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# What Can We Learn from Three-Dimensional Infrared Spectroscopy?

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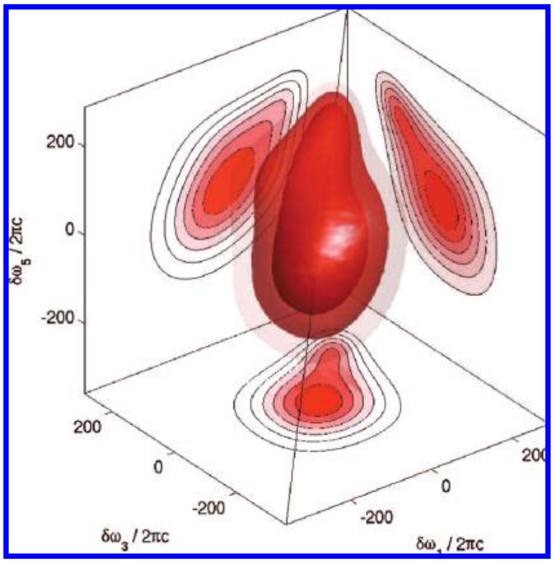
## CONSPECTUS



The low-frequency part of the vibrational spectrum of a liquid is dominated by intermolecular degrees of freedom. Hence, it reports on the motion of solvent molecules with respect to each other rather than on the intramolecular details of individual molecules. In hydrogen-bonded liquids, in particular water, a detailed understanding of the low-frequency spectrum is enormously complicated because of the complex hydrogen-bond network, which constantly rearranges on an ultrafast femtosecond to picosecond time scale. Many of the peculiar properties of water have their origin in these processes. Conventional far-infrared (far-IR) or Raman spectroscopy, as well as two-dimensional IR (2D-IR) spectroscopy, are all linear with respect to the intermolecular (solvent) degrees of freedom. These spectroscopies tell us much about the density of states in the low-frequency range but little about the dynamics of the hydrogen-bond making and breaking.

In this Account, we propose three-dimensional IR (3D-IR) spectroscopy as a novel tool that is nonlinear with respect to these low-frequency degrees of freedom; hence, it may provide much more detailed insights into intermolecular dynamics. The first experimental realizations of 3D-IR spectroscopy have been demonstrated in the literature; the information it affords is similar to that of 2D-Raman spectroscopy. Three-dimensional IR spectroscopy will, for the first time, reveal whether the low-frequency part of the vibrational spectrum of liquids has to be considered mostly homogeneously or inhomogeneously broadened. Alternately, we may find that either of these classifications is completely wrong because the normal mode picture fails when thermal energy is of the same order of magnitude as the ruggedness of the intramolecular potential energy surface.

We briefly introduce the theoretical background of 3D-IR spectroscopy and discuss two of its most promising applications: (a) the more thorough characterization of non-Gaussian stochastic processes such as the hydrogen-bond dynamics of water and (b) non-Markovian ultrafast exchange processes. In the ultrafast regime, many of the otherwise valid simplifying assumptions of nonequilibrium statistical mechanics (for example, linear response and Markovian dynamics) are likely to fail; 3D-IR spectroscopy will allow us for the first time to experimentally explore their range of validity.

## Introduction

In a seminal paper, Tanimura and Mukamel proposed an experiment for two-dimensional (2D) femtosecond vibrational spectroscopy of liquids.[1] The goal of this experiment would be to resolve the dynamics responsible for the spectral broadening of low-frequency librational and translational modes of liquids. The low-frequency part of the spectrum is related to inter- rather than the intramolecular degrees of freedom of a liquid, that is, report on the dynamics of the individual solvent molecules as they move with respect to each other. These dynamics determine, to a large

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extent, the properties of a liquid. They are important in a larger context than neat liquids; for proteins, these low-frequency modes are the conformational degrees of freedom of the backbone. The modes below $\sim$200 cm$^{-1}$ are thermally excited at room temperature, and, hence are the active degrees of freedom.

In the most simple picture (the so-called Bloch picture), one often classifies spectral broadening as homogeneous (Lorentzian line shape), as inhomogeneous (Gaussian line shape), or, sometimes, as a convolution of both (Voigt profile). Homogeneous broadening would be related to infinitely fast dynamics, whereas inhomogeneous broadening would be related to infinitely slow dynamics. Needless to say, the truth lies in between. Water is a particularly interesting example: liquid water builds a complex network of hydrogen bonds that constantly rearrange, and the dynamics of those hydrogen bonds are largely important for many of the peculiar properties of water. The event of an exchange of a hydrogen bond takes on the order of 100 fs;[2] hence it is not infinitely fast, whereas the typical lifetime of such a hydrogen bond is $\sim$1 ps, certainly not infinitely slow. The low-frequency spectrum of water below ca. 1000 cm$^{-1}$ consists of very broad and largely unstructured bands, which are due to intermolecular (librational and translational) degrees of freedom of the different water molecules relative to each other (not to be confused with the higher frequency *intra*molecular modes, that is, the OH-stretch and bend vibrations). It is totally unclear whether these low-frequency modes are homogeneously or inhomogeneously broadened, or whether these two pictures are both wrong. A nonlinear spectroscopy in this low-frequency range, such as a photon echo or 2D spectroscopy, could potentially answer these questions. That is, the information on the dynamics of the making and breaking of the hydrogen bond network is, in principle, contained in these modes, and it is the goal of nonlinear spectroscopy to extract this information.

It is well established that one cannot unambiguously extract information on the dynamics of line broadening mechanisms from linear spectroscopy, such as far IR or terahertz absorption spectroscopy. Loring and Mukamel showed quite some time ago that this is also true for Raman spectroscopy, even though Raman is nonlinear in a power expansion with respect to the laser electrical fields.[3] This is because the Raman response is a function of only one time variable, or one frequency variable after a Fourier-transform, because nonresonant Raman scattering goes through a virtual level with zero lifetime, so two of the field interactions necessarily occur at the same instant in time. Hence, a low-frequency IR absorption spectrum and a Raman spectrum reveal essentially the same information on the spectral density of modes (apart from the fact that IR and Raman processes have different selection rules and hence are sensitive to different modes). Either of these experiments is done on an equilibrium ensemble, which *per se* is time-stationary. In order to extract dynamical information, one must correlate the status of the system during one time period with that at some later time period. In simple words, this is the reason that more than one time variable is needed to learn about the dynamics of an equilibrium ensemble.

The paper by Tanimura and Mukamel[1] triggered an enormous experimental[4−8] effort. These experiments utilize five incident laser pulses with two experimentally controllable time variables in between and hence are nonlinear in the sense discussed above. However, minimizing the number of field interactions to five in a Raman experiment necessarily implies that one of the transitions is a two-quantum transition, which would be forbidden in the harmonic case and becomes only weakly allowed in the presence of anharmonicity. As a result, the fifth-order 2D-Raman response is very weak and gets easily masked by cascaded third-order processes.[9,10] That is, light emitted from a conventional (third-order) Raman process is recycled for a subsequent Raman process. Since each of these third-order Raman processes contains only one-quantum transitions, the cascading signal can easily exceed the desired fifth-order signal (several groups have devised strategies to suppress the cascading signal[5−8]).

