Biological Effects of Nonionizing Radiation

Karl H. Illinger

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Biological Effects of Nonionizing Radiation

Karl H. Illinger, EDITOR
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PREFACE

Considerable advances have been made in recent years in the development of experimental techniques and in the refinement of theoretical models for the interaction of electromagnetic fields with biological systems. The primary objective of this volume is to focus on the current state of these methodologies, and to examine their consequences in elucidating the chemical physics and biophysics of such systems. Four sections trace the development of these topics along a hierarchy of systems of increasing complexity: the ubiquitous milieu of biological structures, water, and macromolecular systems of biological interest; the bulk dielectric and spectroscopic properties of membrane and cellular systems; nonequilibrium properties of biological systems; and the best documented sensory-system effect of nonionizing radiation, the microwave acoustic effect. A brief synopsis of each section is provided below.

In the microwave and far-infrared regions, the dielectric properties of free water dominate the bulk response of biological tissue to electromagnetic fields. Recent accurate determinations of the millimeter-wave complex permittivity of water permit a definitive analysis of the dielectric absorption arising from its rotational diffusion, and provide a connection to its far-infrared absorption stemming from the translational and librational motion of molecular clusters of water. The structure of water in the vicinity of macromolecules is modified by its interaction with such molecular surfaces. Conversely, the structure of macromolecules in aqueous solution is altered by the same interaction. The dielectric properties of water in solution with biopolymers, such as myoglobin, are beginning to be examined in detail, with a frequency resolution heretofore unattainable. The electrical response of biopolymers in aqueous solution, from the regime of low frequencies to the microwave region, is determined by a complex set of interactions. They involve not only the overall rotational diffusion of the macromolecule and the internal rotational diffusion of its segments, but also the dynamically coupled response of its counter-ion atmosphere. New developments in experimental methods and more accurate theoretical models provide an avenue toward the analysis of these interactions. In the far-infrared region, and penetrating into the microwave region, the low-frequency vibrational dynamics of biological polymers arise. The aqueous environment constitutes a refractory experimental

system for dielectric spectroscopy and photon (Raman) and phonon (Brillouin) scattering. Nonetheless, recent refinements are beginning to address salient questions concerning the spectroscopic properties of biopolymers in aqueous solution in the far-infrared and millimeter-wave regions.

Molecular dynamics in aqueous solution embody one sector of the dielectric and spectroscopic properties of biological tissue, and serve as a partial guide toward the analysis of the more complex molecular aggregates and biophysical systems comprised by such structures. A considerable body of information has been amassed on the bulk dielectric properties, into the millimeter-wave region in some cases, and the refinement of mechanisms of electromagnetic-field interaction has been substantial. In parallel, the phenomenology of the (dielectric) frequency response of both artificial and biological membranes has been well documented, particularly in the frequency regime below the microwave region. The dielectric properties of molecular systems in aqueous solution, below the far-infrared region, are characterized by relaxation processes depending only on the nature of the solute molecule and its interaction with the solvent, with a resultant set of (molecular) relaxation times for the dynamical processes involved. In the biological membrane, apart from the modification of the relaxation processes of macromolecules which are embedded in the membrane, additional (biophysical) processes, with characteristic response times, arise from the interactions and biochemical events occurring at this higher level of molecular organization. One set of such characteristic response times has a lower bound dictated by the velocity of ion transport across the membrane. Nonlinear dielectric properties have been invoked for biological membranes in the low-frequency regime. In particular, the voltage–current properties of excitable cellular membranes have been examined in an electromagnetic-field perturbation model, employing the phenomenological Hodgkin–Huxley model as the unperturbed system.

