Terahertz response of dipolar impurities in polar liquids: On anomalous dielectric absorption of protein solutions

Dmitry V. Matyushov
Center for Biological Physics, Arizona State University, PO Box 871604, Tempe, AZ 85287-1604

A theory of radiation absorption by dielectric mixtures is presented. The coarse-grained formulation is based on the wavevector-dependent correlation functions of molecular dipoles of the host polar liquid and a density-density structure factor of the positions of the solutes. A nonlinear dependence of the absorption coefficient on the solute concentration is predicted and originates from the mutual polarization of the liquid surrounding the solutes by the collective field of the solute dipoles aligned along the radiation field. The theory is applied to terahertz absorption of hydrated saccharides and proteins. While the theory gives an excellent account of the observations for saccharides without additional assumptions and fitting parameters, experimental absorption coefficient of protein solutions significantly exceeds theoretical calculations within standard dielectric models and shows a peak against the protein concentration. A substantial polarization of protein’s hydration shell is required to explain the differences between standard theories and experiment. When the correlation function of the total dipole moment of the protein with its hydration shell from numerical simulations is used in the present analytical model an absorption peak similar to that seen is experiment is obtained. The result is sensitive to the specifics of protein-protein interactions in solution. Numerical testing of the theory requires the combination of terahertz dielectric and small-angle-scattering measurements.

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I. INTRODUCTION

Dielectric spectroscopy of mixtures is a well-established technique which requires theoretical modeling for the data interpretation. The models of dielectric response of mixtures traditionally operate by assuming that a mixture can be separated into macroscopic dielectric bodies. Among the commonly used models are the Maxwell-Wagner theory [1] and various formulations of the effective-medium approximation [2]. Both assume that a dielectric constant can be assigned to each component, and the latter also requires that the physical properties of the host and the impurity are not dramatically different.

The recent rapid development of dielectric techniques to study mixtures [3], in particular in the terahertz (THz) frequency window [4], aims at a different length-scale. The interest is mainly driven by the desire to learn about electrostatics of nano-scale objects, such as biopolymers [5, 6, 7, 8, 9, 10, 11], nano-crystals [12], and nano-confined fluids [13]. In particular, one hopes that the properties of the nano-scale interface between the solvent and the solute can be effectively probed by the dielectric response. This goal is complicated by the fact that essentially any relaxation event linked to electrical dipoles in the system contributes to the integral experimental signal, and theory is required to separate different components. While fully atomistic models will be the ultimate goal of the theory, it is still useful to develop coarse-grained approaches employing the length-scale intermediate between macroscopic dimensions of classical theories [1, 2] and fully atomistic length-scale.

This paper presents a coarse-grained model of the dielectric response of dipolar mixtures, aiming in particular at the THz frequency window. The model does not assume that solutes can be described as dielectric bodies, neither does it assume dielectric continuum for a polar solvent. The polar liquid is characterized by its wavevector-dependent correlation functions [14], and a similar approach is invoked for the solutes characterized by their density structure factor. However, instead of using completely atomistic structures, the solutes are modeled by effective spheres characterized by dipole moments, polarizabilities, effective radii, etc. The assumption of solute sphericity does not pose a fundamental restriction on the theory since it can be extended to solutes of non-spherical shapes made by overlapping vdW spheres of the composing atoms [15]. However, this simplification allows us to come up with a set of compact analytical equations applicable to analyzing experimental data.

The theory is applied to the analysis of the absorption coefficient of THz radiation. Recent measurements on hydrated saccharides [16] and proteins [17] have shown qualitatively different types of dependencies of THz dielectric absorption on concentrations of these two types of solutes. The current theory gives an excellent account of the observations on saccharides, but fails to reproduce the protein experiments when the dipole moment of the protein is assigned to the solute. It is suggested that hydrated proteins introduce solvation electrostatics qualitatively different from the dielectric response of
such that the field in the dielectric is $E$ of dielectric is perpendicular to the plane of the liquid film. The polarization of the cavity enhances both the dielectric response and the depolarization field of the empty cavity.

The situation becomes more complex for a finite concentration of solute dipoles when an additional effect of their collective field gains in importance. The alignment of solute dipoles in the external field creates a net average dipole moment $m_0$ (Fig. 1) and a corresponding non-zero net electric field that can potentially polarize cavities and alter their cavity dipoles. Since internal fields are commonly large compared to the external field, this effect, nonlinear in the solutes' concentration, can be potentially significant.

The arguments we have presented so far apply to the standard dielectric impedance measurements employing longitudinal electric fields. THz experiments employ a different geometry where the absorption of a pulse of electromagnetic wave propagating orthogonally to a thin (ca. 100 µm) film is measured [8, 9]. In this case, the electric field is transversal, i.e. it is perpendicular to the direction of axial symmetry breaking introduced in the isotropic liquid by the direction of the wavevector [22, 23]. One measures then the transverse dielectric response and the cavity is polarized differently. The dipole moment of the cavity along the field becomes $M_T^c = \langle P_l^c \epsilon_0/\epsilon \rangle$, where the transverse polarization (superscript "T") is $P_l^c = (\epsilon - 1)E_0/\epsilon$. It is clear that the cavity dipole produced in response to the transversal field is not screened by the high dielectric constant of a polar liquid. Microwave absorption measurements are therefore expected to be significantly more sensitive to impurities than conventional dielectric measurements. This distinction is the physical basis of the sensitivity of the transversal absorption experiments to electrostatic changes in molecular or nano-scale solutes.
III. RESPONSE FUNCTION

We now turn our attention to a detailed analysis of the transverse dielectric response of dipolar mixtures. In order to approach this problem we will use the approximation of linear response of the solvent to the electric field of the solute. The linear response approximation states that the solvent response function is insensitive to the magnitude of the solute electric field and in fact can be calculated for a fictitious solute with all partial charges turned off (zero dipole for a dipolar solute) \[13\]. Even though the electrostatic response is linear, the response to the solute repulsive core cannot be calculated within linear models since the repulsive potential of the solute produces a large and nonlinear perturbation of the solvent structure. This perturbation renormalizes the spectrum of the solvent fluctuations modifying the linear (Gaussian) response function \[24\]. In dielectric theories, this modification is included by imposing boundary conditions on the solution of the Poisson equation. The problem becomes way more complex at the molecular level and is commonly solved in terms of angular-dependent distribution functions \[23\].

