Extracting Frequency-Frequency Correlation Function from Two-Dimensional Infrared Spectroscopy: Peak Shift Measurement

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Two-dimensional infrared (2D-IR) spectroscopy can probe the fast structural evolution of molecules under thermal equilibrium. Vibrational frequency fluctuation caused by structural evolution produced the time-dependent line shape change in 2D-IR spectrum. A variety of methods has been used to connect the evolution of 2D-IR spectrum with Frequency-Frequency Correlation Function (FFCF), which connects the experimental observables to a molecular level description. Here, a new method to extract FFCF from 2D-IR spectra is described. The experimental observable is the time-dependent frequency shift of maximum peak position in the slice spectrum of 2D-IR, which is taken along the excitation frequency axis. The direct relation between the 2D-IR peak shift and FFCF is proved analytically. Observing the 2D-IR peak shift does not need the full 2D-IR spectrum which covers 0-1 and 1-2 bands. Thus data collection time to determine FFCF can be reduced significantly, which helps the detection of transient species.

Key Words : Two-dimensional infrared spectroscopy (2D-IR), Frequency-Frequency correlation function (FFCF), 2D-IR peak shift, Fast data acquisition

Introduction

Two-dimensional Infrared vibrational spectroscopy (2D-IR) has proven to be a powerful tool for studying dynamical process in condensed phase by spreading spectral information over two frequency axes.7 2D-IR experiments have been successfully applied to study ultrafast dynamics of the hydrogen bond in water, the equilibrium dynamics of aqueous and membrane bound proteins, fast chemical exchange and isomerization, intramolecular vibrational energy relaxation, and dynamical solute-solvent interactions.2-6

In a 2D-IR experiment, three input electric fields (Mid-IR laser pulses) tuned to the vibrational frequency of interest applied on the sample. With the delay stage, properly time-ordered electric field-matter interactions manipulate quantum pathways through which system evolves. After three successive interactions with the vibrational oscillators, third-order polarization is generated in the sample and emits the vibrational echo signal into the phase-matched direction. The first field excites the molecules in the ground state to the coherent superposition of the ground and the first excited state. Then the second field is applied after the evolution period, \( \tau \), and moves the molecules to the ground or excited state. After waiting time, \( T_w \), the final electric field brings the molecules again into the coherent superposition state between ground and first excited state or between the first and the second excited state. Finally the generated echo signal is overlapped with local oscillator for heterodyne detection. The oscillation frequencies during two coherent states make two frequency axes in 2D-IR spectrum. The initial frequency from the first coherent state is obtained through numerical Fourier-transform of the interferogram produced by heterodyne detection. The final frequency from second coherent periods is directly obtained from monochromator. If the signal involves the coherent superposition between the first and the second excited state during the final coherence periods, the final resonance frequency is red-shifted by the vibrational anharmonicity. In order to get the full 2D-IR spectrum covering this anharmonically shifted peak, monochromator should be tuned several times to cover wide frequency range depending on the spectrum width and vibrational anharmonicity.5,6

2D-IR spectrum directly provides the correlation between initial and final frequency in two-dimensional space. Measuring dynamics with 2D-IR corresponds to observing time-dependent frequency correlation during the waiting time. Qualitatively, the waiting time-dependent spectral change of 2D-IR can be ascribed to the molecular dynamics in the following manner. In the first coherent state, the molecules are labeled with the initial frequencies. Fast dynamic events can cause the frequency-labeled molecules to evolve to different frequencies during the waiting time. In the second coherent state, the final frequencies of initially frequency-labeled molecules are read out. The horizontal axis, the \( \omega_c \) axis, of 2D spectrum shows initial frequencies of molecules and the vertical axis, the \( \omega_w \) axis, represent the final frequencies after dynamic changes. A couple of 2D spectra is measured as a function of \( T_w \). The frequency evolution of the molecules which is called as spectral diffusion causes the shape of the 2D spectrum change as \( T_w \) is increased. In addition to this apparent change in line shape, the amplitude, position, and peak shape of the 2D spectra provide detailed information on molecular dynamics and structure.7