Section 1 *in toto* and aspects of Section 2 treat the equilibrium characteristics of biological tissue and its molecular subsystems. Although the bulk properties of even in vivo biological tissue are dictated by (high-concentration) molecular systems near equilibrium, in order for the in vivo state to be maintained (low-concentration) molecular subsystems obeying steady-state nonequilibrium thermodynamics must exist. While such nonequilibrium systems are not confined to biological structures, they are requisite for biological processes. Section 3 focuses on the dielectric and spectroscopic behavior of nonequilibrium systems. Such biophysical constructs play a crucial role in developmental bioelectricity (the role of intrinsic electric fields in signal propagation and developmental patterns in living systems) over a wide span of morphological complexity, from cellular systems on upward. At the level of what appears to be the irre-

ducible biophysical system exhibiting nonequilibrium dissipative properties, the in vivo biological membrane, coherent processes, and their perturbation by millimeter-wave and far-infrared electromagnetic fields have been studied in theoretical models in some detail. The boson (phonon and photon) distribution associated with chemically pumped, dissipative molecular subsystems is expected to show deviations from the Planckian (equilibrium) distribution, with attendant consequences for the phonon and photon spectroscopy of such systems in the far-infrared region. The same intransigence displayed by the aqueous environment toward the millimeter-wave and far-infrared spectroscopy of biopolymers (Section 1), and the dominance of the bulk properties in the observables, have placed severe limitations on experimental work in this area. In addition to the alterations in the high-frequency spectroscopic properties predicted upon onset of (time-variant) nonequilibrium structures, the response of associated coupled biochemical reaction systems to low-frequency oscillatory stimuli has been examined. Finally, in a category that may be related to nonequilibrium properties in systems consisting of macromolecular polyelectrolytes and ions, the effect of amplitude-modulated electromagnetic fields in the radiofrequency region on Ca^{+2} efflux in biological tissue has been studied extensively. While the mosaic of properties assembled in Section 3 under the rubric of nonequilibrium systems forms, as yet, a far less rigorous structure than that of the more mature fields treated in Sections 1 and 2, even their tentative connection may prove to be suggestive for future development of this field.

At the interface between the areas treated in Sections 1–3 and the virtually unlimited field of nonionizing radiation research involving levels of higher biological complexity, a well-documented effect exists that can be cast into well-defined biophysical models, discussed in Section 4. The microwave acoustic effect involves the auditory-system response to pulsed microwave radiation. The initial step, dielectric interaction with tissue components, can be modeled within the constructs of the previous treatment. However, a higher level of biological organization becomes engaged in subsequent steps of the interaction. The dielectric response is transformed into an (acoustic) compressional wave, and if the (temporal) pulse characteristics of the electromagnetic field are within certain boundaries, the pulses are perceived by the auditory sensory system.

In the attempt to focus the volume on the fundamental chemical physics and biophysics of electromagnetic-field interactions, and to connect hitherto disparate areas of research, an artificial boundary had to be drawn to encompass well-defined aspects of such a focus and hence exclude a multitude of others. In order that the volume may not only depict the state of the art, within its stated objectives, but also stimulate its development, one may only hope that such exclusions will not have been procrustean.

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Electromagnetic-Field Interaction with Biological Systems in the Microwave and Far-Infrared Region

Physical Basis

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The physical basis for the interaction between biological systems and electromagnetic (EM) fields must rest, in part, on the separate dielectric and spectroscopic properties of the molecular constituents and aggregates that comprise the biological system. A fundamental question, to which the simplest answer has frequently been tacitly assumed, is whether this physical basis, even at the cellular level, is completely given by those properties, or whether non-trivial extensions of such a model are necessary to predict all of the salient EM interactions. In spite of certain shortcomings, which continue to evade exact treatment (1), the interaction between EM radiation and ordinary molecular fluids is adequately represented by existing molecular models, and it would appear unlikely that wholly unexpected features will emerge for such systems. While similar considerations apply to the dominant contributions to the attenuation function for biological systems, evidence is gradually accumulating to suggest that the treatment of biological systems (even at the cellular level) exclusively in such terms may be inadequate. In particular, conclusions drawn from such a restrictive model concerning the behavior of biological response functions, as a function of the frequency and intensity of an external field, may, in certain respects, be not only quantitatively inaccurate but qualitatively misleading. Salient physical features, absent in ordinary molecular fluids, may be present in in vivo biological systems, and thus require modeling of additional, non-trivial biophysical processes. These considerations suggest a treatment along the lines presented in Sections 2 and 3 below.