We will adopt here Chandler’s formulation of the Gaussian model \[24\] in which the linear response function, modified by the presence of solute, is sought by imposing the condition of vanishing solvent density from the solute’s hard core. In case of polarization response, this condition implies the polarization field \( \mathbf{P} \) vanishing from the hard core of the solute. One can then define a generating functional of the polarization field as follows \[14\]

\[
\mathcal{G}[\mathbf{E}_0] = \int \exp \left[ -\frac{\beta}{2} \mathbf{P} \bullet \chi_s^{-1} \bullet \mathbf{P} + \beta \mathbf{E}_0 \bullet \mathbf{P} \right] \prod_{i, \Omega_0} \delta [\mathbf{P}(\mathbf{r})] \, d\mathbf{P}.
\]

Here, \( \mathbf{E}_0 \) is an external electric field, the asterisk denotes both the volume integration and tensor contraction, and \( \beta = 1/(k_B T) \) is the inverse temperature. Further, \( \chi_s \) is the 2-rank tensor of the Gaussian fluctuations of the polarization field in the homogeneous solvent and the product of delta functions runs over all points within solute’s hard-core of volume \( \Omega_0 \) and over all solutes (index \( i \)). This term ensures that the polarization field vanishes from the volume of each solute in the mixture.

Functional derivatives of \( \mathcal{G}[\mathbf{E}_0] \) over the external field \( \mathbf{E}_0 \) produce correlation functions of the polarization field of the solvent in the presence of solutes. The Gaussian integral over the polarization field \( \mathbf{P}(\mathbf{r}) \) can be calculated exactly resulting in a Gaussian functional in the external field \( \mathbf{E}_0 \). The corresponding renormalized response function \( \chi \) gains most compact representation in the inverted \( k \)-space \[14\]. It can be written in the \( k, \omega \)-representation in the following form

\[
\chi(k_1, k_2, \omega) = \chi_s(k_1, \omega) \delta_{k_1, k_2} - \sum_i \chi^R(k_1, \omega) \cdot e^{i(k_1-k_2) \cdot \mathbf{r}} \theta_0(k_1 - k_2) \cdot \chi_s(k_2, \omega).
\]

Here, \( \delta_{k_1, k_2} = (2\pi)^3 \delta(k_1 - k_2) \) and \( \theta_0(k) \) is the Fourier transform of the step function defining the excluded volume of the solute the translational dynamics of which are neglected. The direct-space Heaviside function \( \theta_0(\mathbf{r}) \) is equal to unity within the solute and is equal to zero outside the solute. The inverted-space function is given by the Fourier transform

\[
\theta_0(k) = \int_{\Omega_0} e^{i\mathbf{k} \cdot \mathbf{r}} d\mathbf{r},
\]

where integration is over the solute volume \( \Omega_0 \).

The response function of the mixture \( \chi(k_1, k_2, \omega) \) depends on two wavevectors \( k_1 \) and \( k_2 \) separately, instead of \( k_1 - k_2 \) of the homogeneous liquid, because of the inhomogeneous response produced by each solute marked by index \( i \). This response function combines the dipolar response function of the homogeneous liquid \( \chi_s(k, \omega) \), the information about the solute shape incorporated into \( \theta_0(k) \), and the renormalized function \( \chi^R(k, \omega) \) (see below).

The response function of an axially-symmetric dipolar liquid is expandable into longitudinal (L) and transverse (T) projections \[25, 26\]

\[
\chi_s(k, \omega) = \chi^L(k, \omega)\mathbf{J}^L + \chi^T(k, \omega)\mathbf{J}^T,
\]

where \( \mathbf{J}^L = \mathbf{k} \mathbf{k} \) and \( \mathbf{J}^T = 1 - \mathbf{k} \mathbf{k} \) are the orthogonal longitudinal and transverse dyads. The \( k = 0 \) values of the response projections are directly related to the frequency-dependent dielectric constant of the host liquid

\[
4\pi \chi^L_s(0, \omega) = 1 - \epsilon(\omega)^{-1},
\]

\[
4\pi \chi^T_s(0, \omega) = \epsilon(\omega) - 1.
\]

The entire \( k, \omega \)-dependence of the projections \( \chi^{L,T}(k, \omega) \) is given in Ref. \[27\], but only the transverse projection is required for the problem considered here (see below).

The last function in Eq. (2) that requires definition is \( \chi^R(k, \omega) \). This function appears in the solution for the generating functional in Eq. (1) as a result of renormalizing the dipolar response of the homogeneous liquid by the solute cavity. It thus contains the information about both the solvent and the solute \[14, 27\]. Only \( k = 0 \) transverse projection of this function appears in the equations for the transverse dielectric response of the dipolar mixture and that is given by the following equation

\[
\chi^{R,T}_s(0, \omega) = \frac{3\epsilon(\omega)}{2\epsilon(\omega) + 1}.
\]

We will now use Eq. (2) to calculate the transverse dipole moment \( M^T(\omega) \) of the dielectric sample produced
in response to the electric field of the electromagnetic radiation oscillating with frequency ω
\[ E_0(t) = \hat{e}^T E_0 e^{i\omega t}. \] (7)

Here, the polarization unit vector \( \hat{e}^T \) is perpendicular to the direction of propagation \( \mathbf{k} \).