The frequency-frequency correlation function (FFCF) is the direct quantification of spectral diffusion dynamics of the molecules, which appears as frequency evolution in the
2D-IR spectrum. The FFCF is an essential quantity to understand the dynamic evolution of molecular systems in terms of amplitudes and time scale of the dynamics. The FFCF is the joint probability distribution that the frequency has a certain value at \( t = 0 \) and another value at a later time \( t \). Once the FFCF is known, all linear and nonlinear optical experimental observables can be calculated by time-dependent diagrammatic perturbation theory.\(^5\)

The apparent line shape change of 2D-IR spectrum lead researchers to analyze the time-dependent line shape change in order to extract the information about the dynamics. The most rigorous method is a global fitting, which compares the entire experimental 2D-IR spectrum with the simulated 2D-IR spectrum. For the simulation, the amplitudes and time constants for FFCF is used as input parameter to calculate 2D-IR and linear IR spectrum through linear and nonlinear response function calculation. Parameters in FFCF are adjusted to produce the best fitting results.\(^5\) To avoid questionable convergence of multi-variable fitting, a variety of methods has been devised to extract FFCF from 2D-IR spectrum without fitting the 2D-IR spectrum. 2D-IR observable like the ellipticity, eccentricity, and dynamic line spectrum without fitting the 2D-IR spectrum. Parameters in FFCF are two-dimensional array detectors are introduced to minimize the number of monochromator block. Experimentally multi-dimensional array detectors are introduced to minimize the number of monochromator block.

In this paper, a new FFCF extraction method is presented and numerically tested with nonlinear response function calculation. Like the CLS methods, this new method utilizes the \( T_\omega \)-dependent maximum positions of slice spectrum taken from 2D-IR spectrum along the \( \omega_\tau \) axis at one \( \omega_\alpha \) position. However, this method requires the slice spectrum just at one \( \omega_\alpha \) point instead multiple slice spectra taken at a range of \( \omega_\alpha \) frequencies which cover 0-1 or 1-2 band. In the first part, the direct relationship between FFCF and normalized peak shift is proved analytically within the short-time approximation. Second, with the known FFCF, the 2D-IR spectra at multiple waiting times are simulated. The new method will be applied to these simulated 2D-IR spectra to confirm the validity of the proposed method to extract FFCF. Third, the advantage and disadvantage of the new methods will be discussed. Especially it will be emphasized that this new methods will reduce the data collection time significantly and extend the application of 2D-IR experiment into the investigation of slowly degrading species like Amyloid.\(^14\)

**Theoretical Development**

**Simplified 2D-IR Line Shape Function.** A 2D-IR spectrum can be simulated from the third order nonlinear response function after a two dimensional Fourier-transform about the two coherence periods, \( \tau \) and \( t \). Within Condon approximation, the orientational part can be separated from the vibrational part which describes the line shape. The resulting four point dipole correlation function for the vibrational part can be written with the product of transition dipoles and the line shape function, \( g(t) \), with cumulant approximation.\(^8\) This line shape function results from the double integral of frequency-frequency correlation function (FFCF). In addition to the 2D-IR spectrum, line shape of linear IR spectrum can be described with one common line shape function, \( g(t) \). The positive going band (0-1 band) of 2D-IR spectrum results from the ground state bleaching and stimulated emission which involves the transition only between the ground and the excited state. This is the same for linear IR spectrum so they share the common line shape function, \( g(t) \), which include autocorrelation function between the ground and the first excited state. In contrast, the negative going band that arises from excited state absorption crosses correlation function between 0-1 and 1-2 transition as well as autocorrelation because it consists of the transition between the first excited state and second excited state (1-2) as well as that between the ground state and first excited state (0-1).