Absorption and Emission of Radiation in Ordinary Molecular Fluids (Equilibrium Systems)

General Theory of Collision Broadening. A molecular component in an ordinary fluid, in the presence of an electromagnetic field $E(\omega,t)$ and the collisional perturbation $V^0(\omega,t)$, due to interactions with other molecules, will experience a total Hamiltonian:

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$$H(\omega,t) = H^0 + \mu\cdot E(\omega,t) + V^0(\omega,t) \qquad (1)$$

where H^0 is the Hamiltonian for the molecule in the absence of the EM-field interaction and the intermolecular perturbations described by $V^0(\omega,t)$ and μ is the electric dipole moment. The EM field can be described by an angular frequency ω, a field strength E_0, and a distribution over frequencies, $\rho(\omega)$, as follows:

$$E(\omega,t) = E_0(e^{i\omega t} + e^{-i\omega t})\ \rho(\omega) \qquad (2)$$

General methods exist (1-7) for determining the complex permittivity $\kappa^*(\omega)$ of a molecule in the presence of collisional pertubations. Crucial to the form of $\kappa^*(\omega)$, and the attenuation function $\alpha(\omega)$, descriptive of interaction with an EM field of frequency ω, is whether the collisional perturbation $V^0(\omega,t)$ occurs on a time scale which is short, intermediate, or long compared to the period of the field, $(2\pi/\omega)$. In the limit of collisional perturbations which are sudden (of very short duration) within the time-frame of one period of the external field, every collision is effective in interrupting the absorption-emission process (8), and, in the limit of a large number of collisions per unit time, as in a fluid, a totally collision-broadened, relaxation-type spectrum results (1,9-12). Conversely, in the limit of collisional perturbations which are of very long duration compared to a period of the EM field, even in the presence of the large number of collisions, per unit time, operative in a fluid, a resonant-type spectrum results. Since the duration of a typical collision in a molecular fluid is fixed, at a given temperature and pressure, the field frequency ω becomes the crucial variable in determining the diabatic regime (relaxation spectrum) and the adiabatic regime (resonance spectrum). Whether interaction with a field at frequency ω_{ij} leads to a resonant or a relaxation spectrum, in the presence of the intermolecular perturbations described by Eq. (1), can be decided by examing the status of the inequality (13):

$$f(\omega_{ij}) = \left|\int_0^t (h\omega_{ij})^{-1}\ (dH/dt)\ \{\exp(i\int_0^t \omega_{ij}\ dt''\}dt'\right| \qquad (3)$$

For $f(\omega_{ij})\tilde{>}1$, a limit attained as ω_{ij} tends toward zero, a relaxation spectrum is obtained; for $f(\omega_{ij})<<1$, a limit attained as ω_{ij} tends toward ∞, a resonance spectrum is obtained. Although ignorance concerning the detailed form of the time development of the collisional perturbation in a molecular fluid prevents a sharp definition of this criterion, Eq. (3) indicates that the regime of strongly adiabatic interactions (resonant absorption) lies considerably above $\sim$ 1 cm^{-1} ($\sim$ 30 GHz) (14,15). No compelling experimental evidence (16) exists for resonance absorption in ordinary molecular fluids below $\sim$ 100 cm^{-1} ($\sim$ 3000 GHz)(17-23), and experimental claims of resonant features in the attenuation function, at millimeter wavelengths, of biological preparations (24-25) are made tenuous in view of the difficulty of eliminating

experimental artifacts in the millimeter-wave spectroscopy of fluids.