The dipole moment \( M^T(\omega) \) combines two contributions: the dipole moment induced directly by the external field of the radiation (radiation wave-length is much larger than any molecular scales in the system) and an additional collective polarization induced by the solute dipoles aligned along the external field. These two contributions are described by correspondingly the first and the second summands in the following relation
\[ M^T(\omega) = \hat{e}^T \cdot \chi(0, 0, \omega) \cdot \hat{e}^T E_0 + \hat{e}^T \cdot \chi(0, \mathbf{k}, \omega) \cdot \sum_i \mathbf{T}(\mathbf{k}) e^{i\mathbf{k} \cdot \mathbf{r}_i} \cdot \mathbf{m}_{0,i}(\omega), \] (8)

where \( \mathbf{T}(\mathbf{k}) \) is the Fourier transform of the dipolar tensor \( \mathbf{T} = -\nabla_r \nabla_r |\mathbf{r} - \mathbf{r}'|^{-1} \) and, as above, the asterisk refers to integration over \( \mathbf{k} \)-space and tensor contraction. In addition, \( \mathbf{m}_{0,i}(\omega) \) is the solute’s dipole moment aligning itself with the oscillating external field.

The dipole moment \( \mathbf{m}_0(\omega) \) is a sum of two components: the electronic dipole induced instantaneously (on the time-scales of interest) by the external field and a permanent dipole inertially rotated by the torque imposed by the external field. The inertial component can be calculated from the linear-response approximation \[ \hat{e}^T \cdot \mathbf{m}_0(\omega) = (\alpha_{0,e} + \alpha_{0,n}^T [1 - i\omega \Phi(-\omega)]) f_d(\omega) E_0. \] (9)

Here, \( \alpha_{0,e} \) is the solute electronic polarizability and the permanent dipole polarizability is given as
\[ \alpha_{0,n}^T = (3\beta m^2_0/2) g_{0,K}^T, \] (10)
where \( g_{0,K}^T \) is the transverse Kirkwood factor \[ \hat{e}_j \) are the unit vectors of the solute dipoles. If the dielectric constant \( \varepsilon_0 \) can be assigned to the solutes, then \( \varepsilon_0 = 1 + 2\pi\beta m^2_0 \rho_0 g_{0,K}^T, \rho_0 = N_0/V. \) We also assumed isotropic polarizability of the solute and, in addition, for solution problems, the permanent dipole \( m_0 \) should be properly renormalized from the gas-phase value by the effect of the solute polarizability. Further, the factor \( f_d(\omega) \) in Eq. (9) is the Onsager directing field correction accounting for the difference between the electric field of the radiation and the local electric field imposing torque on the solute dipole.

The Laplace-Fourier transform \( \Phi(\omega) \) in Eq. (10) represents correlated rotational dynamics of the solute dipole
\[ \Phi(\omega) = (m_0^2 g_{0,K}^T)^{-1} \int_0^\infty \hat{e}^T \cdot (\mathbf{m}_0(t) \mathbf{M}_0(0)) \cdot \hat{e}^T e^{i\omega t} dt, \] (12)

where \( \mathbf{M}_0 = \sum_j \mathbf{m}_{0,j} \) is the total solute dipole in the sample. In case of a single-time Debye rotational relaxation with the relaxation time \( \tau_0 \) the term in the square brackets in Eq. (9) gains the form
\[ 1 - i\omega \Phi(-\omega) = (1 + i\omega \tau_0)^{-1}. \] (13)

The Debye approximation in Eq. (13) is typically sufficient for rigid dipoles dissolved in a polar solvent. The situation potentially becomes more complex for soft nano-scale solutes, biopolymers in the first place. The dynamics of the dipole moment is then affected by low-frequency vibrations altering \( \Phi(-\omega) \). As we discuss below, the inclusion of a non-vanishing dipole moment of the protein’s hydration shell, with its own dynamics, makes the problem even more non-trivial, further complicating the form of \( \Phi(-\omega) \).

The first term in Eq. (8) can be easily calculated by combining Eqs. (5) and (6) and noting that \( \theta_i(0) = \Omega \) [Eq. (3)]. This calculation then results in a simple relation for the difference between the response function of the mixture \( \chi_{\text{mix}}(\omega) = M^T(\omega)/(VE_0) \) and of the homogeneous liquid \( 4\pi\chi(\omega) = \epsilon(\omega) - 1 \)
\[ 4\pi \Delta\chi = -\eta_0 f(\omega). \] (14)

Here, \( \Delta\chi = \chi_{\text{mix}}(\omega) - \chi(\omega) \), \( \eta_0 = N_0\Omega_0/V \) is the volume fraction of the solutes in the mixture with the overall volume \( V \), and
\[ f(\omega) = \frac{3\epsilon(\omega)(\epsilon(\omega) - 1)}{2\epsilon(\omega) + 1}. \] (15)

We note here that a more simple (and elegant) derivation of the response function of a low-concentration mixture as given by Eqs. (14) and (15) can be found in Ref. 24. Equations (14) and (15) also represent a low-concentration limit of the Maxwell-Wagner formula [1]. Our microscopic consideration is thus consistent with macroscopic arguments. The microscopic description is however required to get correctly the second summand in Eq. (8) describing the collective response of an ensemble of solute dipoles. This is what we consider next.

The response function of the solvent to the presence of the solute includes two parts corresponding to two summands in Eq. (2). The first summand represents the response of the liquid to an infinitely small solute which does not perturb the spectrum of dipolar fluctuations of the liquid. This part is easy to calculate and its relative contribution to the response is \( \Delta\chi(\omega)/\chi(\omega) = g_0(\omega)/f_d(\omega) \), where
\[ g_0(\omega) = (4\pi/3)\rho_0 \alpha_{0,e} + (2\pi/3)\beta m_0^2 g_{0,K}^T [1 - i\omega \Phi(-\omega)] \] (16)

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is the dipolar density of solutes defined in analogy with a similar quantity of homogeneous liquids [1].

