Models for nonlinear optical spectra of coupled oscillators
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Simulation of vibrational dynamics in the amide I and II bands of an α-helix

We theoretically investigate the transport of vibrational energy in the amide I and II bands of a model α-helix. The vibrational dynamics are simulated by numerically integrating the Schrödinger equation. We find transport of amide I quanta over a few turns within a picosecond (which is the lifetime of the amide I mode). The amide I and II band are coupled by fluctuations originating from interactions with the solvent, which lead to interband relaxation with a time constant of 2 ps. With the same theoretical model, two-dimensional infrared (2DIR) spectra are simulated. We find that both the intraband and interband dynamics are reflected in the waiting time dependence of the diagonal peak anisotropies and the cross peak intensities in the 2DIR spectra. In the construction of the peptide model, we need to account for the couplings between amide I and amide II vibrations. Because the couplings between neighboring amide groups are not well described with electrodynamic models, these are obtained from density functional theory (DFT) calculations on a dipeptide. We present a new and robust method to construct a dual mode coupling map from these calculations.

6.1 Introduction

In the 1970’s, Davydov proposed that the energy released by adenosine triphosphate (ATP) hydrolysis is transported through the amide I vibrations in α-helices [Davydov 1985]. The amide I vibration is associated with the stretching mode of the double C=O bond, which is present in the backbone of each peptide group. Focusing on
this particular mode, the helix can be described as a regular lattice of vibrational oscillators. Davydov explained how vibrational solitons, stabilized by phonons in the helix, would be an efficient channel to transport energy.

Although experimental evidence for solitonic transport in the N-H stretch mode in \( \alpha \)-helices has been presented [Edler et al. 2004], no direct transport in C=O stretch modes has been observed. On the contrary, recent experiments on the dynamical evolution of an excited C=O stretch mode in a model peptide were explained with an entirely different mechanism [Backus et al. 2008]. Instead of traveling along the helix, a vibrational excitation on an oscillator with a frequency outside the main band was seen to relax to vibrations with a frequency on the order of 100 cm\(^{-1}\). These low-frequency quanta have a delocalized character, which enables fast heat transport. The experimental results do, however, not fully clarify the role of direct transport through high-frequency modes.

In this chapter, we study the direct transport of high-frequency vibrational excitations through a model \( \alpha \)-helix in a numerical simulation. Apart from the amide I modes, we explicitly take into account the amide II vibrations, because we expect relaxation between these two modes to take place on roughly the same time scale as the dynamics in the amide I band [Dijkstra et al. 2007; Jansen and Knoester 2008].

One of the important challenges in such modeling is the connection with experimental methods. Two-dimensional infrared (2DIR) spectroscopy is a tool that allows for the study of vibrational dynamics. We therefore aim at the calculation of the 2DIR experiment from the same model as the vibrational dynamics. The time constants of the vibrational dynamics and the evolution of spectral features can be compared directly in calculations, and we will indeed see how both the intra- and interband dynamics can be followed in the spectrum.

2DIR spectroscopy, which has been developed over the past ten years, uses ultrafast infrared laser pulses to probe vibrations [Hochstrasser 2007b; Cho 2008]. It has frequently been applied to the amide I modes in polypeptides. In the experiment, short infrared laser pulses coherently excite a vibrational state in the molecule. The subsequent dynamics of the excitation can be followed with a time resolution of tens of femtoseconds. Analysis of the spectra can then give information on the variation in local structure of the polypeptide and its environment, which influence the state of the observed amide vibrations. One furthermore obtains direct information on the dynamics of these excitations themselves.