As a result of these very general considerations, one expects the dielectric response function, as expressed by the complex permittivity, $\kappa^*(\omega)$, or the attenuation function, $\alpha(\omega)$, of ordinary molecular fluids to be characterized, from zero frequency to the extreme far-infrared region, by a relaxation spectrum. To first order, $\kappa^*(\omega)$ may be represented by a sum of terms for individual relaxation processes k, each given by a term of the form:

$$(\kappa^*_k(\omega) - \kappa_{\infty k}) = (\kappa_0 - \kappa_\infty)_k \, (1 + j\omega \langle\tau_k\rangle)^{-1} \qquad (4)$$

$$\kappa_0 = \lim_{\omega \to 0} \kappa^*(\omega); \; \kappa_\infty = \lim_{\omega \to \infty} \kappa^*(\omega) \qquad (5)$$

Eq. (4) gives $\kappa^*(\omega)$ for a relaxation process, with a relaxation time $\langle\tau_k\rangle$ and with zero-frequency and high-frequency limits for $\kappa'(\omega)$ of κ_0 and κ_∞, respectively. Two complicating features render the Debye equation, Eq. (4), approximate, and require emendation: (a) a given relaxation process may be associated with a distribution of relaxation times (9-12), and (b), even for a non-distributed relaxation time, Eq. (4) leads to a physically incorrect high-frequency limit for $\kappa^*(\omega)$ or $\alpha(\omega)$. Empirical functions for a distribution of relaxation times have been applied to a wide variety of molecular (27) and biological (28) fluids, with considerable success. With respect to (b), the Debye equation is consistent with an exponential decay function for the electric dipole moment, thus predicting an instantaneous response to the external field being turned off, a physically untenable assumption (29). Several modifications (1,29-32) have been discussed; the effect of this feature on the interpretation of the millimeter-wave and far-infrared spectrum of $H_2O(\ell)$ will be sketched in Section 2.3. However, even for H_2O, the system with the smallest relaxation time expected in a biological context, deviations from Debye behavior, in the sense of (b) above, are not apparent at frequencies below $\sim$ 100 GHz (15,30). As a result, proper modification having been made in those cases where a distribution of relaxation times obtains, the relaxation-type contributions to the bulk complex permittivity in the microwave region are well understood and have been analyzed in some detail (28,33,34).

The entire analysis presented here has assumed, inter alia, thermal equilibrium among the components of the molecular fluid, and a Planck-type equilibrium for the photons absorbed or emitted in the interactions among the molecules and the external EM field.

The Attenuation Function. The complex permittivity $\kappa^*(\omega)$ and the attenuation function $\alpha(\omega)$ are related by basic electromagnetic theory, and independently of any molecular model, as follows:

$$\alpha(\omega) = (\omega/2)(1/2c) \, [\{\kappa'(\omega)\}^2 + [\kappa''(\omega)]^2\}^{1/2} - \kappa'(\omega)]^{1/2} \qquad (6)$$

where c is the velocity of light in vacuo. A closely related quantity is the dielectric conductivity, $\sigma(\omega)$:

$$\sigma(\omega) = \varepsilon_0 \omega \kappa''(\omega) \tag{7}$$

Here, ε_0 is the permittivity of free space. For a simple Debye-type relaxation process, Eq. (4), and owing to the incorrect representation of the high-frequency limit inherent in any expression for $\kappa^*(\omega)$ consistent with an exponential decay function for the electric moment, one obtains for the high-frequency limit of $\alpha(\omega)$ from Eqs. (4) and (6) (30):

$$\lim_{\omega \to \infty} \alpha_{\text{Debye},k}(\omega) = (1/2c)\,[\kappa_0 - \kappa_\infty]_k \langle \tau_k \rangle^{-1} [\kappa_{\infty_k}]^{-1/2} \tag{8}$$

