecular heat diffusion by concurring to change the energy migration.[44] A linear correlation between the Boson peak frequency and the energy of the soft optical-like modes has been also reported in the phonon spectrum of host-guest crystalline solids with avoided crossing.[45]

Overall, these findings reveal that the coupling between modes leads to a remarkable redistribution of the vibrational energy. In the following we will provide an interpretation of the associated collective dynamical behaviours, by means of a careful correlation to the structure of the studied MBP and an evaluation of the origin of the modes.

The first anti-crossing point corresponds to an intramolecular distance $D_I \approx \frac{2\pi}{Q_I} \approx 20$ Å and matches the hierarchical structure level of the inter-domain correlations $\left(0.25 < Q < 0.5 \text{ Å}^{-1}\right)$.[46] Indeed, a peak at about $Q = 0.3$ Å^{-1} has been observed in the diffraction spectra of MBP,[47] reflecting the structural correlations of its two N-terminal and C-terminal domains flanking the ligand-binding cleft. The LA mode can be interpreted as a collective vibration spanning the whole protein. On the other hand, the spectra of C atoms of methyl groups (CH_3), which can be considered as reporters of side-chain dynamics,[48] are dominated by an optic-like excitation at ~10 meV, close to the energy of the O-low mode (Fig. 3). This finding suggests that the first anti-crossing event arises from the dynamic coupling between elastic waves propagating through large regions of the protein and the optical vibrations originating in the protein side-chains.

A similar anti-crossing behaviour is suggested also for protein hydration water by MD simulations and INS experiments,[26,49] thus supporting the hypothesis of a vibrational protein-solvent coupling.

The second anticrossing point corresponds to a distance $D_{II} \approx \frac{2\pi}{Q_{II}} = 9$ Å and lies in the same region of a broad peak in the structure factor of MBP[24] and several other proteins[19,50] $\left(0.6 - 0.7 \text{ Å}^{-1}\right)$, that can be attributed to the correlation between intra-domain secondary structures.[24,46] As for the origin of the O-high mode, our analysis showed that an optic-like mode at ~14–15 meV clearly emerges only for the heavy atoms involved in hydrogen bonds (HBs) (see Figs. 3 and S4 in the supplementary material), which is not found for the not-HB selection (Fig. S5 in the supplementary material). Low frequency bands at ~12–19 meV have been observed in proteins, and assigned to HB collective motions.[51–54] We interpret the second anti-crossing phenomenon as due to the interaction between the LA mode and the HB sustained optic-like excitations within secondary structures.

In the present picture, in the mesoscopic Q range ($Q > Q_{II}$) the protein collective dynamics is thus characterized by a strong redistribution of the vibrational energy and a non-propagating behaviour, in analogy to other disordered systems such as quasicrystals[55] and glasses.[56,57] This range corresponds to a spatial distance where the structural disorder comes into play and the systems can no longer be described as isotropic elastic solids within the continuum description.

In conclusion, the main findings of our study reveal that (1) longitudinal and transverse acoustic-like modes with a mixed-symmetry character propagate in proteins and that (2) the LA mode interacts via avoided-crossing mechanisms with two low-energy optic-like modes, here attributed to the side-chains and to the HB structure, both significantly influencing the collective dynamics of the whole protein. The interactions between modes via avoided crossing events give rise to energy flow pathways through optic-like vibrational states, possibly affecting the mechanisms of thermal transport in proteins. As for the biological functionality, the correlation between side-chains seems key for the transmission of allosteric signals, even in the absence of significant backbone motions,[58] while, the collective dynamics of HB-connected atoms, spanning the entire protein structure and interacting with the solvent,[59] may play a role for protein activity and stability. Very interestingly, the H-bond connectivity has been found to govern thermal transport and modulate the energy transfer efficiency between residues or helices in proteins.[60,61]

Most importantly, our work suggests that the previous interpretations of protein collective dynamics in terms of a single longitudinal mode,[17–22] as for simple liquids, may have described the most prominent excitation and have thus provided an oversimplified description of indeed very complex collective motions. The scenario proposed by the present Molecular Dynamics simulation study calls for experimental verifications, and can thus be considered preparatory for the challenging experimental studies on protein