To obtain an analytical equation for a 2D-IR spectrum, the short time approximation for each coherence period was applied and a simplified 2D-IR line shape equation including spectral diffusion is employed. This approach has been used previously.\(^1,2\) Here we will use the short time approximate 2D-IR line shape equation to prove the direct proportionality between the new method and FFCF. Within the short time approximation, the 2D-IR line shape function is

\[
R(\omega_m, \omega_\tau) = \frac{4\pi}{\sqrt{C(0) - C(T_\tau)}} \exp \left( \frac{C(0)(\omega_m^2 - 2C(T_\tau)\omega_m\omega_\tau + C(0)\omega_\tau^2)}{2\sqrt{C(0)^2 - C(T_\tau)^2}} \right) - \frac{2\pi^2}{\sqrt{C(0)C(0) - C(T_\tau)C(T_\tau^2)}} \exp \left( \frac{C(0)(\omega_m^2 + \Delta) - 2C(T_\tau)(\omega_m + \Delta)\omega_\tau + C(0)\omega_\tau^2}{2\sqrt{C(0)C(0) - C(T_\tau)^2}} \right)
\]

(1)

Here, \( \Delta \) is the anharmonicity (the difference in frequency between the 0-1 and 1-2 transitions) and \( s = \mu_\tau/\mu_\omega \), where
μ is the transition dipole matrix element for the two transitions between i and j states. S is $\sqrt{2}$ in the harmonic approximation (harmonic oscillator. Three different correlation functions in the above equation are defined as

\begin{align*}
C_1(t) &= \langle \delta \omega_{10}(\tau_1) \delta \omega_{10}(0) \rangle \\
C_2(t) &= \langle \delta \omega_{21}(\tau_1) \delta \omega_{10}(0) \rangle \\
C_3(t) &= \langle \delta \omega_{21}(\tau_1) \delta \omega_{21}(0) \rangle
\end{align*}

The first correlation function (Eq. 2) is the autocorrelation function between ground and first excited state. The positive 0-1 peak can be described with only this correlation function. Within the remaining two terms, the first one (Eq. 3) is autocorrelation function between first and second excited state and the second one (Eq. 4) is the cross correlation function for the 0-1 and 1-2 transitions. As shown in the following section these two correlation function concerns the negative peaks and cannot be separately measured.

**Slice Spectrum Along \( \omega_r \) Axis at Fixed \( \omega_m \).** The slice spectrum can be taken from the 2D-IR results along the \( \omega_r \) axis at arbitrary frequency position away from resonance frequency, \( \omega_m + \omega_0 + \delta \), which can be written as

\[
R(\omega, \omega_m) = \frac{4\pi \delta^2}{\sqrt{\left( \omega - \omega_0 \right)^2 - C_1(T_0)^2}} \exp \left( \frac{C_1(0)\delta - 2C_1(T_0)\delta\omega + C_1(0)\omega^2}{\left( \omega - \omega_0 \right)^2} \right)
\]

Depending on the displacement value of \( \delta \), positive 0-1 peak or negative 1-2 peak can be selected separately. When positive peak is chosen, the maximum position of slice spectrum can be easily derived from the first derivative of the Eq. (5).

\[
\omega_r(T_w, \omega_m = \omega_0 + \delta) = \omega_0 + C_1(T_w) \delta
\]

When negative going peak is chosen, the slice spectrum is taken at \( \omega_r = \omega_0 + \delta \), so minimum peak position of slice spectrum taken from 1-2 band can be written as

\[
\omega_r(T_w, \omega_m = \omega_0 + \delta) = \omega_0 + C_1(T_w) \delta
\]

Here, \( C_1(T_w) \) represent the normalized FFCF. It shows the direct relationship between the FFCF and the time-dependent maximum frequency of slice spectrum.

Slice spectrum should be taken at the position other than resonance frequency in order to observe the peak shift. At the resonance position, the slice spectrum shows the broadening following the increase of the waiting time without the maximum peak shift. The resonance frequency, \( \omega_{00} \), is easily read from the IR spectrum and the displacement \( \delta \) is determined by the frequency position where we take the slice spectrum. Thus, \( T_w \)-dependent maximum position is the only observable from the experiment. The above equation can be written in order to direct relationship between experimental observable and FFCF as,

\[
\omega_r(T_w, \omega_m = \omega_{00} + \delta) = C_1(T_w) \delta
\]

From this result, it is clear that the experimental observable is the normalized peak shift in the 2D-IR spectrum. By this normalization, the frequency position where we take slice spectrum does not affect the result if all the molecules within the absorption spectrum follow the same dynamics.