For fundamental physical reasons, the attenuation function for any process must vanish as $\omega \to \infty$. This expectation is borne out by far-infrared measurements of $\alpha(\omega)$ for a variety of molecular systems exhibiting a relaxation-type absorption in the microwave and millimeter-wave region (17-23). While H_2O as a solute in nonhydrogen-bonding solvents also shows this behavior (35), the millimeter-wave and far-infrared spectrum of $H_2O(\ell)$ is complicated by contributions to $\alpha(\omega)$ due to intermolecular vibrations involving a cluster of H_2O molecules (libration and translation), in addition to the high-frequency tail of the relaxation absorption. A heuristic treatment of the general problem (30) makes the relaxation time, Eq. (4), frequency-dependent, such that the limit for $\alpha(\omega)$ in Eq. (8) becomes physically acceptable. Under conditions appropriate to the correct limit, the normalized real and imaginary parts of the complex permittivity and the normalized dielectric conductivity take on the form depicted in Fig. (1). Here, $\langle \tau_k(0) \rangle$ is the relaxation time in the limit of zero frequency (diabatic limit). Irrespective of the details of the model employed, both $\alpha(\omega)$ and $\sigma(\omega)$ must tend toward zero as $\omega \to \infty$, in contrast to Eq. (8), for any relaxation process. In the case of a resonant process, not expected below the extreme far-infrared region, $\alpha(\omega)$ is given by an expression consistent with a resonant dispersion for $\kappa^*(\omega)$ in Eq. (6), not the relaxation dispersion for $\kappa^*(\omega)$ implicit in Eq. (4). Models for collision-broadened lineshapes have been treated in detail (1-7), in the adiabatic as well as the diabatic limit. As expected, the intermediate case, i.e. strongly damped resonant transitions, is most difficult to treat accurately.

In summary, it is expected that the bulk attenuation function for ordinary molecular fluids is reasonably well represented by relaxation-type processes in the microwave region. At high frequencies, in the region of the extreme far-infrared, deviations from Eq. (4) will occur, even for a process with a single relaxation time. Phenomenologically, as $\omega \to \infty$, the efficiency with which a representative collision interrupts the absorption or emission of radiation in a molecular fluid must decrease toward zero, and the relaxation time in Eq. (4) must become frequency-dependent.

H_2O: The Pure Liquid. Because of the large magnitude of the attenuation of $H_2O(\ell)$ and the ubiquitous presence of water in biological systems, the bulk attenuation function of most biological fluids is dominated by the attenuation due to $H_2O(\ell)$. Until recently, wide gaps existed inthe experimental characterization of $\alpha(\omega)$ for $H_2O(\ell)$ in the millimeter-wave and far-infrared region (36-41). These lacunae are now inthe process of being filled. Measurements in the extreme far-infrared (6 - 450 cm^{-1}) (42) and a measurement of high precision at 70 GHz (43) on $H_2O(\ell)$ have recently been reported, to complement existing measurements at lower and higher frequencies. Fig. (2) summarizes the measurements of Grant, and Asfar and Hasted, carried out by a high-loss, travelling-wave technique at 70 GHz and reflection-dispersive-Fourier-transform spectroscopy in the far-infrared, respectively. Also represented is the contribution to $\alpha(\omega)$ from the Debye-type relaxation process calculated from the model (30). It would appear that deviations from the Debye-type behavior are not yet operative at 70 GHz. At frequencies above $\sim$150 GHz, the intermolecular vibrations begin to make their contribution, before the asymptotic limit predicted by the Debye model, Eq. (8), is reached. Owing to the complexity of the intermolecular interactions in a strongly hydrogen-bonded liquid, like $H_2O(\ell)$, detailed and unambiguous analysis of the attenuation function above $\sim$100 GHz is difficult to achieve (41,42).

Schematically, the total attenuation function for $H_2O(\ell)$ is given in Fig. 3. The relaxation contribution goes as ω^2 in the low-frequency limit and dominates the attenuation characteristics up to $\sim$100 GHz. The quasi-lattice vibrations involving clusters of strongly interacting molecules begin to contribute, in a preponderant fashion, above $\sim$100 GHz. While the relaxation contribution $\alpha_{REL}(\omega)$, must begin to decrease at frequencies in excess of $\sim 10^3$ GHz, the quasi-lattice vibrations persist in a set of very broad bands into the far-infrared, (42), attaining extremely high values for $\alpha(\omega)$. As a result, $H_2O(\ell)$, always present, to some degree, in biological systems, provides very efficient attenuation to EM fields in the millimeter-wave and far-infrared regions. Although millimeter-wave measurements on liquids in the category of highest accuracy are typically single-frequency measurements, and while the far-infrared Fourier-spectroscopic measurements have a finite resolution, neither these nor recent swept-frequency measurements (44) provide any experimental evidence which would compel invoking physical mechanisms other than those sketched in Section 2.1 and 2.2. The broad attenuation due to $H_2O(\ell)$ becomes the more effective as the far-infrared region is reached from lower frequencies. As a result, other possible molecular absorption processes occurring in the interior of a biological system are more strongly shielded by the $H_2O(\ell)$ absorption at higher frequencies in the millimeter-wave and far-infrared range, as indicated