Two-dimensional IR spectroscopy was being developed at about the same time[11] (see refs 12−16, as well as the other articles from this issue, for recent reviews). However, since available femtosecond IR light sources as well as IR detectors work best in a spectral range above $\sim$1000 cm$^{-1}$, these experiments concentrate on high-frequency intramolecular modes rather than on low-frequency intermolecular modes. A 2D-terahertz experiment has yet to be demonstrated. Nonlinear terahertz spectroscopy requires extremely high-energy terahertz pulses, and at the present stage, such experiments are feasible only for solid-state samples such as semiconductors.[17,18]

High-frequency modes may still provide a way to observe intermolecular dynamics. Just as optical chromophores sense solvent reorganization in a solvation experiment, so high-frequency vibrational modes can serve as spectator modes of the low-frequency equilibrium intermolecular fluctuations of a liquid. Going back to the example of water, the frequency of the O−H stretch is sensitive to the local hydrogen bonding structure: it is dominated by the forces from the nearest neighbor or hydrogen bonding partner; however, the electric field from

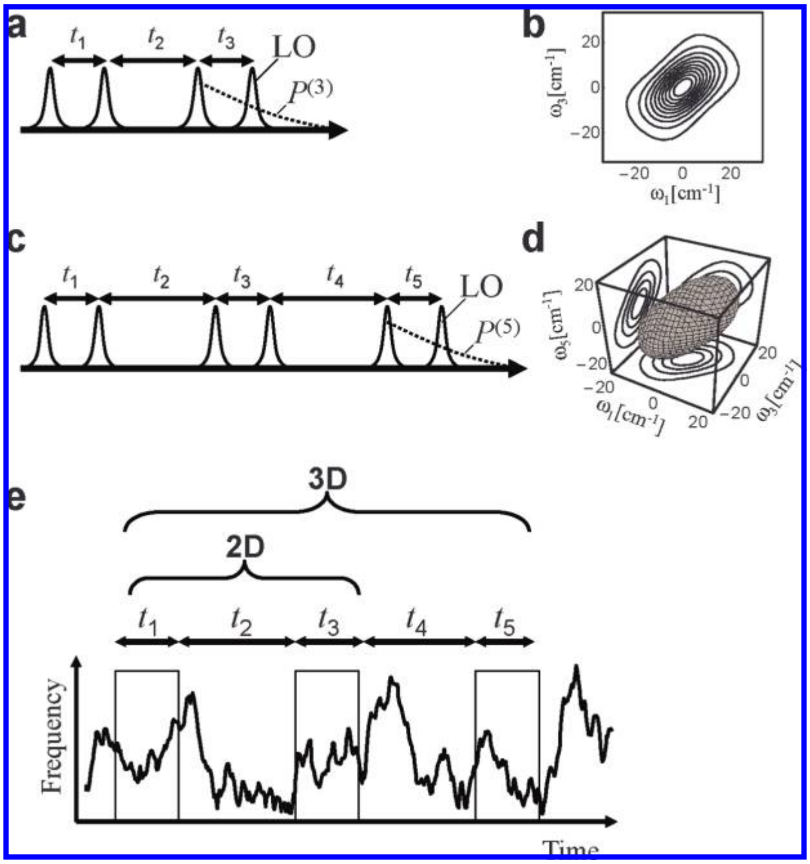

**FIGURE 1.** Principle of 2D-IR and 3D-IR spectroscopy: (a, c) pulse sequences; (b, d) model spectra; (e) an example $\omega$-trajectory.

more distant water molecules contributes as well.[19−21] As the local solvent shell fluctuates, the frequency of the O−H stretch fluctuates. The low-frequency, red-shifted part of the OH-stretching band corresponds to O−H groups in strong hydrogen bonds, and the high-frequency, blue-shifted side of the spectrum corresponds to O−H's involved in weak or broken hydrogen bonds. If one can measure the O−H frequency fluctuations then one can learn about the local dynamics of the fluid.

Figure 1a,b shows the principle idea of 2D-IR spectroscopy. Consider the instantaneous frequency of a vibrational probe that responds to the fluctuating environment (Figure 1e). One measures those instantaneous frequencies $\omega_1$ and $\omega_3$ during a time period $t_1$ and $t_3$, respectively, by the help of corresponding Fourier transforms, with a waiting time $t_2$ in between (Figure 1a). For short enough times $t_2$, there will be a certain degree of correlation between frequencies $\omega_1$ and $\omega_3$ and the 2D-IR line shape is elongated along the diagonal (Figure 1b). As time $t_2$ increases, the memory about the initial frequency $\omega_1$ gets lost (we call this process spectral diffusion), and the 2D-IR line shape becomes more round.

Two-dimensional IR spectroscopy is nonlinear for the high-frequency spectator mode in the sense discussed above, since it contains three experimentally controllable time variables, $t_1$, $t_2$, and $t_3$. However, if we consider the OH stretch vibration just a spectator mode that helps us to elucidate the intermolecular dynamics, times $t_1$ and $t_3$ are no longer dynamical time variables. They are required to define two instantaneous frequencies, $\omega_1$ and $\omega_3$, each of which is a measure of the instantaneous hydrogen bond configuration during the corresponding time period (it takes some time to define a frequency; hence time periods $t_1$ and $t_3$ cannot be infinitesimally short). In that sense, 2D-IR spectroscopy is a linear spectroscopy with respect to the low-frequency intermolecular modes for the very same reason Raman spectroscopy is a linear spectroscopy:[3] it contains only one dynamical time variable, $t_2$. In fact, one can think about such a 2D-IR experiment as a *resonance* Raman experiment of the intermolecular hydrogen bond modes that are resonantly enhanced by the OH-stretch vibration. The frequency fluctuation correlation function deduced from a $t_2$-series of 2D-IR spectra is directly related to the spectral density of modes that couple to the OH-stretch vibration. For example, one could describe the frequency fluctuation correlation function as a Fourier transform of a distribution of infinitesimally narrow, harmonic modes, that is, purely inhomogeneously broadened without any dephasing.[22]

Mathematically speaking, this model may always reveal exact fits, but it obviously does not describe the physics of liquids correctly. In order to go beyond this level of description, a logical extension would be 3D-IR spectroscopy, which introduces a second dynamical time variable $t_4$ (Figure 1c) and is nonlinear with respect to the low-frequency modes. Hence, the motivation for doing 3D-IR spectroscopy would be similar to 2D-Raman spectroscopy;[1,4−8] however, they differ significantly in terms of their detailed information content. It is nevertheless interesting to note that 3D-IR spectroscopy contains exclusively resonant and one-quantum transitions and therefore produces significantly stronger signals that do not suffer from cascading signals.[23,24]

In a recent paper,[25] we had found by analyzing data from transient 2D-IR spectroscopy that the solvation of a C═O mode of a metal−carbonyl dissolved in DMSO does not necessarily occur in the linear response regime. That is, the relaxation time of the system brought into a nonequilibrium state was *different* from that of equilibrium fluctuations (as opposed to Onsager's regression hypothesis). Similar conclusions have been drawn by Blank and co-workers[26] who probe the low-frequency (1−500 cm$^{-1}$) response of a solvent through a heterodyne-detected nonresonant Raman signal to the electronic excitation of a solute chromophore. Both types of experiments[25,26] have two variable time delays, one for the time after the excitation of the chromophore, which brings the system into a nonequilibrium state, and a second time delay between the second and third nonresonant Raman excitations. The first time delay allows the solvent some time to respond to the solute, and the second time delay allows the experiment to probe different parts of the solute's response, which is to say, which of the solvent's low-frequency modes respond to the solute and when. Three-dimensional IR spectroscopy is going to be performed on an equilibrium ensemble; nevertheless, we will see that the principle idea behind it is very much related.