The nature of the vibrational excitations in a polypeptide is determined by a competition between coherent coupling and environment-induced fluctuations. Electrodynamic and mechanical coupling between the amide I vibrations is known to be strong enough to lead to partially delocalized vibrations [Hamm et al. 1998]. The geometry determines the exact coupling pattern, which, in turn, can be observed in the spectral signature [Torii and Tasumi 1992; Demirdöven et al. 2004; Chung et al. 2007; Maekawa et al. 2008]. Interactions of the amide vibrations with all other modes in the peptide and the solvent tend to destroy the coherence and localize the excitations. The partially delocalized vibrations that result from the competition between coherent couplings and interaction with the environment move through the polypeptide on a picosecond time scale.
The effect of the environment on the amide I modes in polypeptides has been included in theoretical models in various ways. The resulting dynamics can not be understood without also taking into account the coherent couplings between amide I vibrations. Because these couplings lead to hopping of excitations between oscillators which have the same average frequency, they can in general not be treated perturbatively. A simple model can be obtained by treating the coherent couplings exactly, and rephrasing the problem in a basis of delocalized, uncoupled oscillators. When the interaction of the environment is then approximated by a combination ultrafast and very slow fluctuations only, spectra can be calculated from summing over the resulting time-independent eigenstates [Hamm et al. 1998; Abramavicius et al. 2004]. Computationally, it can be advantageous to use the nonlinear exciton equations [Mukamel and Abramavicius 2004]. The validity of the separation of time scales limits, however, detailed modeling of the interaction with the environment. The spectral lineshapes can be calculated in more detail from given correlation functions of the environment-induced fluctuations with the cumulant expansion method [Mukamel 1983; Sung and Silbey 2001]. However, these methods do not include the nonadiabatic vibrational dynamics observed during the waiting time of a 2DIR experiment. The effect of the environment on the population dynamics and the infrared spectra can be included correctly by numerical integration of a time dependent Schrödinger equation (NISE) [Jansen et al. 2004; Torii 2007], which we will use in this chapter.

Apart from intraband dynamics, an excited amide I vibration will relax into other states. The lifetime of the amide I state is in the order of 1 ps [Hamm et al. 1998], and intraband relaxation happens on the same time scale [Jansen and Knoester 2008]. Although other mechanisms play a role as well [Nguyen and Stock 2003; Fujisaki et al. 2006; Fujiisaki and Straub 2007; Pouthier 2008; Fujiisaki and Stock 2008], we believe that the amide II vibration forms one of the important relaxation channels out of the amide I mode [Dijkstra et al. 2007]. Direct evidence of this relaxation process can be obtained from dual mode 2DIR spectra [DeFlores et al. 2006]. In these experiments, the laser bandwidth is large enough to excite the two modes coherently. Multimode 2DIR opens extra possibilities for the study of proteins. Apart from the obvious hope that each mode gives independent information on protein structure, intermode cross peaks show the presence of mode coupling [Rubtsov et al. 2003c]. By following these cross peaks in time, information about the vibrational relaxation pathways between two modes can be obtained. The amide II mode is one of the obvious modes to study in combination with amide I, because of its proximity in frequency. In experimental infrared spectra of N-methylacetamide-d7 (NMA-d7), a small molecule with a single amide group, the amide I and II modes indeed appear close in frequency. No other modes are seen between 1300 and 2000 cm⁻¹ [DeFlores et al. 2006]. This suggests a description of the amide I - amide II pair as an isolated unit. Extensions to the amide III mode, which is also known as a probe of biomolecular structure [Cai and Singh 2004], or the amide A mode [Rubtsov et al. 2003b] further increase the range of possibilities.

The remainder of this chapter is organized as follows. The model used to simulate the vibrational dynamics in the amide I and amide II bands of an α-helix in water
is introduced in Section 6.2. To parametrize the model, we present density functional (DFT) calculations combined with molecular dynamics (MD) simulations on NMA-d$_7$ (Section 6.3.1). Interactions between vibrations on neighboring amide groups, obtained from DFT calculations on a dipeptide, are presented in Section 6.3.2. Vibrational dynamics in the model helix introduced in Section 6.3.3 are discussed in Section 6.4, along with simulated dual mode 2DIR spectra. The effects of the intra- and interband dynamics on the spectra are discussed. In Section 6.5, we conclude.