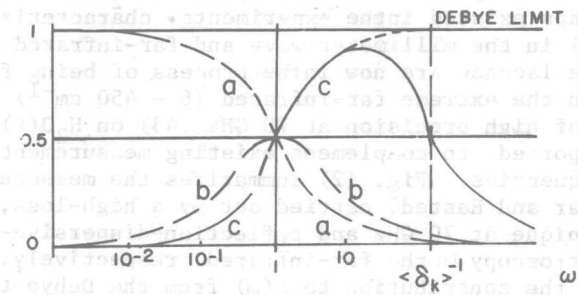

Figure 1. Normalized complex permittivity $\kappa^*(\omega) - j\kappa''(\omega)$ and conductivity $\sigma(\omega)$ for a relaxation process of type k.

Curve a: $[\kappa'(\omega) - \kappa_\infty][\kappa_0 - \kappa_\infty]^{-1}$; *Curve b:* $\kappa''(\omega)[\kappa_0 - \kappa_\infty]^{-1}$; *Curve c:* $\sigma(\omega) < \tau_k(0) > [\varepsilon_0(\kappa_0 - \kappa_\infty)]^{-1}$; *$\omega$: the angular frequency;* $< \tau_k(0) >$*: the relaxation time at zero frequency;* κ_0*: the low-frequency limit of* $\kappa'(\omega)$; κ_∞*: the high-frequency limit of* $\kappa'(\omega)$; $< \delta_k >$*: the average duration of a collision.*

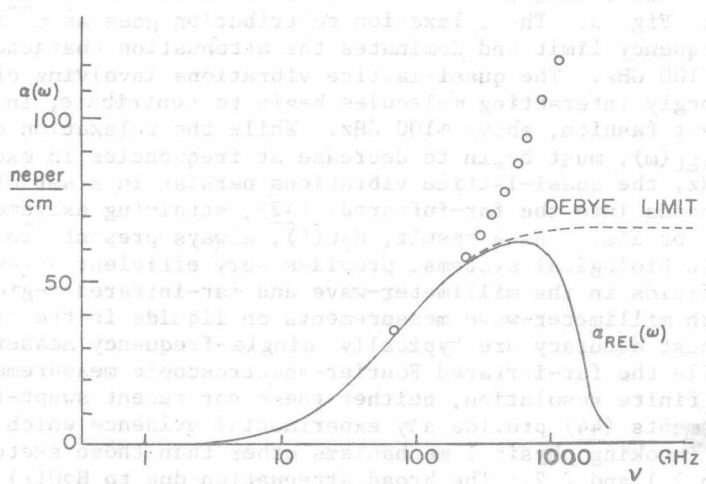

Figure 2. Attenuation function for $H_2O(l)$. $\alpha_{REL}(\omega)$ is the contribution to the total attenuation function due to the rotational relaxation, as calculated from the model in Ref. 30. *The circles are the experimental points from Refs.* 42 *and* 43.