## Recent 3D-IR Experiments

Before we start, we wish to specify what exactly we mean by 3D spectroscopy. In the context of this paper, 3D spectroscopy is not just spectroscopy as a function of three time variables, but we wish to limit it to spectroscopy where the molecular system is in a coherent state through three time periods. It is then meaningful to perform a 3D Fourier transform with respect to these coherence times. In simple words, in the context of this paper, 3D spectroscopy plots spectra as a function of three frequencies (Figure 1d) and possibly additional waiting times. Various efforts to perform 3D spectroscopy have appeared in literature, which shall be briefly discussed in the following.

Nelson and co-workers have recently presented a three-pulse third-order 3D spectrum of excitons in GaAs quantum wells.[27] In these experiments, the second laser pulse excites the system into a two-quantum coherence state; hence the system is in coherence during all time periods of the experiment (in contrast to most third-order experiments where the system is in a population state during the second time period). Consequently, a Fourier transform with respect to all three coherence times will lead to a 3D spectrum, where the frequency $\omega_2$, related to the second coherence time, will be roughly twice that of $\omega_1$ and $\omega_3$ (because of the two-quantum coherence).

Zanni and co-workers have presented a series of fifth-order nonlinear experiments based on three input laser pulses,[23] which can in fact been used to produce 3D-IR spectra.[28] This approach takes two field interactions each from two of the input laser pulses (like a two-pulse photon echo experiment, which is third-order despite the two pulses). Making use of phase-matching, that is, by putting the detector at the $k_1 - 2k_2 + 2k_3$ direction, one can discriminate the fifth-order signal from the third-order signal. Very recently, the group has extended the work to a five-pulse 3D-IR experiment using pulse shaping techniques.[29]

We have presented two theoretical studies that explore the potential information content of 3D-IR spectroscopy in general,[30] as well as applied to the spectral diffusion of the OH-stretch vibration in liquid water.[31] We have furthermore presented the first experimental demonstration of a purely absorptive 3D-IR spectrum of the asymmetric stretch vibration of $CO_2$ dissolved in water (Figure 2).[24] This transition is essentially homogeneously broadened,[12] hence these results serve here only as a demonstration example. Nevertheless, as discussed in detail in refs 23 and 24, the perfect agreement between theory and experiment, as well as the concentration dependence of the signal, unambiguously prove that cascading problems do not really play a role in 3D-IR spectroscopy. Experimental work on the 3D-IR spectroscopy of water is in progress.[32]

In the following, we outline two possible applications of 3D-IR spectroscopy:

## Applications of 3D-IR Spectroscopy

**Non-Gaussian Statistics.** The instantaneous frequency, $\omega(t)$, of a molecular probe is a (complicated) function of the geometrical conformation of the solvent molecules surrounding it; hence, we should think about the instantaneous frequency as

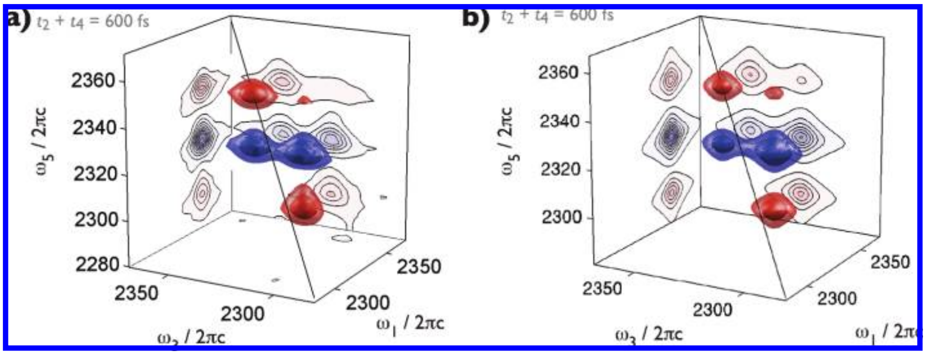

**FIGURE 2.** (a) Experimental and (b) simulated 3D-IR spectrum of the asymmetric stretch vibration of $CO_2$ dissolved in water. The five peaks with varying intensities and signs (color coded in red and blue) originate from the different possible pathways of up-climbing the vibrational ladder in a weakly anharmonic oscillator. Adapted from ref 24.

$\omega(\vec{R}(t))$ with $\vec{R}(t)$ a multidimensional coordinate vector of the surrounding. What we are after, would, in principle, be this conformation of the surrounding, $\vec{R}(t)$; however, our window to observe these coordinates is a one-dimensional "coordinate" $\omega(\vec{R})$. We call $\omega$ a spectroscopic coordinate, onto which the multidimensional motion, $\vec{R}$, of the surrounding is projected. That spectroscopic coordinate might or might not be a good order parameter (or reaction coordinate); in other words, it might or might not decisively discriminate among various substates of the surrounding. For our water example, the OH-stretch frequency is believed to be a decisive coordinate that reports on the strength of the hydrogen bond. The aim is to extract as much as possible information about the dynamics of these hydrogen bonds from a one-dimensional observable, $\omega(t)$.