### 6.2 Model

The Hamiltonian used to describe the $\alpha$-helix (see Figure 6.1) in solution is split into a system part $H_S$, an environment part $H_B$, and an interaction term $H_{SB}$. The system contains the high-frequency degrees of freedom ($\omega/2\pi c = 1500 - 1700$ cm$^{-1}$) which are excited by infrared light - the amide I and amide II vibrations in the peptide. Everything else is the environment. Of particular relevance are the low-frequency vibrations ($\omega/2\pi c < 200$ cm$^{-1}$) in the water and the peptide. These modes couple to the amide I and II vibrations, and lead to an effective fluctuating Hamiltonian for these modes. This fluctuating Hamiltonian results in an equation of motion for the system’s reduced density matrix. Propagating this equation yields the system dynamics and infrared spectra.
6.2.1 Peptide Hamiltonian

The high-frequency oscillators in the helix, which enter the system part of the Hamiltonian, are labeled with $n$ or $m$. The labels refer to both the position in the helix (the amide group) and the vibrational mode (amide I or II). At this stage, it is not necessary to distinguish between the two types of vibrations. The Hamiltonian of the peptide can be expanded in the local basis set in the usual way. Under the assumption that the couplings and the anharmonicities are much smaller than the vibrational frequencies, one obtains the Hamiltonian [Hamm et al. 1998]

$$H_S = \sum_n \epsilon_n b_n^\dagger b_n + \sum_{n \neq m} J_{nm} b_n^\dagger b_m - \frac{1}{2} \sum_n A_n b_n^\dagger b_n^\dagger b_n b_n,$$

where $\epsilon_n$ is the average amide I or amide II frequency in solution ($\hbar = 1$), and $A_n$ the quartic anharmonicity. The operators $b_n^\dagger$ and $b_n$ are the usual bosonic creation and annihilation operators on the $n$th vibration. Bilinear interactions between the vibrations give rise to the coupling matrix elements $J_{nm}$, the higher order terms in the expansion of the coupling are not included. The interactions arise from two mechanisms. The electrodynamic interaction that results from moving charges couples all vibrations. Assuming that the moving charge clouds associated with each vibration are non-overlapping, we include these interactions by the transition charge coupling (TCC) model [Hamm and Woutersen 2002; Jansen et al. 2006]. In this model, the transition charge density of each oscillator is approximated by point charges on the atoms. When two vibrations lie in amide units which are nearest neighbors along the backbone, the electrodynamic coupling does not adequately describe their interaction [Torii and Tasumi 1998]. Direct mechanical coupling through covalent bonds is important. Coupling constants between vibrations on nearest neighbor amide vibrations can be obtained from a DFT map. A quantum chemical calculation is used to find the vibrational eigenstates in a dipeptide. From a reconstruction method, one then finds couplings between local modes that reproduce these eigenstates. The procedure is repeated for several dipeptides with varying dihedral angles to obtain a map that relates the coupling to the peptide structure. Such calculations have been used by several authors to parametrize the coupling between amide I vibrations [Torii and Tasumi 1998; Hamm and Woutersen 2002; Choi et al. 2003; Gorbunov et al. 2005; Watson and Hirst 2005; Jansen et al. 2006]. Here, we have extended these methods in a systematic way to include the amide II mode, as described in detail in Section 6.3.2. These couplings lead to coherent transport of vibrational excitations along an isolated helix. On the other hand, interactions with the environment induce fluctuations in the peptide Hamiltonian which destroy the coherence.

6.2.2 Interaction with the environment

The peptide Hamiltonian needs to be supplemented to include the effects of the environment. In a water solution, the amide vibrations in the peptide are constantly perturbed. In a reduced description that includes only the peptide coordinates, this interaction leads to fluctuations in the peptide Hamiltonian. In the fluctuating oscillator Hamiltonian, the coupling between the system and the environment is included
Simulation of vibrational dynamics in the amide I and II bands of an α-helix

as a time-dependent contribution in the Hamiltonian [Cho 2008],

\[ H_{SB}(t) = \sum_n \xi_{nn}(t) b_n^\dagger b_n + \sum_{n \neq m} \xi_{nm}(t) b_n^\dagger b_m, \quad (6.2) \]