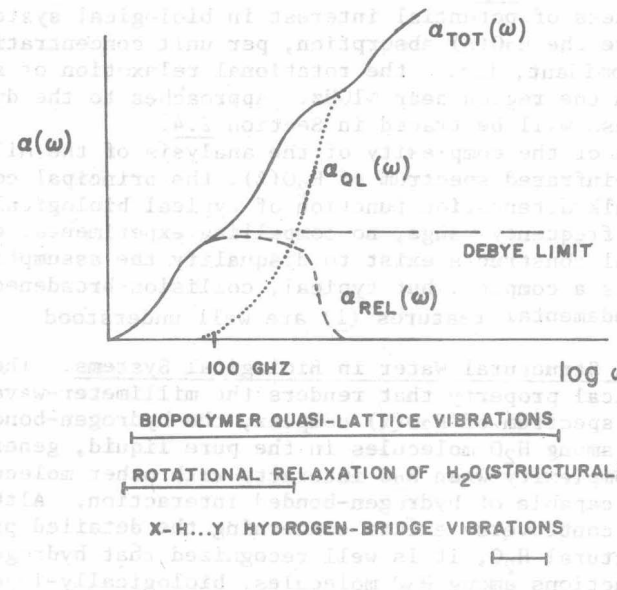

Figure 3. Schematic of the total attenuation function $\alpha_{TOT}(\omega)$, and its contributions, for $H_2O(l)$ at millimeter and far-infrared wavelengths.

$\alpha_{REL}(\omega)$ is the contribution due to the rotational relaxation, and $\alpha_{QL}(\omega)$ is the contribution due to the quasi-lattice vibrations of $H_2O(l)$ clusters. ω is the angular frequency.

schematically in Fig. (3). In particular, quasi-lattice vibrations of biopolymeric systems (Section 2.6) and the vibrations of the bridge-heads (X,Y) of hydrogen-bonded systems X-H...Y (14) fall into this category. Thus, the unusually strong molecular interactions present in $H_2O(\ell)$ produce broad attenuation in a frequency range ($\gtrsim$ 100 cm^{-1}) where the onset of (damped) resonant-type absorption occurs for non-hydrogen-bonded liquids (17) and for the quasi-lattice vibrations of polymeric systems. In contrast, in the low-frequency ($\lesssim$ 1GHz) regime, contributed to virtually exclusively by the $H_2O(\ell)$ relaxation spectrum, $\alpha(\omega)$ falls off as ω^2. Whereas resonant processes in $\alpha(\omega)$ are not expected as $\omega \to 0$, Eq. (3), in any system, there exists a (relaxation) absorption process of potential interest in biological systems, in a region where the $H_2O(\ell)$ absorption, per unit concentration, is not wholly dominant, i.e. the rotational relaxation of structural H_2O, in the region near $\sim$1GHz. Approaches to the dynamics of that process will be traced in Section 2.4.

In spite of the complexity of the analysis of the millimeter-wave and far-infrared spectrum of $H_2O(\ell)$, the principal contributor to the bulk attenuation function of typical biological systems in this frequency range, no compelling experimental evidence or theoretical constructs exist to disqualify the assumption that this system is a complex, but typical, collision-broadened system whose fundamental features (1) are well understood.

Free and Structural Water in Biological Systems. The same salient physical property that renders the millimeter-wave and far-infrared spectrum of $H_2O(\ell)$ complex, the hydrogen-bonded interactions among H_2O molecules in the pure liquid, generates an additional complexity when H_2O interacts with other molecular systems also capable of hydrogen-bonded interaction. Although considerable controversy exists concerning the detailed properties of structural H_2O, it is well recognized that hydrogen-bonded interactions among H_2O molecules, biologically-important molecules, and the biological membrane play a crucial role in biological systems (45,46). The hydrogen-bond interaction exhibits energetics intermediate between those characteristic of ordinary molecular interactions and weak chemical interactions and, importantly, possesses directional properties not so fully articulated in the first. In a mixture of biopolymers, ions and H_2O, in vitro, as well as in an actual biological context, the total number of H_2O molecules will be distributed in a complicated fashion over sites which range from loci within essentially pure clusters of H_2O molecules (the "free" water) and sites directly interacting with other molecular entities (the "structural" water). Clearly, the instantaneous distribution and the dynamics of the set of H_2O molecules among such sites, of which these are the extreme cases, are exceedingly complex. With respect to the contribution to the total attenuation function, $\alpha(\omega)$, due to structural H_2O, one requires knowledge of the concentration of