In the framework of Kubo's stochastic theory of line shapes, and within the Condon approximation (which is not always valid),[33] the linear response function is given by

$$R^{(1)}(t_1) = \langle \exp(-i\int_0^{t_1} \omega(\tau)\,\mathrm{d}\tau) \rangle \qquad (1)$$

where $\omega(t)$ is the fluctuating transition frequency around its average value (we skip the average frequency here for clarity, which reveals just a frequency shift). The related expressions for 2D and 3D spectroscopy are

$$R^{(3)}(t_1, t_2, t_3) = \langle \exp(\pm i\int_0^{t_1} \omega(\tau)\,\mathrm{d}\tau - i\int_{t_2+t_1}^{t_3+t_2+t_1} \omega(\tau)\,\mathrm{d}\tau) \rangle$$

$$R^{(5)}(t_1, t_2, t_3, t_4, t_5) = \langle \exp(\pm i\int_0^{t_1} \omega(\tau)\,\mathrm{d}\tau \pm i\int_{t_2+t_1}^{t_3+t_2+t_1} \omega(\tau)\,\mathrm{d}\tau - i\int_{t_4+t_3+t_2+t_1}^{t_5+t_4+t_3+t_2+t_1} \omega(\tau)\,\mathrm{d}\tau) \rangle \qquad (2)$$

respectively. The corresponding 1D, 2D, and 3D spectra are obtained by a Fourier transform with respect to the coherence times $t_1$, $t_3$, and $t_5$ (see ref 30 for technical details). These expressions are typically evaluated using the so-called cumulant expansion truncated after second order. In this case, all orders of nonlinear spectroscopy (i.e., eq 1 as well as eq 2) can be expressed in terms of *one and the same* line shape function, $g(t)$:[22]

$$g(t) = \int_0^t \mathrm{d}\tau' \int_0^{\tau'} \mathrm{d}\tau'' \,\langle \omega(\tau'')\omega(0) \rangle \qquad (3)$$

which contains the so-called frequency fluctuation correlation function (FFCF) $\langle \omega(t)\omega(0) \rangle$.

It turns out that if the frequencies $\omega$ are Gaussian distributed, then the cumulant expansion truncated after second order is exact[22] and the FFCF contains all information we can possibly extract from the system. In other words, if the statistics are Gaussian, then a given FFCF uniquely defines the stochastic process. We need third-order nonlinear spectroscopy (2D-IR spectroscopy) to unambiguously determine the FFCF, but we would not get *any* additional information from any higher order (3D) spectroscopy.

Before we continue, one remark is in order here. It might seem surprising that 1D-IR spectroscopy is not sufficient to determine the FFCF. After all, when evaluating the cumulant expansion, the linear response function eq 1:

$$R^{(1)}(\omega_1) = \mathscr{R}\int_0^\infty e^{i\omega_1 t}\, e^{-g(t)}\,\mathrm{d}t \qquad (4)$$

is expressed explicitly in terms of the FFCF through the line shape function, $g(t)$ (eq 3). Mathematically speaking, the inversion of eqs 3 and 4 would be unique (i.e., an inverse Fourier transform and a second derivative). It has been attempted in ref 34 to deduce the FFCF directly from a linear absorption spectrum by such an inversion, and the result has been compared with that obtained from a nonlinear three-pulse photon echo peak-shift experiment. The inversion works in principle, but the results are extremely poor. It turns out that the inversion of these two equations is an ill-conditioned problem that is not feasible in the presence of experimental noise.

Fluctuations are often Gaussian distributed, to a very good approximation, owing to the central limit theorem. The central limit theorem states that if a random process is the sum of many contributions, then it will be Gaussian distributed regardless of what the details of the individual contributions. Consider, for example, the electronic transitions of a chromophore that interacts with hundreds of solvent molecules surrounding it through Coulombic interaction, which is long-ranged. The central limit theorem holds in this case, and the statistics are indeed Gaussian (linear response regime). Vibrational transitions interact much more locally, however. In particular for hydrogen-bonded systems, like water, it is often a single hydrogen bond that may have the dominating effect on the transition frequency of the OH-stretch vibration, whereas the contribution from other water molecules is significantly less.[20,35] In fact, the frequency distribution of the OH-stretch vibration of water is profoundly non-Gaussian.[20,36,37]

In the non-Gaussian case, truncation of the cumulant expansion after second order is no longer exact, and higher order FFCFs become relevant, such as the three-time FFCF $\langle\omega(t' + t'')\omega(t')\omega(0)\rangle$. Strictly speaking, all orders of spectroscopy (linear, 2D, and 3D) will then have contributions from all orders of FFCFs. Nevertheless, in terms of sensitivity we have shown numerically that 2D spectroscopy is a sensitive probe of only the two-time point FFCF, $\langle\omega(t)\omega(0)\rangle$,[30] whereas one has to go to 3D spectroscopy in order to measure the three-time point FFCF, $\langle\omega(t' + t'')\omega(t')\omega(0)\rangle$. The argument is similar to the discussion above: even though the 2D spectrum contains contributions from higher order FFCFs, one could not invert the problem and extract them from a measured 2D spectrum. For example, one can construct two random processes with nearly identical two-time point FFCFs but different higher order FFCFs. The resulting 2D-IR spectra are practically indistinguishable,[30] whereas the 3D-IR spectra allows one to discriminate the two processes.

The three-point correlation functions contain different information than two-point correlation functions. The two-point FFCF is well understood as describing the width of the two-point joint probability density (the second central moment) as a function of time. The three-point correlation functions, on the other hand, are analogous to a skewness. They derive from the *difference* in dynamics as a function of the initial frequency, $\omega_1$. This difference is necessarily zero if the system is purely harmonic, by symmetry, so it is tuned to the anharmonicity of the low-frequency modes of the system under study. Each initial frequency tags a subensemble that is interrogated by the later steps. The experimental analogy is that this is like a hole burning experiment with 2D detection. The first time point divides the system into subensembles labeled by their initial frequency, and the later time points provide the resolving power of a 2D experiment to see things like the homogeneous and inhomogeneous line shape, the rate of spectral diffusion, and the appearance of cross peaks, all as a function of the initially excited frequency.

From another point of view, it is often helpful to think about a 2D-IR spectrum as a two-time-point joint probability function. That is, a 2D-IR spectrum (Figure 1b) represents the conditional probability $p(\omega_3,t_2|\omega_1,0)$ of the frequency of the OH-stretch vibration being at $\omega_3$ at time $t_2$, provided it was at a frequency $\omega_1$ at time 0. If these two frequencies are correlated, then the 2D-IR line shape will be tilted and elongated along the diagonal. The correlation coefficient,

$$q_{13}(t_2) \equiv \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \omega_1\omega_3 R^{(3)}(\omega_1, t_2, \omega_3)\, \mathrm{d}\omega_1\, \mathrm{d}\omega_3 \qquad (5)$$

resembles the two-time point FFCF,[30]

$$q_{13}(t_2) \approx \langle\omega(t_2)\omega(0)\rangle \qquad (6)$$

The correlation diminishes as time $t_2$ increases due to spectral diffusion, and the 2D-IR line shape will become more and more round.

Similarly, a 3D-IR spectrum (Figure 1d) can be considered a three-time-point joint probability function $p(\omega_5,t_2 + t_4|\omega_3,t_2|\omega_1,0)$, that is, the conditional probability of the frequency of the OH-stretch vibration being at $\omega_5$ at time $t_2 + t_4$, provided it was at a frequency $\omega_3$ at time $t_2$, provided it was at frequency $\omega_1$ at time 0. Conceptually speaking, this thought can be extended to any order of nonlinear spectroscopy, emphasizing the possibility to map out complex pathways in frequency space. Thereby part of the information loss that originates from ensemble averaging can be regained. It has been shown that this mapping of multidimensional spectra onto the corresponding multi-time-point joint probability functions is exact in the so-called inhomogeneous limit,[30] in which the time scale of fluctuations is much longer than the time it takes to measure a frequency. In this limit, one can rigorously classify any higher-order nonlinear spectroscopy in terms of certain frequency fluctuation correlation functions. When fluctuations are faster, motional narrowing blurs this classification to some extent.