where \( \xi_{nn}(t) \) and \( \xi_{nm}(t) \) denote fluctuations in the energies and the couplings. They replace the quantum mechanical bath coordinates that appear in a fully quantum-mechanical model. For Gaussian fluctuations, the properties of the stochastic variables \( \xi(t) \) are fixed by their second order correlation functions, \( \langle \xi_{nm}(t) \xi_{n'm'}(0) \rangle_C \). The notation \( \langle \cdot \cdot \cdot \rangle_C \) refers to a classical, stochastic average. We assume that the average of the stochastic variables is zero, nonzero shifts can be included in the system Hamiltonian (Eq. 6.1). Replacing quantum mechanical with classical averaging is an approximation, which is valid in the high temperature limit. This limit can be used if the zero point energy of all relevant bath oscillators is smaller than the thermal energy. Assuming that only bath oscillators with a frequency smaller than a certain value \( \omega_C \) are relevant to the system’s dynamics, the high temperature limit can be applied if \( k_B T \gg \hbar \omega_C / 2 \).

For Gaussian fluctuations, the two-point correlation functions fully determine the stochastic variables \( \xi_{nm}(t) \). In calculations, we take into account the time dependence of the frequencies and the intermode coupling in each amide group. The couplings between different groups are assumed to be constant. Typically, these latter fluctuations are found to be much smaller than fluctuations in the oscillator frequencies. From MD simulations of trialanine, coupling fluctuations of a few wavenumbers were found [Gorbunov et al. 2005], and we expect these fluctuations to be smaller in the more rigid helix. Furthermore, while the fluctuating quantities within an amide group are correlated, we do not include correlations between different groups. This approach will allow us to parametrize the time dependence of the Hamiltonian from simulations of a single peptide group. Also, we excluded possible fluctuations in the anharmonicity in Eq. 6.2. The effect of such fluctuations on the spectra of the amide I mode is known to be small [Jansen and Knoester 2006a].

### 6.2.3 Propagation

Numerical evaluation of the matrix exponent of the time dependent Hamiltonian in short time steps yields the propagator required to calculate population dynamics, linear absorption spectra and 2DIR spectra [Torii 2006; Jansen and Knoester 2006b]. We neglect effects due to a finite pulse duration [Gelin et al. 2005; Brüggemann et al. 2007]. All the observables involve the one-quantum propagator \( U^{(1)}(t; t_0) = T e^{-i \int_{t_0}^t d\tau H^{(1)}(\tau)} \), which is a time ordered exponential of the one-quantum Hamiltonian \( H^{(1)}(t) \). In the site basis, the matrix elements of the one-quantum Hamiltonian are given by \( H^{(1)}_{nm}(\tau) = \langle 0 | b_n (H_S + H_{SB}(\tau)) b_m^\dagger | 0 \rangle \). The time-ordered exponential is evaluated by the multiplication of propagators for short time steps, during which the Hamiltonian is assumed to be constant [Jansen and Knoester 2006b]. In the final coherence time in a 2DIR calculation, the propagation of two-quantum matrix elements of the Hamiltonian is needed. This can be simplified by separating the propagation
into the harmonic and the anharmonic part as described in Section 2.4.

6.3 Parametrization of the model

6.3.1 NMA-d$_7$

The building block of the peptide backbone is a single amide group (see Figure 6.1). To parametrize our model, we need to find the frequencies of the amide I and II modes, and the coupling between them in a single group. In addition, fluctuations in these parameters describe the dephasing and relaxation processes. A simple molecule which contains a single amide group is NMA-d, which has a deuterium atom connected to the nitrogen, but normal hydrogen atoms on the methyl groups. We studied the relaxation dynamics and the infrared spectra of this molecule in earlier work [Dijkstra et al. 2007; Bloem et al. 2008]. However, in the amide II vibration in NMA-d, the methyl group hydrogen atoms move considerably. This molecule is therefore not a suitable model for the amide group in a peptide, where the methyl groups are replaced by $\alpha$-carbon atoms.