The contribution from the second term in Eq. (2) is the correction of the solvent response introduced by the excluded volume of the solute. This calculation is more complex. After some algebra one arrives at the mixture susceptibility relative to the susceptibility of the homogeneous liquid

$$\Delta \chi(\omega)/\chi(\omega) = -\eta_0 \frac{3\epsilon(\omega)}{2\epsilon(\omega) + 1} + y_0(\omega) f_d(\omega) \left(1 - \frac{3\epsilon(\omega)}{2\epsilon(\omega) + 1} I(\omega, \eta_0, R)\right).$$

(17)

The only non-trivial part in this equation is the integral $I(\omega, \eta_0, R)$, arising from the combined effect of the volume excluded by the solute from the solvent, many-body solute-solute correlations, and microscopic correlations between the dipoles of the solvent. It is given by the relation

$$I(\omega, \eta_0, R) = \frac{6R \epsilon(0) - 1}{\pi \epsilon(\omega) - 1} \int_0^\infty dk j_1^2(kR) S_0(k, \eta_0) \chi^T_s(k, \omega) \chi^T_s(0, 0),$$

(18)

in which $j_1(x)$ is the first-order spherical Bessel function and $R = (\sigma_0 + \sigma)/2$ is the distance of the closest approach of the water molecules with the effective hard-sphere diameter $\sigma$ to the solute characterized by its hard-sphere diameter $\sigma_0$.

The density-density structure factor $S_0(k, \eta_0)$ in Eq. (18) is responsible for a nonlinear dependence of the volume of the mixture on the solute concentration. The $k = 0$ value of the structure factor $S_0(0, \eta_0)$ ($S_0(0, \eta_0) \to 1$ at $\eta_0 \to 0$) is the reduced compressibility of the solute component of the mixture. It is equal to the experimentally measurable osmotic compressibility [31, 32]

$$S_0(0, \eta_0) = \chi_{\text{osm}} = \left(\frac{\partial \rho_0}{\partial \Pi_0}\right)_{\text{osm}},$$

(19)

where $\Pi$ is the osmotic pressure and the derivative is taken under the condition of osmotic equilibrium.

The transverse dipolar correlation function $\chi^T_s(k, \omega)$ in Eq. (18) does not depend on the solute concentration, but incorporates spacial transverse correlations between dipoles in the polar liquid. We provide its functional form here for completeness and refer the reader to Refs. 27 and 33 for a more detailed account of this problem

$$\frac{\chi^T_s(0, 0)}{\chi^T_s(k, \omega)} = \frac{S^T(k)}{S^T(0)} + \frac{1}{1 + p'(k\sigma)^2} \left(\frac{\epsilon(0)}{\epsilon(\omega)} - 1 - 1\right).$$

(20)

In this equation, $S^T(k)$ is the static structure factor of transverse dipolar fluctuations. A simple extension of the mean-spherical solution for dipolar fluids [28] gives $S^T(k)$ consistent with numerical simulations [33]. This formalism is used here for numerical calculations of the function $I(\omega, \eta_0, R)$ in Eq. (18). Finally, the parameter $p'$ in Eq. (20) quantifies the relative contribution of translational vs rotational motions of liquid’s dipoles in the overall response as discussed in Ref. 34.

The approximation of continuous dielectric corresponds to the neglect of the $k$-dependence in the transverse response function $\chi^T_s(k, \omega)$ in Eq. (18) assuming $\chi^T_s(k, \omega) \approx \chi^T(0, \omega)$. The dependence of frequency then disappears from the integral $I(\omega, \eta_0)$ which simplifies to

$$I(\eta_0, R) = \frac{6R}{\pi} \int_0^\infty dk j_1^2(kR) S_0(k, \eta_0).$$

(21)

The dielectric-continuum integral $I(\eta_0, R)$ is equal to unity for an ideal solution when $S(k, 0) = 1$. This ideal-solution/continuum limit then results in a simple equation for the mixture’s dielectric response

$$\Delta \chi(\omega)/\chi(\omega) = -\eta_0 \frac{3\epsilon(\omega)}{2\epsilon(\omega) + 1} - y_0(\omega) f_d(\omega) \left(\frac{\epsilon(\omega)}{2\epsilon(\omega) + 1} - 1\right).$$

(22)

It shows that the presence of very dilute solute dipoles lowers the transverse response because an enhanced depolarization of the cavity wins over the direct alignment of the solute dipoles by the external field. It is clear that this result cannot sustain itself as the concentration of dipolar impurities grows since the limit of a negative dielectric constant can potentially be reached. Solution non-ideality must slow the negative decay of the mixture susceptibility or change its sign to positive.

The continuum integral $I(\eta_0, R)$ can be rewritten in $r$-space as

$$I(\eta_0, R) = 1 + (\rho_0/\Omega_0) \int d\mathbf{r}_1 d\mathbf{r}_2 f_0(\mathbf{r}_1) h_0(\mathbf{r}_{12}) f_0(\mathbf{r}_2),$$

(23)

where $h_0(\mathbf{r}_{12})$, $\mathbf{r}_{12} = \mathbf{r}_2 - \mathbf{r}_1$ is the pair correlation function of the solutes and $f_0(\mathbf{r})$ are Mayer $f$-functions representing hard cores of the solutes. If long-ranged interactions between the solutes are neglected, the lowest-order density expansion of the pair correlation function
h_0(r_{12}) yields the third virial coefficient C_{112} of the mixture of hard spheres of diameter R (components 1) and diameter σ_0 (component 2): I = 1 - (3ρ_0/Ω_0)C_{112}, Ω_0 = (4π/3)R^3. The third virial coefficient of the hard-sphere mixture is known [35, 37]. For solutes much larger than solvent, one can put R ≈ σ_0/2 with the result I(η_0) = 1 - (η_0/8)(3 + 65/24). This simple equation compares reasonably well with the direct numerical integration using the Percus-Yevick (PY) density structure factor. The numerical integrals can be approximated by a polynomial of R/σ_0 and η_0, and this fit is provided in Appendix for 0 ≤ η_0 ≤ 0.3.