**Application to Water.** Recent ultrafast 2D-IR experiments have concentrated on measuring and understanding the dynamics of isotope-diluted water, that is, either the OD or OH vibration of HOD in $H_2O$ or $D_2O$, respectively.[21,38,39] Due to isotope dilution, frequency fluctuations are mostly due to local hydrogen bonding while coupling to other OD or OH modes plays only a minor role (the 2D-IR spectroscopy of pure water has been reported as well[40] but will not be discussed here). There is a general consensus regarding the two-time FFCF of the OH stretch vibration of water, and the molecular motions responsible for the overall time scales. The two-time FFCF decays very quickly, within about 1 ps, in a highly nonexponential manner with some underdamped, oscillatory contribution. Looking more closely at the time evolution of the 2D-IR line shape, some researchers have described the frequency fluctuations of the OH-stretch on the high-frequency side of the OH-stretching band to be much faster than those on the low-frequency side of the band.[21] This language of a "frequency-dependent FFCF" is very appealing for gaining insight into the variation of the dynamics but is dissatisfying at a fundamental level because the frequency fluctuations are much larger than any window of frequency for which the FFCF is initially defined. These effects are explicitly due to the breakdown of linear response and the presence of nonvanishing higher order correlations, so higher order experiments are required to unambiguously describe the dynamics. It is already evident from the linear absorption spectrum of the OH-stretch vibration that the distribution of frequencies is profoundly non-Gaussian, that is, strongly skewed to the low-frequency side and a bump on the high-frequency side. Two-dimensional IR spectroscopy contains the influence of the nonlinearity of the low-frequency modes, but it is not able to completely unravel those nonlinearities. Three-dimensional IR spectroscopy, in contrast, allows one to determine the difference in line shape for different initial frequencies (which translates to different hydrogen bonding structures), to see how rapidly and how uniformly different parts of the stretching band intermix or to track the detailed frequency trajectory of a OH further along its stochastic path.

We developed a theoretical approach based on molecular dynamics (MD) simulations to build some intuition for what might be observed in a 3D-IR experiment of water.[31] Molecular dynamics simulations generate a structures that can be converted to frequency trajectories. From these frequency trajectories, we tag the frequency at three instants and build a three-point joint probability density, which is a function of two time intervals, $t_2$ and $t_4$ (Figure 3a). When these times are short, then the joint-probability density is stretched along the body diagonal of the 3D frequency space. As the time increases, it becomes an approximately spherical distribution. But, in between, the joint probability has pronounced structure. When projected onto any of the Cartesian planes, however, this complicated 3D shape becomes symmetric indicating that there is nontrivial information in 3D that is not available in 2D.

Let us focus on one part of the 3D joint-probability density, namely, slices from the high-frequency side of the spectrum (associated with weaker hydrogen bonds) (Figure 3b). These slices show that indeed some of the distribution has dynamics that are extremely fast; the weak bonds seem to snap back to their hydrogen bonding partner. On the other hand, some of the distribution moves extremely slowly doing something qualitatively different (Figure 3c). Now, in a liquid without long-range crystalline ordering, there will always be a great variety of stochastic paths that different molecules follow. The joint probability density gives the statistical weight for each kind of process and shows that these statistical weights do not fit to a linear theory. There is no 1D effective potential of mean force guiding the dynamics of a distribution which is nearly bimodal in terms of rates.

A different picture for what drives these dynamics is developing.[2,21,31,41,42] Potentials of mean force with multiple coupled degrees of freedom seem necessary to describe the frequency fluctuations of water. For example, one proposed 2D free energy surface has one coordinate that is the spectroscopic degree of freedom, and perpendicular to that, is a hydrogen bond exchange coordinate like the difference between nearest and next-nearest neighbor distances to the proton. As the hydrogen bond exchanges, this parameter goes from negative to positive. There are two basins for each hydrogen bond connected by a bottleneck or transition state on the blue side of the spectrum. Different parts of the 3D joint probability (Figure 3a) can selectively pick out different regions of this free energy surface (Figure 3d). The part marked in blue comes from trajectories that wander across the bottleneck, while the part marked in green sweeps across the basins going from weak to strong to weak again.

This description is all in the limit of inhomogeneous broadening. One can incorporate motional narrowing effects by using standard response function calculations. The motional narrowing does significantly reshape the spectrum, but there is a distinct signature of these 3D shapes that we hope to extract from the measurement.

MD simulations based on the most primitive water model, SPC water, agree surprisingly well with IR photon echo and 2D-IR experiments of isotope-diluted water.[21,35] This agreement is startling given the simplicity of the approach: the use of classical mechanics, the complete neglect of polarizibility and the reduction to only three independent parameters (one Lennard-Jones term and a partial charge for the oxygen; the partial charges of the hydrogens are calculated accordingly,