Eqs. (1) and (2) tells us that we should select the slice spectrum along the \( \omega_r \) axis at one fixed \( \omega_m \) other than the resonance frequency. At each \( T_w \), the slice spectrum cut along the \( \omega_r \) axis has one maximum peak position ( \( \omega_m \) ) for 0 → 1 peak and one minimum peak position ( \( \omega_m' \) ) for 1 → 2 peak. The normalized peak shift of the maximum position is directly proportional to the normalized FFCF,
δ = \omega_m(T_w) - \omega = \omega_{10} + \delta_{10} = C(T_w) . \text{ Here } \delta \text{ is frequency difference between the resonance position and the selected position for the slice spectrum. At multiple } T_w, \text{ a series of the normalized peak shift can be obtained from the slice spectra. The derived normalized FFCF from the normalized peak shift can be converted to the full FFCF with the additional information from the linear IR spectrum. The detailed procedures for reconstruction full FFCF from normalized FFCF were already explained in the previous publications and will be used in the following section.}^{12}

\begin{align*}
\omega_m(T_w, \omega) &= \omega_{10} + \delta_{10} = C(T_w) .
\end{align*}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
& $T_1$ (ps) & $\Delta_1$ (rad/ps) & $\tau_1$ (ps) & $\Delta_2$ (rad/ps) & $\tau_2$ (ps) \\
\hline
Experiment & 7.5 & 0.58 & 1.5 & 1.06 & 21 \\
2D-IR peak shift (norm) & NA & 0.09 & 1.4 & 0.74 & 22 \\
2D-IR peak shift and linewidth & 3.7 & 0.36 & 1.4 & 1.03 & 22 \\
2D-IR peak shift and line shape & 7.8 & 0.59 & 1.4 & 1.03 & 22 \\
\hline
\end{tabular}
\caption{Frequency-frequency correlation function (FFCF) for Horse Radish Peroxidase taken from 2D-IR experiment, which is used as input parameters for simulation. The FFCF extracted from the simulation with 2D-IR peak shift methods as explained in the text.}
\end{table}

\textbf{Numerical Test of the 2D-IR Peak Shift Measurement.}

2D-IR spectra at multiple $T_w$ were simulated using the numerically calculated third-order nonlinear response functions in order to test the validity of peak shift measurement. The input FFCF for the calculation was chosen as experimentally determined FFCF taken from the 2D-IR spectrum which covers the CO stretching mode of horseradish peroxidase (HRP) isoenzyme C in the free form.\textsuperscript{15} FT-IR spectrum shows two CO peaks with the resonance frequencies at 1932.7 cm$^{-1}$ and 1903.7 cm$^{-1}$, which are caused by two conformational substrates related to the distal residues. The low frequency conformer (HRP red) shows various FFCF components which represent homogeneous, fast, and slow dynamics. Thus it provides good model system to test if peak shift measurement can distinguish different dynamics and extract each dynamics component from the measurements. In Table 1, each component for input FFCF was listed. In general, homogenous contribution consists of pure dephasing, vibrational relaxation, and orientational relaxation. The orientational relaxation time of HRP is so slow compared to the time scale of pure dephasing and vibrational relaxation. Thus homogenous component of HRP can be written with pure dephasing time ($T_1$) and vibrational relaxation time ($T_2$).

\begin{equation}
\frac{1}{T_2} = \frac{1}{T_{21}} + \frac{1}{2T_1}
\end{equation}

2D-IR measurement cannot separately measure these two components. The measure value of vibrational life time is 8ps and is used as input for simulation. Only the magnitude of homogenous contribution can be determined. Polarization controlled pump-probe measurement can be used for measuring vibrational relaxation time. With homogenous magnitude from 2D-IR and vibrational lifetime from pump-probe experiment, we can determine the pure dephasing time. For the numerical calculation of third order response function, experimentally measured lifetime and pure dephasing time were used as inputs.