The interactions between hydrated proteins are complex, and the structure factor from hard-sphere repulsions can be used only for a limited range of ionic strengths when Coulomb forces are sufficiently screened [37, 39]. The structure factor S_0(k, η_0) is directly measured by small-angle scattering [38, 39] and can be numerically reconstructed from a linear combination of a repulsive and attractive potentials; a combination of Yukawa potentials is often used [39]. The small-k part of the structure factor is strongly affected by long-range interactions, and there is a peak at q_m ≈ 2π√η_0 at the average distance between the solutes in solution. Since the amplitude of the peak is relatively small [38], a general insight into how correlations between hydrated proteins affect the dielectric response can be gained from an empirical approximation for S_0(k, η_0). The following approximation (analogous to the empty core model [40]) follows directly from the low-density expansion of the direct correlation function of a hard sphere

S_0(k, η_0) = [1 + a_j1(kσ_0)/(kσ_0)]^{-1} \tag{24}

in which the constant a is chosen to reproduce the osmotic compressibility a = 3S_0(0, η_0)^{-1} - 1. The resulting integral is just a function of a (R ≈ σ_0/2). Its numerical value can be approximated by a Padé form, I(a) = \{1 + 0.0908308a - 0.00226567a^2\}/\{1 + 0.131266a - 0.0043402Aa^2\}, which allows one to use the osmotic compressibility, affected by both repulsions and attractions, as input to obtain the dielectric response. The approximation in Eq. (24) is accurate up to η_0 ≈ 0.1 when compared to the direct integration with the PY density structure factor.

It is worth noting at this point that the continuum approximation is inaccurate at low frequencies ω ≈ 0 overestimating the cavity polarization in the entire range of solute sizes of common interest (Fig. 2). This happens because of a very sharp decay of the structure factor ST(k) at small k-values [33] which, in the continuum limit, is replaced by its k = 0 value ST(0). The continuum approximation becomes more accurate as the frequency increases and the dielectric constant decreases (Fig. 2), but it needs to be tested before applied in a frequency range of interest. Nevertheless, in the range of THz frequencies, the continuum limit [Eq. (21)] presents a useful simplification of Eq. (13), which, in conjunction with Eq. (24), yields the dielectric response solely in terms of observable quantities.

The actual dependence of the dielectric response on the solute volume fraction is more complex than a nearly linear decay suggested by Eq. (22). It is shown in Fig. 3 where a static ω = 0 response is calculated for paramters specific to λ_5-s5 protein discussed below. Baxter’s solution of the PY closure [25] for S_0(k, η_0) was used in these calculations. In addition, the microscopic transverse response function of the solvent dipoles was taken according to Ref. 27 and the static structure factor was calculated from a corrected mean-spherical approximation suggested in Ref. 33. The dependence of the dielectric response on η_0 is curved down, thus eliminating the dielectric catastrophe following from the linear extrapolation of Eq. (22). However, the shape of the concentration dependence depends on frequency, and the curvature is just the opposite one for the THz response (see below).

A notion regarding theory’s approximations is relevant here. One might argue that the point-dipole model is too restrictive for the electrostatic field of a protein with typically a non-zero overall charge and the prevalence of charged residues on its surface. We believe that the approximations adopted here are adequate, and the theory might actually be more quantitative than it seems. First, the solvent response function is independent of the solute charge in the linear response approximation [33] and is identical to the one obtained for a fictitious solute with all charges turned off. The linear response approximation might obviously fail, and that certainly puts a restriction on the current theory. Second, the perturbation Hamiltonian for the current problem is the interaction of the sample dipole moment with the external electric field of the radiation. Since the THz wavelength obviously exceeds any molecular dimension, a dipolar approximation is appropriate for solutes of nano-scale dimension. Finally, the total solute charge can contribute to conduc-

FIG. 3: Relative change in the absorption coefficient of the mixture at ω = 0 [see Eqs. (26) and (27)] as a function of the volume fraction of the solute η_0. The solid line refers to the entire response function from Eq. (17), while the dashed line shows the contribution of the first term only. The latter, linear in η_0, is the limit of zero solute dipole. The overall non-linear dependence on η_0 is the result of mutual polarization of the cavities by the solute dipoles. The solute size and dipole are those of the λ_5-s5 protein.
tivity \[41\] that is normally subtracted from the dielectric response and is insignificant in the THz frequency range. The dipole moment of charged solutes is then defined relative to the solute’s center of mass \[41\].

### IV. COMPARISON TO EXPERIMENT

One of parameters reported in THz dielectric measurements is the relative absorption coefficient \(\Delta \alpha(\omega)/\alpha(\omega)\), where \(\Delta \alpha(\omega) = \alpha_{\text{mix}}(\omega) - \alpha(\omega)\) is the change in absorption coefficient of the mixture relative to the pure liquid. The absorption coefficient is defined \[42, 43\] as the ratio of the rate of energy dissipation by the medium \(\langle \dot{E} \rangle\omega\) over the Poynting vector \(S(\omega)\) of the incident radiation

\[
\alpha(\omega) = \frac{\langle \dot{E} \rangle \omega}{S(\omega)}
\]

By combining the standard equations for the Poynting vector in dielectric media \[20, 43\] with energy dissipation in terms of the dielectric response function \(\chi(\omega)\) one gets the equation

\[
\alpha(\omega) = \frac{4\pi \omega \chi''(\omega)}{c \sqrt{\epsilon'(\omega)}}
\]

which can be applied either to the mixture or to the pure liquid (\(c\) is the speed of light in vacuum).