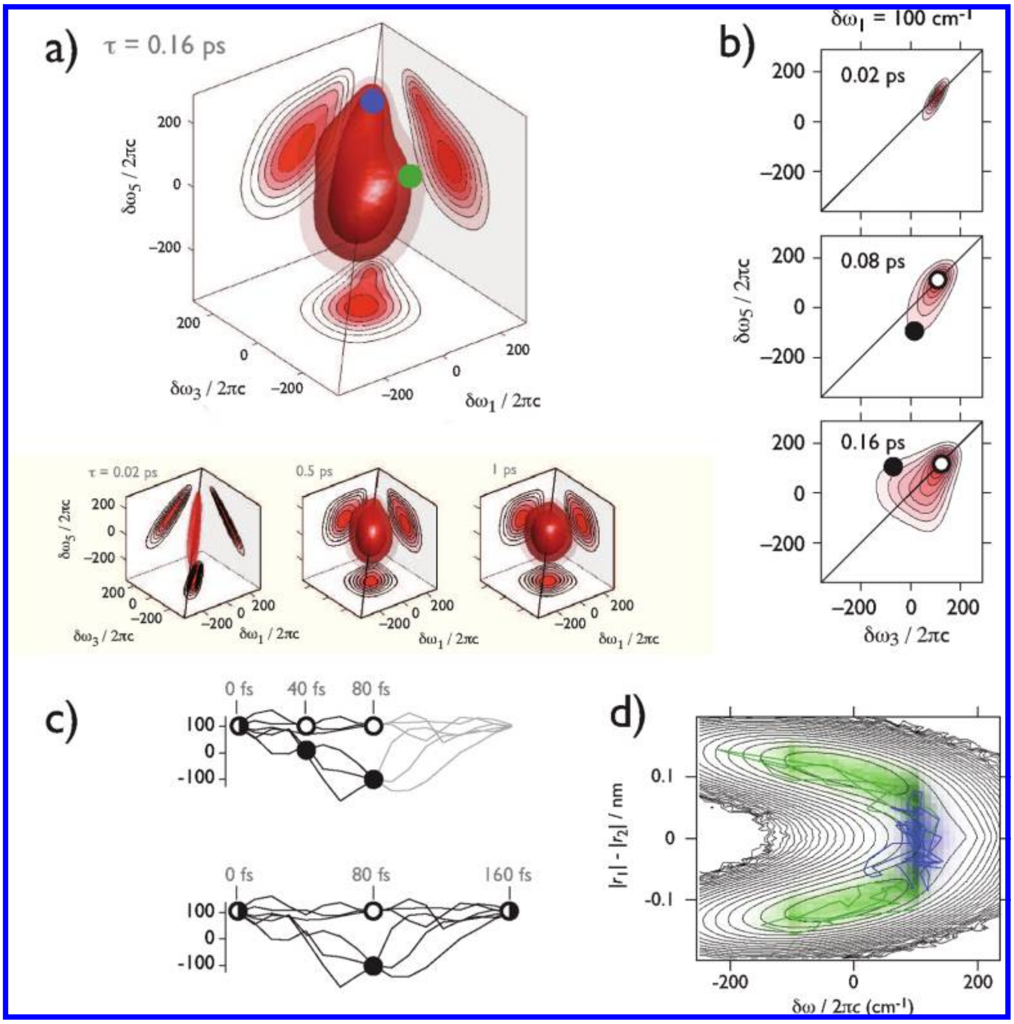

**FIGURE 3.** (A)Three-dimensional joint probability densities for the OH-stretch of water and (b) slices of the joint probablities. (c) The slices show both slow and fast dynamics for the same initial conditions on the blue side of the absorption band. (d) Different parts of the 3D probability distribution select different parts of a 2D potential of mean force for hydrogen bond rearrangements. Adapted from ref 31.

while they do not carry any Lennard-Jones term). It is currently not known whether this good agreement reflects the fact that the model really describes water correctly (which is somewhat questionable) or whether 2D-IR spectroscopy effectively just measures to what these parameters have initially been fitted (e.g., the self-diffusion coefficient). Three-dimensional spectroscopy will eventually provide a much more stringent test of the dynamical properties of water models.

## Non-Markovian Exchange

In a chemical exchange experiment, a molecule exists in two distinct configurations, for example, hydrogen-bonded and non-hydrogen-bonded. If these two configurations cause a frequency shift of a particular vibrational mode, one would observe a double peak in the linear absorption spectrum (provided that the exchange rate is slower than the inverse of the line splitting). In a 2D-IR experiment, then, one can directly observe the rate of the chemical exchange.[43−45] That is, a first pulse pair tags the vibrational transition in the one configuration, and when the molecule hops into the other configuration, it carries this tag with it. As a result, cross peaks grow in a 2D-IR spectrum as a function of population time, $t_2$, the kinetics of which directly reflects the exchange rate. One can think of chemical exchange as a spectral diffusion process but along a discrete or binary coordinate rather than a continuous coordinate.

Nevertheless, there is again a trivial solution to the dynamics when the exchange is Markovian. In this case, the probability of hopping from one site to the other does not depend on the history. In the Markovian case, chemical exchange occurs monoexponentially, and consequently, the two-point FFCF and all higher order FFCFs will decay monoexponentially as well with the same rate (Figure 4a). In the Markovian case,

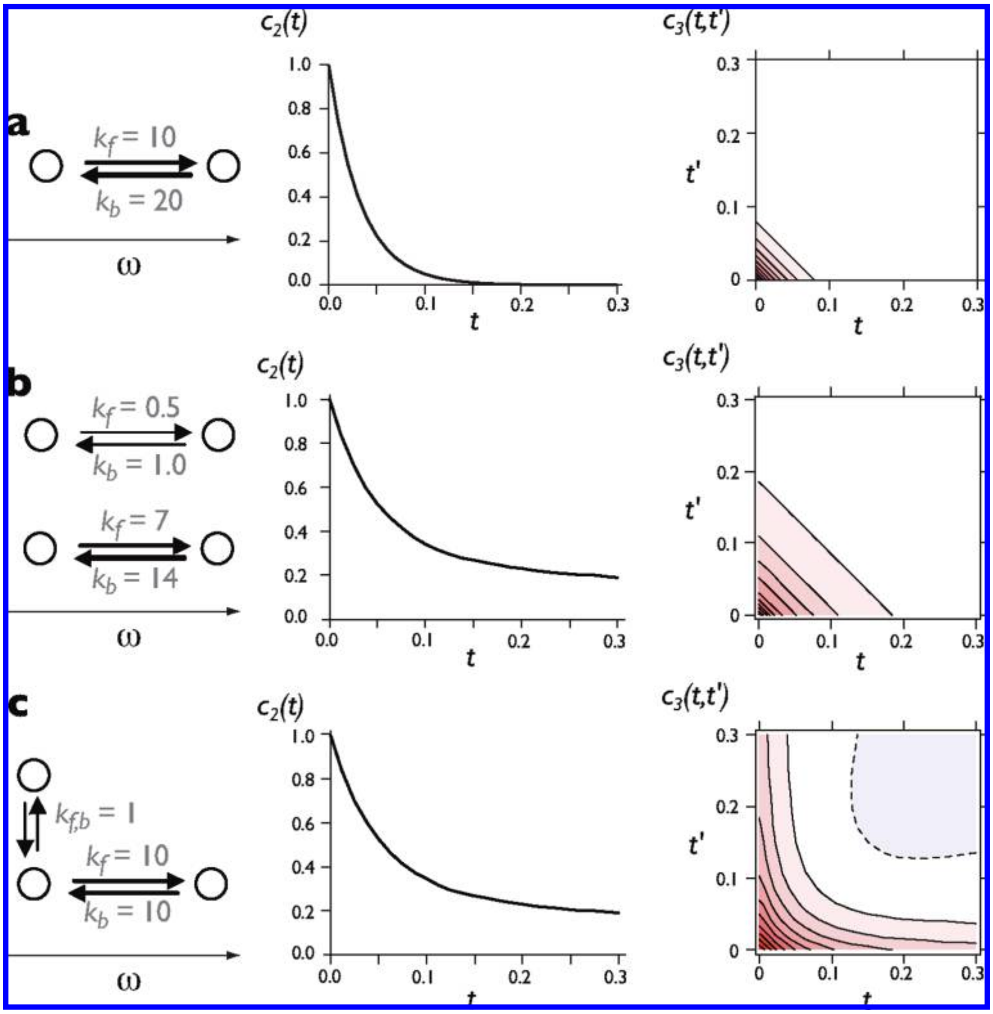

**FIGURE 4.** (a) Markovian exchange between two states, in which case both the two-point (middle) and three-point (right) FFCFs decay monoexponentially. The same for (b) heterogeneous exchange and (c) non-Markovian exchange with a hidden coordinate.

we would not gain any new information from higher order nonlinear spectroscopies that would not already be contained in 2D-IR spectroscopy.