Two 2D-IR spectra at short (0.2 ps) and long (50 ps) waiting time were plotted in the Figure 1. At short waiting time, 2D-IR spectrum shows elongation along the diagonal line following the inhomogeneous distribution of resonance.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{(a) Slice spectra taken at $\omega_m = 1910$ cm$^{-1}$. From the left, each spectrum corresponds to slice spectrum at $T_w = 0.2, 1, 10, 20, 30, 40, 50$ ps. Following the increase of waiting time ($T_w$), the maximum peak position of each slice spectrum moves to the right, in other words, to the peak position of IR spectrum (resonance frequency). (b) The normalized 2D-IR peak shift at each waiting time is plotted as close squares. For comparison, time dependent part of input FFCF is shown as a thick line. This shows that 2D-IR peak shifts reproduce FFCF of simulated 2D-IR spectra very well.}
\end{figure}
frequencies. Following the spectral diffusion dynamics, the elongated spectrum becomes symmetrically round after long waiting time. Slice spectrum was taken at $\omega_m = 1910 \text{ cm}^{-1}$ and the line for taking slice spectrum was plotted on top of the 2D-IR spectrum as thick line. It should be emphasized that 2D-IR peak shift measurement needs just one slice spectrum instead of a series of slice spectra from a range of $\omega_m$ or $\omega_r$ in CLS measurements. The slice spectra at a few selected waiting times were shown in Figure 1(b). In order to clearly show the peak shift following the waiting time, all slice spectra were normalized and plotted in the same figure. At short waiting time, peak position is on the blue side of resonance frequency ($1903.7 \text{ cm}^{-1}$) and line width (FWHM) is quite narrower (9.4 cm$^{-1}$) than the width of linear IR spectrum (15 cm$^{-1}$). With the increase of lifetime, peak moves toward the resonance frequency and also the line width of slice spectrum approaches to the line width of linear IR spectrum. This line width change was already reported as adjustable parameter, the full FFCF was assumed and used as an experimental observable which is sensitive to the spectral diffusion dynamics or FFCF. The so called dynamic line width is very susceptible to the various line shape distortion effect so we will not treat this dynamic line width for extracting FFCF. Thirty one 2D-IR spectra were calculated with the selected waiting time from 0.1 ps to 50 ps.

For peak shift measurement, slice spectra at $\omega_m = 1910 \text{ cm}^{-1}$ were obtained from each 2D-IR spectrum. Maximum peak frequency of each slice spectrum was recorded without any fitting procedure and the magnitude of shift from the resonance frequency was divided with the displacement $\delta$ for normalization, which corresponds to 6.3 cm$^{-1}$ in this calculation. In Figure 3, this normalized peak shift is plotted with the increase of waiting time and this quantity is equal to the normalized FFCF. Although the calculation produces the 2D-IR spectrum at any waiting time which is many times of vibrational lifetime, signal to noise ratio will limit maximum waiting time for data collection. Also in this experiment, maximum waiting is 32 ps.\textsuperscript{15} We try to simulate experimental condition as close as possible so the simulated 2D-IR spectra until 30 ps were used for this demonstration. To extract the time constant and relative magnitude of each dynamic component, normalized peak shift is fitted with bi-exponential decay function (thick line in the Figure 2(b)). As listed in the Table 1, the resulting time constant reproduce the input decay time very well. The relative ratio of each component from exponential decay fitting can be converted into the absolute magnitude of frequency fluctuation for each component with the information about the line width of linear IR spectrum. As shown in Table 1, the full FFCF reproduced with 2D-IR peak shift and IR line width is quite close but shows significant discrepancy from the input FFCF. This difference is caused by the short-time approximation we used to derive the simplified 2D-IR line shape function.\textsuperscript{12} Dynamic time constants and the amplitude of slow dynamic component were reproduced reasonably well so we fix those values. With the homogenous and fast dynamic component as adjustable parameter, the full FFCF was assumed and linear response function was calculated. The simulated IR spectrum with linear response function is compared with experimental IR spectrum until two matches well. Then, the amplitude of homogenous and fast dynamic component becomes quite close to the input FFCF. All these procedures were fully explained in the previous publication. Finally the 2D-IR peak shift measurement and the information from IR spectrum reproduced FFCF from 2D-IR spectrum.