Assuming that the deviation of the response \(\Delta \chi(\omega)\) caused by impurities is small compared to the dielectric response of the pure liquid, one can easily derive an expression for the relative change of the absorption coefficient

\[
\frac{\Delta \alpha(\omega)}{\alpha(\omega)} = \frac{4\pi \Delta \chi''(\omega)}{\epsilon''(\omega)} - \frac{2\pi \Delta \chi'(\omega)}{\epsilon'(\omega)}
\]

In this equation, the variation of both the imaginary and the real parts of the response are taken into account when impurities are introduced into the polar liquid. In particular, for solutes with small dipole moment, one can drop the term proportional to \(y_0(\omega)\) in Eq. \[17\] and arrive at a simple relation

\[
\frac{\Delta \alpha(\omega)}{\alpha(\omega)} = -\eta_0 \left[\frac{f''(\omega)}{\epsilon''(\omega)} - \frac{f'(\omega)}{2\epsilon'(\omega)}\right]
\]

where \(f(\omega)\) is given by Eq. \[18\].

Figure 4 shows the comparison of Eq. \[28\] (lines) with the experimental dependence (points) of the absorption coefficient on the concentration of trehalose dissolved in liquid water \[16\]. The details of the calculations and the parameters used to produce the plot are given in the Appendix. Because of the small dipole moment of trehalose, a complete calculation of the dielectric response function of the mixture is not required (the term proportional to \(y_0(\omega)\) in Eq. \[17\] is small) and Eq. \[28\] is sufficient. The dashed and dash-dotted lines in Fig. 4 show the first (imaginary part) and second (real part) terms in Eq. \[28\]. It is clear that changes in the imaginary and real parts of the dielectric susceptibility upon the addition of impurities are comparable in magnitude and should both be included. The only solute parameter entering Eq. \[28\] is its volume. Equation Eq. \[28\] can therefore be used to determine molecular volumes of weakly polar solutes by means of dielectric measurements.

In an attempt to see what might be the theory prediction for the case of protein solutions we have mimicked the conditions reported in Ref. \[17\] where the absorbance of the solution of a five helix bundle protein \(\lambda_{6-85}\) \[46\] showed a maximum at the volume fraction of protein...
below 1% (points in Fig. 5). The calculations (see Appendix for the parameters used) show almost no effect of proteins’ dipoles and a negative contribution to the absorption, as in the case of trehalose above and in an obvious disagreement with the experiment.

There is also a clear difference between Figs. 3 and 5. While Fig. 3 shows a clear effect of the mutual cavity polarization by solutes’ dipolar fields for the same set of parameters, there is almost no effect of the solute dipolar component in Fig. 5 (cf. solid and dashed lines). The difference comes from the dynamical effect. The solute dipoles do not have time to reorient on the time-scale of the THz pulse and the corresponding contribution is strongly diminished by the relaxation $1/\langle \omega \tau_0 \rangle$ term. The THz pulse thus probes almost exclusively the electronic polarizability of the solvated proteins.

For the solute dipoles to be seen in the THz response, either a much faster relaxation or a significantly larger effective dipole are required. Faster relaxation of protein’s dipole seems improbable given that numerical simulations show an almost exclusively single-component rotational relaxation with the relaxation time in the range $3–6$ ns [41]. The hydration shell thus emerges as the most probable candidate to explain the differences between the theory and experiment.

In order to obtain more quantitative insights into the problem, results of numerical simulations of protein solutions are required. We found recently [18,19] that, in accord with the suggested interpretation of experimental THz data [17], proteins are capable of polarizing their hydration shells $\approx 10–15$ Å into bulk water. This polarization results in a significant non-zero average dipole moment of the hydration shell $\langle |\mathbf{m}_w| \rangle$, which reached the value of $\approx 10^3$ D in simulations of metalloprotein plastocyanin [18]. The dynamics of this ferroelectric cluster around the protein are however decoupled from a much slower tumbling of the protein occurring on the time-scale of nanoseconds. The relaxation of the shell’s dipole $\mathbf{m}_w$ is clearly two-component, with a very fast initial relaxation on a sub-picosecond time-scale, followed by a low-amplitude tail lasting hundreds of picoseconds. The fast component correlates with low-frequency vibrations of the protein deforming water’s “elastic ferroelectric bag” [19].

In this picture, the solute dipole $\mathbf{m}_0$ should be replaced with the sum of protein’s and shell’s dipoles $\mathbf{M} = \mathbf{m}_0 + \mathbf{m}_w$. The dynamics of this total dipole gives input to determine function $\Phi(\omega)$, which, together with $\langle M^2 \rangle$, yields $y_0(\omega)$ [Eq. (18)]. These parameters were extracted from simulations of plastocyanin carrying the negative charge of $−8$ in its oxidized state and hydrated by $N_w = 21076$ TIP3P waters [18,19]. The shell of water molecules of width $20$ Å was added to the effective radius of the protein to obtain the effective radius of the protein/water cluster and the volume fraction of coupled protein/water dipoles in solution (see Appendix for details). The dielectric response of the solution was then calculated from Eqs. (17) and (23).

Figure 6 shows the concentration dependence of the solution absorption coefficient with the PY hard-sphere structure factor $S_0(k, \eta_0)$ (solid line). The points, shown for reference, are data on $\lambda_{\alpha–85}$ protein [17] rescaled with the volume of the plastocyanin/water cluster. The calculation indeed yields a maximum in the absorption coefficient which turns to negative values with increasing volume fraction. The outcome of these calculations is sensitive to the form of the density structure factor and, therefore, to protein-protein interactions in solution. In order to illustrate this point, the dashed line in Fig. 6 shows the result of calculations with a stronger effect of repulsions and thus a steeper decay of $S_0(0, \eta_0)$ with increasing $\eta_0$.