The Markovian approximation will be very good if chemical exchange is much slower than the sampling within the individual basins. For elementary chemical reactions, the latter is on the order of 100 fs (i.e., the pre-exponential factor, $k_BT/\hbar$, in transition state theory), whereas the exchange rate can be orders of magnitudes slower when a large barrier, $E_a \gg k_BT$, has to be surmounted. However, with 2D-IR spectroscopy, we enter the picosecond regime,[43−45] and we can time-resolve chemical exchange reactions whose barriers are marginal. In this regime, the Markovian approximation becomes questionable, and 3D-IR spectroscopy might test its validity.

This is illustrated in Figure 4b,c, which shows the two-point and three-point FFCFs of two non-Markovian exchange processes (non-Markovian with respect to the spectroscopic coordinate taken by itself), which would be indistinguishable in 2D-IR spectroscopy but would differ in 3D-IR spectroscopy. The first example (Figure 4b) assumes heterogeneous exchange, that is, the exchange rate is modulated by, for example, the barrier height but the environment is assumed to be static on the time scale of the chemical exchange. Obviously, the kinetics would then occur in a multiexponential manner reflecting the different exchange rates. Berg and coworkers have recently studied exactly this situation for the internal conversion of an electronically excited chromophore, using multiple population period transient spectroscopies (MUPPETS).[46,47] The second example (Figure 4) introduces a hidden coordinate, that is, a third state whose frequency coincides with one of the other states but that is nonreactive (the two-point and three-point FFCFs can be calculated analytically, see ref 31). One can easily construct a situation where the two-point FFCF is mathematically identical to that of the previous example (Figure 4b,c, middle column); nevertheless, the three-point FFCF would be distinctively different (Figure 4b,c, right column). Only 3D-IR spectroscopy could tell the difference. Because these pictures are very general, we expect that these ideas will find application beyond the specific case of chemical exchange.

## Conclusion

In conclusion, we have summarized the theoretical background of 3D-IR spectroscopy and discussed possible applications. The experimental realization of 3D-IR spectroscopy is just in its infancy;[24,28,29,32] nevertheless, the experimental methodology of nonlinear spectroscopy has advanced to the stage that higher order experiments than 2D-IR are no longer out of reach. Three-dimensional IR spectroscopy will explore regimes where simple theoretical pictures, such as linear response or Markovian exchange, break down. Whether the breakdown of these regimes is of particular importance for ultrafast molecular dynamics of a condensed phase system is currently not clear, mostly because established spectroscopies cannot rigorously test their range of validity. Three-dimensional IR spectroscopy circumvents many of the experimental problems other approaches pose and hence will become a versatile tool to explore these questions.

The counterpart of 2D-IR spectroscopy in NMR would be just the most elementary pulse sequences COSY, NOESY, and EXSY. The real success of NMR came about only once more sophisticated pulse sequences, containing hundreds of pulses, have been developed.[48] This number of pulses is probably out of reach in IR, because we cannot generate $\pi/2$ or $\pi$ pulses. IR spectroscopy is in the small signal limit and loses about 1 order of magnitude of signal intensity per additional pulse. Nevertheless, the two additional pulses in fifth-order nonlinear spectroscopy open up a large variability of pulse sequences, and what is being discussed here is probably just a small subset of possible applications.

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BIOGRAPHICAL INFORMATION

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FOOTNOTES

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REFERENCES

1 Tanimura, Y.; Mukamel, S. 2-Dimensional femtosecond vibrational spectroscopy of liquids. *J. Chem. Phys.* **1993**, *99*, 9496–9511.

2 Laage, D.; Hynes, J. T. A molecular jump mechanism of water reorientation. *Science* **2006**, *311*, 832–835.

3 Loring, R. F.; Mukamel, S. Selectivity in coherent transient Raman measurements of vibrational dephasing in liquids. *J. Chem. Phys.* **1985**, *83*, 2116–2128.

4 Tokmakoff, A.; Lang, M. J.; Larsen, D. S.; Fleming, G. R.; Chernyak, V.; Mukamel, S. Two-dimensional Raman spectroscopy of vibrational interactions in liquids. *Phys. Rev. Lett.* **1997**, *79*, 2702–2705.

5 Blank, D. A.; Kaufman, L. J.; Fleming, G. R. Direct fifth-order electronically nonresonant Raman scattering from $CS_2$ at room temperature. *J. Chem. Phys.* **2000**, *113*, 771–778.

6 Kubarych, K. J.; Milne, C. J.; Miller, R. J. D. Fifth-order two-dimensional Raman spectroscopy: A new direct probe of the liquid state. *Int. Rev. Phys. Chem.* **2003**, *22*, 497–532.

7 Golonzka, O.; Demirdöven, N.; Khalili, M.; Tokmakoff, A. Separation of cascaded and direct fifth-order Raman signals using phase-sensitive intrinsic heterodyne detection. *J. Chem. Phys.* **2000**, *113*, 9893–9896.

8 Li, Y. L.; Huang, L.; Miller, R. J. D.; Hasegawa, T.; Tanimura, Y. Two-dimensional fifth-order Raman spectroscopy of liquid formamide: Experiment and theory. *J. Chem. Phys.* **2008**, *128*, 234507.

9 Ulness, D. J.; Kirkwood, J. C.; Albrecht, A. C. Competeing events in fifth-order time resolved coherent Raman scattering: Direct versus sequential processes. *J. Chem. Phys.* **1998**, *108*, 3897–3902.

10 Blank, D. A.; Kaufman, L. J.; Fleming, G. R. Fifth-order two-dimensional Raman spectra of CS2 are dominated by third-order cascades. *J. Chem. Phys.* **1999**, *111*, 3105–3114.

11 Hamm, P.; Lim, M. H.; Hochstrasser, R. M. Structure of the amide I band of peptides measured by femtosecond nonlinear-infrared spectroscopy. *J. Phys. Chem. B* **1998**, *102*, 6123–6138.

12 Hamm, P.; Hochstrasser, R. M. Structure and dynamics of proteins and peptides: Femtosecond two-dimensional infrared spectroscopy. In *Ultrafast Infrared and Raman Spectroscopy*; Fayer, M. D., Eds.; Marcel Dekker: New York, 2001; pp 273−347.

13 Cho, M. Coherent two-dimensional optical spectroscopy. *Bull. Korean Chem. Soc.* **2006**, *27*, 1940–1960.

14 Zheng, J.; Kwak, K.; Fayer, M. D. Ultrafast 2D IR vibrational echo spectroscopy. *Acc. Chem. Res.* **2007**, *40*, 75–83.

15 Ganim, Z.; Chung, H. S.; Smith, A. W.; DeFlores, L. P.; Jones, K. C.; Tokmakoff, A. Amide I two-dimensional infrared spectroscopy of proteins. *Acc. Chem. Res.* **2008**, *41*, 432–441.

16 Hamm, P.; Helbing, J.; Bredenbeck, J. Two-dimensional infrared spectroscopy of photoswitchable peptides. *Annu. Rev. Phys. Chem.* **2008**, *59*, 291–317.