Conclusion

We have presented a new method for extracting frequency-frequency correlation function from 2D-IR experiment. The normalized 2D-IR peak shift is equal to FFCF within the short-time approximation and this relationship is proved analytically and numerically. Like other FFCF extraction method such as center line slope (CLS) and nodal plane slope, 2D-IR peak shift measurement does not need complex multivariable fitting procedure which compares the 2D-IR line shapes of experiments and nonlinear response function simulations. In addition, this new method can provide unique advantages in data collection scheme in that 2D-IR peak shift method along the $\omega_m$ does not require the full 2D-IR spectrum. It just needs the slice spectra at one $\omega_m$ to obtain the FFCF. Usually the full 2D-IR spectrum requires multiple monochromator blocks to cover the 1 $\rightarrow$ 2 peak as well as 0 $\rightarrow$ 1 peak for more phasing constraint and obtaining the slope or line shape change. However, using the 2D-IR peak shift along the $\omega_m$ axis, the same information about the spectral diffusion can be obtained from the single $\omega_m$ frequency point. In other words, single element detector can replace the multi array detector using the monochromator and slit. Even if we used the multi array detector, we don’t need to change the monochromator block to cover all the frequency range for $\omega_m$ axis so the data collection time can be reduced a lot. Also the uncertainty caused by the movement of the monochromator during the experiment will be removed. Even with the array detector, the data or the slice spectrum at one $\omega_m$ frequency comes from the same element through the whole experiment so it will also reduce the possible error with the array detector which is normalized for different element response for different frequencies.

The phasing procedure should be reconsidered for the correct phasing of one slice spectrum. Because just one slice spectrum is given, there can be some arbitrariness on the four phasing parameters we currently used.\textsuperscript{11} It means that there is less constraint for phasing the slice spectrum instead of the full 2D-IR spectrum which includes the 0-1 and also 1-2 transitions. Especially the slice spectrum along the $\omega_r$ axis includes almost no information about the $\omega_m$ axis. Because the pump-probe projection theorem requires the projected spectrum along the $\omega_r$ axis, we need a different phasing procedure for the slice spectrum along the $\omega_r$ axis if it is obtained using the single element detector. However, recently the introduction of pump-probe geometry with pulse-shaper inherently eliminates the need for post phasing procedure with projection theorem and achieves the signi-
significant reduction of data collection time for coherent time scan through rotating frame. Combined with pulse-shaping 2D-IR experiments, the proposed 2D-IR peak shift measurement can be one of the fast methods to extract FFCF, which is free from various experimental error related to the use of monochromator and multi array detectors.

Even without the fitting procedure and comparison with IR spectrum for determining full FFCF, 2D-IR peak shift measurement itself can be used to probe the environment around oscillators. Recently, Fayer group studied the protein denaturization with nitrile as prove in 2D-IR experiment. Through the comparison of spectral diffusion dynamics of denatured sample and nitrile molecules in pure solvent, they can prove that nitrile group hidden in the protein packet in folding structure is exposed to the surrounding solvent after denaturization. Also Hochstrasser group showed that water molecules can exist inside the amyloid fiber film through the observation of fast decay spectral diffusion dynamics. Both of the groups use the CLS to compare dynamics. Basically 2D-IR peak shift method shares the same advantage with CLS method and additionally provides the fast data collection time. Like other FFCF extraction methods, 2D-IR peak shift is very sensitive to the dynamics change appeared in the 2D-IR spectrum.

In conclusion, the peak shift method provides much simpler and robust way to extract FFCF or compare spectral diffusion dynamics from the 2D-IR spectrum when compared with other methods which requires the line shape analysis. The 2D-IR peak shift along the $\omega_t$ axis can be used for the study of spectral diffusion with saving a lot of time because only one slice spectrum is need at the specified $\omega_m$. If the sample is really unstable, taking the echo data without moving the monochromator block will reduce the data collection time twice or three times. This reduction of experimental time really helps for studying unstable molecules or taking the quick scan of the slowly degrading molecules.

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