The hard-sphere model might not be adequate for all proteins and electrolytes. For instance, for the ionic strength employed in Ref. [17] (0.05 M), the interactions between hydrated bovine serum albumin (BSA) proteins are dominated by electrostatic repulsions [17]. These proteins are negatively charged, similarly to plastocyanin, and the long-range interactions are dominated by the screened Coulomb potential. The osmotic compressibility $S(0, \eta_0)$ of BSA quickly drops with increasing protein concentration to the level $S(0, \eta_0) \approx 0.1 – 0.2$ and then does not significantly change when the concentration is further increased [17]. With such a dependence of $S(0, \eta_0)$ on the volume fraction $\eta_0$ the peak in absorption
vanishes (Fig. 6). Note that no absorption peak against protein concentration was detected for BSA in dielectric terahertz measurements at $\omega = 1.56$ THz [8].

The inset in Fig. 6 shows the frequency dependence of the dielectric loss $\Delta \varepsilon''(\omega)$. As is seen, the change of the loss relative to bulk water can be either positive or negative, depending on the frequency range. A complex concentration dependence seen for the absorption coefficient in Fig. 6 is the cumulative effect of the concentration dependencies of $\varepsilon''_{\text{mix}}(\omega)$ and $\varepsilon''_{\text{prot}}(\omega)$.

The $\lambda_{6-85}$ protein is uncharged and the corresponding protein-protein interaction can be modelled either as a sum of soft repulsion and exponentially decaying attraction or, alternatively, as a sum of hard-sphere ($u_{\text{HS}}$) and attractive Yukawa potentials [48]:

$$u(r) = u_{\text{HS}}(r) - \epsilon (\sigma_0/r) e^{-(r-\sigma_0)/\delta}(r-\sigma_0).$$  \hspace{1cm} (29)

In Fig. 7 we used this latter approximation for the interaction potential to calculate $S_0(k, \eta_0)$ [49] and then applied this structure factor to the calculation of the THz absorption coefficient. In the absence of dipole moment dynamics for this protein, we used the normalized self-correlation function of the protein-water dipole from plastocyanin simulations [18, 19]. A set of curves in Fig. 7 refer to different values of the dipole moment of the protein-water cluster, with the lowest curve corresponding to the protein dipole alone. Qualitatively, the absorption curves do go through maxima with increasing dipole of the solute, and the protein solution absorbs stronger than bulk water. However, the maxima are broader than in experiment and the agreement is only qualitative at best.

V. DISCUSSION

The present model of the dielectric response targets physical situations when large solutes dissolved in polar solvents do not extend to dimensions of a dielectric material. Large cavities in polar liquids carry depolarization dipoles oriented oppositely to the external field, with their magnitudes scaling linearly with the solute volume. These depolarization dipoles accumulate a negative contribution to the absorption coefficient. The intrinsic solute dipoles, which align along the external electric field, increase the absorption and also produce a non-zero local electric field that re-polarizes neighboring cavities. This collective effect, non-linear in the solute concentration, is sensitive to the solute-solute correlations and is described by convoluting the solvent dipolar response with the density structure factor of the dissolved solutes.

This model performs exceptionally well when tested against experimental THz measurements for weakly polar impurities (Fig. 7). In this case, only depolarization of cavities contributes to the response, and that part of the problem seems to be well captured by dielectric theories. Even though solvation of saccharides distorts the structure of water on the microscopic scale [50, 51] and slows down the dynamics of the hydration layer [52], THz absorption seems to be insensitive to such changes, and the resulting signal is well described by a purely dielectric response. This conclusion is consistent with the recent light scattering spectra of trehalose solutions [52] suggesting only a local perturbation of the water structure restricted to the first solvation shell, which is typical for many small molecular solutes.

Polar impurities introduce both the effect of individual solute dipoles and their collective polarization effect. The response-function formalism employed here does not involve any large-scale changes in the solvent structure induced by the solute. This formulation then fails to reproduce the anomalous increase in the absorption of protein solutions over that of bulk water [5, 17]. Computer simulations [18] show instead a high extent of cooperativity between hydration shells and protein’s motions. In addition, a significant polarization of the water shell extending 10–20 Å from the protein surface into the bulk is observed. When the magnitude and correlation function of the protein-water total dipole are substituted into the equations for the solution response, the theory shows a maximum in the absorption coefficient qualitatively similar to experimental observations. The maximum can therefore be considered as an observable signature of the “elastic ferroelectric bag” found by simulations [18]. The shape of this anomalous absorption maximum is however sensitive to the interprotein interaction potential and will be affected by several factors including protein’s ionization state and the ionic strength of the solution.
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APPENDIX A: DETAILS OF CALCULATIONS

The dependence of the absorption coefficient on frequency arises predominantly from the frequency-dependent dielectric constant of the solvent. Dielectric measurements of water \[14\] in the THz range, extended to more typical low-frequency dielectric values, have been used to produce Figs. 2 and 3 \[17\]. The dielectric constant is given by the following relation \[44\]:

\[
\epsilon(\omega) = \frac{\Delta \epsilon_1}{1 - i\omega \tau_1} + \frac{\Delta \epsilon_2}{1 - i\omega \tau_2} + \frac{A_S}{\omega^2 - \omega_0^2 - i\omega \gamma_S} + \epsilon_{\infty},
\]

(A1)

where \(\Delta \epsilon_1 = 73.9\), \(\Delta \epsilon_2 = 1.56\), and \(\epsilon_{\infty} = 2.34\). The Debye relaxation times and the parameters of the resonant component are: \(\tau_1 = 8.76\) ps, \(\tau_2 = 0.224\) ps, \(\omega_s/2\pi = 5.3\) THz, \(\gamma_s/2\pi = 5.30\) THz, \(A_S/(2\pi)^2 = 35.1\) THz\(^2\). The parameter \(f_d(\omega)\) \[Eq. (9)\] accounts for the difference between the external and the local directing (torque) fields. It depends on frequency through the dielectric constant. This parameter is often associated with the field within an empty cavity in a liquid \[21\]. An expression recently derived by us for this property \[30\] was used in the calculations: \(f_d(\omega) = [7(\epsilon(\omega)+1)^2 + 8\epsilon(\omega)]/(12\epsilon(\omega)(2\epsilon(\omega)+1))\).