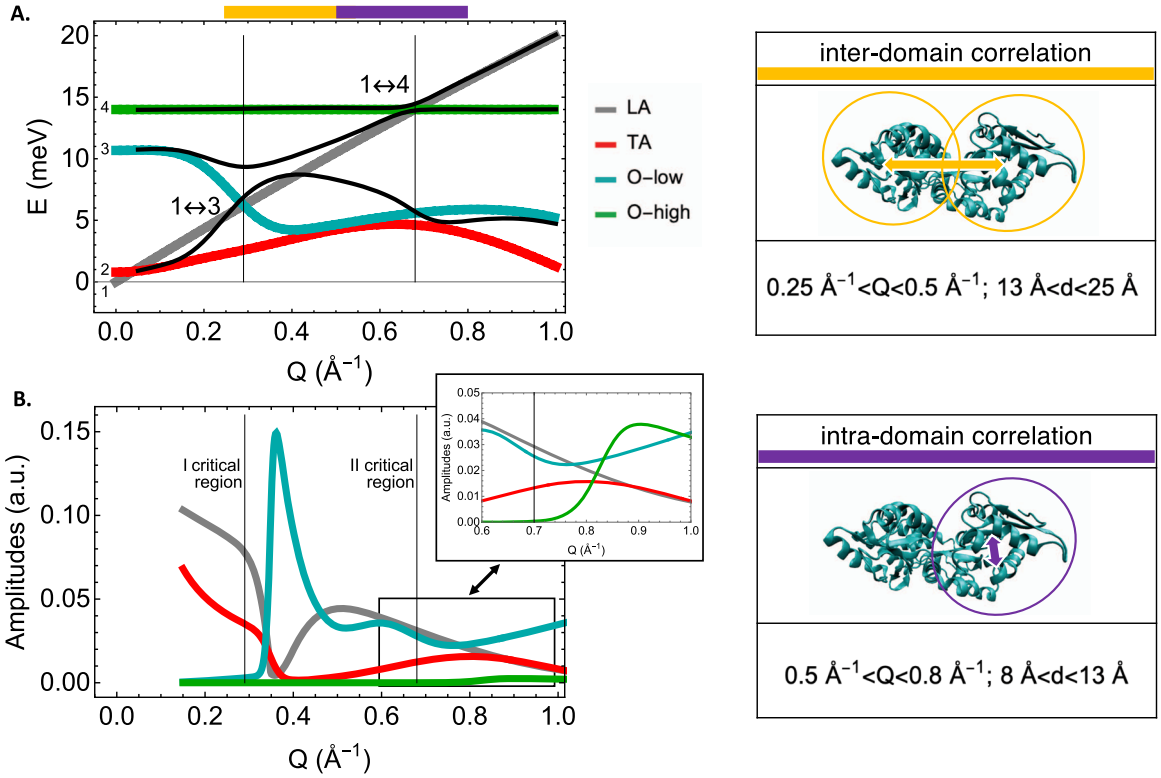

FIG. 2. (a): Dispersion curves of the protein collective modes: dressed and bare excitation energies (black and coloured lines, respectively). Vertical lines are drawn in correspondence of avoided-crossing points. (b): Amplitudes obtained from $C_L(Q,E)$ fits. The inset shows an enlarged view of the range $Q = 0.6 - 1.0$ Å^{-1}, where the amplitude of the O-high mode has been rescaled to better appreciate its trend. Right panels: Cartoon representation of the MBP protein, highlighting the relevant length scales of this study.

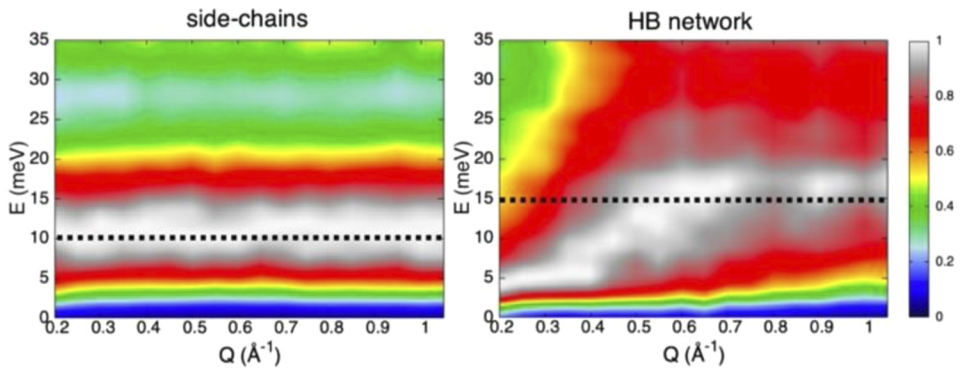

FIG. 3. $C_L(Q,E)$ spectra of the C atoms of the methyl groups, representative of the dynamics of the side-chains (left) and of protein heavy atoms involved in hydrogen bonds (right), shown in a normalised representation.

collective dynamics e.g. by means of an integrated approach of different techniques, such as far-IR, inelastic and time-resolved spectroscopic techniques.[33,62–64] Remarkably, due to their mixed symmetry nature, all of the modes here described can be investigated by INS or IXS experiments that probe $S(Q,E)$, and thus the transverse dynamics with a longitudinal symmetry component.

We expect that studies along these lines of investigations will likely contribute to assess the impact of the low-frequency collective dynamics on the biological activity of proteins. On these grounds, the valuable information provided by these calculations, which reveal the specifics of correlated intramolecular motions and the interactions they result from, can used in conjunction with artifi-

cial intelligence (AI) techniques, which are primarily concerned with protein structural properties.

SUPPLEMENTARY MATERIAL

Simulation protocol; details of the calculation of the correlation functions; description of the interacting phonon model; additional figures of the data analysis.

AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Valeria Conti Nibali: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Software (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Francesco Sacchetti**: Data curation (lead); Formal analysis (lead). **Alessandro Paciaroni**: Conceptualization (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (equal). **Caterina Petrillo**: Validation (supporting); Writing – review & editing (supporting). **Mounir Tarek**: Conceptualization (equal); Methodology (equal); Supervision (equal); Writing – review & editing (equal). **Giovanna D'Angelo**: Conceptualization (equal); Supervision (equal); Writing – review & editing (supporting).

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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