17 Wörner, M.; Gaal, P.; Kühn, W.; Reimann, K.; Elsaesser, T.; Hey, R.; Ploog, K. H. Nonlinear terahertz and midinfrared response of n-type GaAs. *Adv. Solid State Phys.* **2008**, *47*, 237–249.

18 Hebling, J.; Yeh, K. L.; Hoffmann, M. C.; Nelson, K. A. High-power THz generation, THz nonlinear optics, and THz nonlinear spectroscopy. *IEEE J. Sel. Top. Quantum Electron.* **2008**, *14*, 345–353.

19 Pimentel, G. C.; McClellan, A. *The Hydrogen Bond*; Freeman: San Francisco, CA, 1960.

20 Moller, K. B.; Rey, R.; Hynes, J. T. Hydrogen bond dynamics in water and ultrafast infrared spectroscopy: A theoretical study. *J. Phys. Chem. A* **2004**, *108*, 1275–1289.

21 Eaves, J. D.; Loparo, J. J.; Fecko, C. J.; Roberts, S. T.; Tokmakoff, A.; Geissler, P. L. Hydrogen bonds in liquid water are broken only fleetingly. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 13019–13022.

22 Mukamel, S. *Principles of Nonlinear Optical Spectroscopy*; Oxford University Press: Oxford, U.K., 1995.

23 Fulmer, E. C.; Ding, F.; Zanni, M. T. Heterodyned fifth-order 2D-IR spectroscopy of the azide ion in an ionic glass. *J. Chem. Phys.* **2005**, *122*, 034302.

24 Garrett-Roe, S.; Hamm, P. Purely absorptive three dimensional spectra. *J. Chem. Phys.* **2009**, *130*, 164510.

25 Bredenbeck, J.; Helbing, J.; Hamm, P. Solvation beyond the linear response regime. *Phys. Rev. Lett.* **2005**, *95*, 083201.

26 Underwood, D. F.; Blank, D. A. Measuring the change in the intermolecular raman spectrum during dipolar solvation. *J. Phys. Chem. A* **2005**, *109*, 3295–3306.

27 Turner, D. B.; Stone, K. W.; Gundogdu, K.; Nelson, K. A. Three-dimensional electronic spectroscopy of excitons in GaAs quantum wells. Presented atUltrafast Phenomena XVI, Sresa, Italy, 2008.

28 Ding, F.; Zanni, M. T. Heterodyned 3D-IR spectroscopy. *Chem. Phys.* **2007**, *341*, 95–105.

29 Xiong, W.; Zanni, M. T. Unpublished work presented at the 4th International Conference on Coherent Multidimensional Spectroscopy, Kyoto 2008.

30 Hamm, P. 3D-IR spectroscopy: Beyond the two-point frequency fluctuation correlation function. *J. Chem. Phys.* **2006**, *124*, 124506.

31 Garrett-Roe, S.; Hamm, P. Three-point frequency fluctuation correlation functions of the OH stretch vibratiopn in liquid water. *J. Chem. Phys.* **2008**, *128*, 104507.

32 Garrett-Roe, S.; Hamm, P. Unpublished work presented at the 4th International Conference on Coherent Multidimensional Spectroscopy, Kyoto 2008.

33 Schmid, J. R.; Corcelli, S. A.; Skinner, J. L. Pronounced non-Condon effects in the ultrafast infrared spectroscopy of water. *J. Chem. Phys.* **2005**, *123*, 044513.

34 Hamm, P.; Lim, M. H.; Hochstrasser, R. M. Non-Markovian dynamics of the vibrations of ions in water from femtosecond infrared three-pulse photon echoes. *Phys. Rev. Lett.* **1998**, *81*, 5326–5329.

35 Fecko, C. J.; Eaves, J. D.; Loparo, J. J.; Tokmakoff, A.; Geissler, P. L. Ultrafast hydrogen-bond dynamics in the infrared spectroscopy of water. *Science* **2003**, *301*, 1698–1702.

36 Lawrence, C. P.; Skinner, J. L. Vibrational spectroscopy of HOD in liquid D2O. II. Infrared line shapes and vibrational Stokes shift. *J. Chem. Phys.* **2002**, *117*, 8847–8854.

37 Smith, J. D.; Cappa, C. D.; Wilson, K. R.; Cohen, R. C.; Geissler, P. L.; Saykally, R. J. Unified description of temperature-dependent hydrogen-bond rearrangements in liquid water. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 14171–14174.

38 Asbury, J. B.; Steinel, T.; Kwak, K.; Corcelli, S. A.; Lawrence, C. P.; Skinner, J. L.; Fayer, M. Dynamics of water probed with vibrational echo correlation spectroscopy. *J. Chem. Phys.* **2004**, *121*, 12431–12446.

39 Yeremenko, S.; Pshenichnikov, M. S.; Wiersma, D. A. Hydrogen-bond dynamics in water explored by heterodyne-detected photon echo. *Chem. Phys. Lett.* **2003**, *369*, 107–113.

40 Cowan, M. L.; Bruner, B. D.; Huse, N.; Dwyer, J. R.; Chugh, B.; Nibbering, E. T. J.; Elsaesser, T.; Miller, R. J. D. Ultrafast memory loss and energy redistribution in the hydrogen bond network of liquid $H_2O$. *Nature* **2005**, *434*, 199–202.

41 Loparo, J. J.; Roberts, S. T.; Tokmakoff, A. Multidimensional infrared spectroscopy of water. II. Hydrogen bond switching dynamics. *J. Chem. Phys.* **2006**, *125*, 194522.

42 Kumar, R.; Schmidt, J. R.; Skinner, J. L. Hydrogen bonding definitions and dynamics in liquid water. *J. Chem. Phys.* **2007**, *126*, 204107.

43 Woutersen, S.; Mu, Y.; Stock, G.; Hamm, P. Hydrogen-bond lifetime measured by time-resolved 2D-IR spectroscopy: *N*-Methylacetamide in methanol. *Chem. Phys.* **2001**, *266*, 137–147.

44 Zheng, J.; Kwak, K.; Asbury, J.; Chen, X.; Piletic, I. R.; Fayer, M. D. Ultrafast dynamics of solute-solvent complexation observed at thermal equilibrium in real time. *Science* **2005**, *309*, 1338–1343.

45 Kim, Y. S.; Hochstrasser, R. M. Chemical exchange 2D IR of hydrogen-bond making and breaking. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 11185–11190.

46 van Veldhoven, E.; Khurmi, C.; Zhang, X.; Berg, M. A. Time-resolved optical spectroscopy with multiple population dimensions: A general method for resolving dynamic heterogeneity. *ChemPhysChem* **2007**, *8*, 1761–1765.

47 Khurmi, C.; Berg, M. A. Parallels between multiple population-period transient spectroscopy and multidimensional coherence spectroscopies. *J. Chem. Phys.* **2008**, *129*, 064504.

48 Wüthrich, K. *NMR of Proteins and Nucleic Acids*; Wiley Interscience: New York, 1986.