Since the polarizability of many organic substances is close to \(\alpha_0,\epsilon = \sigma_0^3/16\), the parameter of dipolar density of the solutes \[Eq. (16)\] was taken in the form

\[
y_0(\omega) = \left[\frac{1}{2} + 4g_{0,K}(m^*_0)^2(1 - i\omega\Phi(-\omega))\right] \eta_0,
\]

(A2)

where \((m^*_0)^2 = \beta(M^2)/\sigma_0^3\) is a reduced effective dipole, \(M\) is the entire dipole moment of the protein-water cluster.

Simulations of hydrated plastocyanin were reported previously \[15\]. The presently used data \[19\] represent the same simulation protocol applied to the oxidized (total charge \(-8\)) state of plastocyanin extended to a larger number of waters in the simulation box, \(N_w = 21076\). For plastocyanin calculations \(M\) represents the total dipole of the protein and water shell extending 20 Å from the protein surface into the bulk. This latter magnitude was added to the effective radius of the protein listed in Table 1 to obtain the effective radius of the water/protein cluster. The averaged square of the protein/water dipole calculated from the simulation trajectory was \((M^2) = 1.44 \times 10^4\) D\(^2\). The response function \(\Phi(\omega)\) was obtained as a Laplace-Fourier transform of the

TABLE I: Solute parameters used in the calculations.

| Solute       | \((\sigma_0/2)/\text{Å}\) | \(m_0/D\) | \(\tau_0/\text{ns}\) |
|--------------|-----------------|---------|------------------|
| Trehalose    | 8.2             | 1.75    | 0.05             |
| \(\lambda_\infty\) | 12.1\(^a\) | 61\(^b\) | 3                |
| Plastocyanin\(^c\) | 16.8\(^d\) | 248\(^d\) | 2.8\(^f\) |

\(^a\)From Ref. \[13\]. The following set of parameters from Ref. \[48\] was used to represent the protein-protein interaction potential in Eq. (20): \(\sigma_0 = 31.8\) Å, \(\epsilon/k_B = 419\) K, \(\delta = 4.14\) Å.

\(^b\)Calculated from equilibrated protein geometry and atomic partial charges \[53\].

\(^c\)According to MD simulation data from Ref. \[45\].

\(^d\)From the vdW volume of the protein using the Amber FF03 force field.

\(^e\)(\(m_0\)) calculated from the MD trajectory relative the center of mass, total charge of the Ox state of the protein is \(-8\). Fluctuations of the protein dipole are caused by protein’s vibrations.

\(^f\)Calculated from the exponential fit of the time self-correlation function of the protein dipole.

three-exponent fit of the simulated correlation function

\[
\Phi(t) = \sum_{i=1}^{3} A_i e^{-t/\tau_i},
\]

(A3)

where \(A_i = \{0.84, 0.11, 0.05\}\) and \(\tau_i = \{0.14, 1790, 6.3\}\) ps.

Other solute parameters used in the calculations are listed in Table 1: the hard sphere diameter of water was taken at the value of \(\sigma = 2.87\) Å, and the inertial parameter \(\rho'\) in Eq. (20) was set at the value of \(\rho' = 0.1\) \[27\]. The rotational relaxation times of the solutes were taken at \(\tau_0 = 50\) ps for trehalose and \(\tau_0 \approx 3\) ns for the two proteins. The former number is consistent with the second relaxation process extracted from the dielectric response and simulations of hydrated saccharides \[50\], while the latter is typical for rotational dynamics of proteins \[41\].

The calculation of the solute dipole component of the dielectric response simplifies in the continuum limit when the integral in Eq. (15) loses the dependence on frequency and reduces to Eq. (21). This integral depends on two parameters, the volume fraction \(\eta_0\) and the reduced geometry parameter \(r = 1/2 + \sigma/(2\sigma_0)\), when the hard-spheres approximation is used for the density structure factor \(S_0(k, \eta_0)\). The range \(0.5 \leq r \leq 1\) covers most problems of interest. Numerical integration of Eq. (21) with the PY density structure factor \[22\] was done in this range of \(r\)-values and volume fractions in the range \(0 \leq \eta_0 \leq 0.3\). The numerical results were interpolated with the polynomial function

\[
I(\eta_0, r) = a(\eta_0) + b(\eta_0)r^2 + c(\eta_0)r^4 + d(\eta_0)r^6,
\]

(A4)

where

\[
\begin{align*}
a(\eta_0) &= 1 + 0.225\eta_0 + 7.726\eta_0^2 - 13.805\eta_0^3, \\
b(\eta_0) &= -9.694\eta_0 - 18.572\eta_0^2 + 16.642\eta_0^3, \\
c(\eta_0) &= 6.987\eta_0 + 38.913\eta_0^2 - 5.940\eta_0^3, \\
d(\eta_0) &= 2.108\eta_0 - 16.570\eta_0^2 - 10.007\eta_0^3.
\end{align*}
\]

(A5)
The expansion in even powers in $r$ in Eq. (A1) is dictated by the symmetry of the density structure factor $2\delta$, and the density expansion of the polynomial coefficients has been chosen to justify the ideal-solution limit $I(0, r) = 1$. 

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