To create a useful parametrization of a single deuterated amide group, we develop a new DFT map of the amide I and amide II mode in NMA-d$_7$ following the procedure described earlier [Bloem et al. 2008]. In this molecule, the hydrogens on the methyl groups are replaced with deuterium, thereby making these methyl groups heavier. DFT calculations are performed with the ADF program [te Velde et al. 2001; Guerra et al. 1995], using the ADF TZ2P basis set and the RPBE exchange correlation functional [Perdew et al. 1996; Hammer et al. 1999]. We find that, in contrast to the results in NMA-d, the heavier methyl groups in NMA-d$_7$ hardly move. This is an essential property to be able to use this molecule as a building block for larger peptides. As a basis set for the DFT calculations, we use the CC$\alpha$, NC$\alpha'$, CN and CO stretches, and the OCN, DNC, NCC$\alpha$ and CNC$\alpha'$ bends (see Figure 6.1). In the amide I vibration, 94 percent of the amplitude of the wave function squared is found on these modes, in the amide II vibration this is 96 percent.

The fit constants (given in Table 6.1) which describe the response of the two frequencies and of the amide I - amide II coupling to an electrostatic environment are used to obtain a fluctuating Hamiltonian from the MD trajectory of the NMA-d$_7$ molecule in D$_2$O. The trajectory, which was described earlier by Bloem et al. [2008], was generated at a temperature of 300 K using the GROMACS package [Berendsen et al. 1995; Lindahl et al. 2001]. It turns out that the DFT calculation overestimates the energy gap between the two modes, which results in a calculated linear spectrum with the amide I and amide II peaks too far apart. This is not entirely surprising, because it is well known that DFT frequencies are only accurate within a few percent. They are often scaled to correct for rather systematic errors [Jensen 1999]. We therefore multiply the energies obtained in the DFT calculation by a scaling factor, which is $c_1$ for the amide I mode and $c_2$ for the amide II mode. As far as we know, no gas phase spectra of NMA-d$_7$ have been measured. It is therefore not possible to use gas phase experimental results to find the scaling factors, as we did previously for NMA-d [Bloem et al. 2008]. It is, however, possible to compare the average energy gap in the liquid to the experimental spectrum. Following this procedure, we obtain
96 Simulation of vibrational dynamics in the amide I and II bands of an α-helix

<table>
<thead>
<tr>
<th></th>
<th>$\epsilon_1$</th>
<th>$\epsilon_{II}$</th>
<th>$I_{12}$</th>
<th>$\mu_{1I}^i$</th>
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<th>$\mu_{1I}^v$</th>
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<td>$\Omega_0$</td>
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<td>1429.17</td>
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<td>0.070</td>
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Table 6.1: Electrostatic map for the NMA-d$_7$ frequencies, coupling and transition dipoles. The values for $\Omega_0$ are in Debye. Units for the field and gradient coefficients are D/($E_h/e$ Bohr) and D/($E_h/e$ Bohr$^2$), respectively, where $E_h$ is the Hartree.

scaling factors of $c_2 = 1.0248$ for the amide II mode and $c_1 = 0.9693$ for the amide I mode. In this way, we correct for possible differences between the DFT energies and the unknown experimental gas phase frequencies, as well as for possible errors in the predicted solvent shift. Thus, we are not able to assess the reliability of the prediction of the solvent shift, which turned out to be predicted rather poorly in NMA-d [Bloem et al. 2008]. After the scaling, the frequencies of the amide II and the amide I mode averaged over the MD trajectory are 1514 and 1586 cm$^{-1}$, respectively. The average coupling is 36.7 cm$^{-1}$. The average frequencies of the eigenmodes, which are found in each MD snapshot, are then found to be 1495 and 1605 cm$^{-1}$. After this scaling procedure, the frequencies are in agreement with the experimentally obtained peak positions (values of 1495 and 1604 cm$^{-1}$ were measured by DeFlores et al. [2006]).

Other parameters that we use in the peptide model are the anharmonicities, the dipole vectors and the time correlation functions of the amide I and II modes. The anharmonicities are taken to be 16 cm$^{-1}$ for the amide I mode [Hamm et al. 1998], and 11 cm$^{-1}$ for the amide II mode [DeFlores et al. 2006]. From the average over the MD trajectory, the angle between the two dipoles is 79.4 degrees (which compares well to the 75 degrees found experimentally by DeFlores et al. [2006]), and the length of the amide II dipole is 0.64 times the length of the amide I dipole. Auto and cross correlation functions for the frequencies and the coupling are shown in Figure 6.2. They show many features similar to the correlation functions of NMA-d, such as the clear anti-correlation between the frequencies and the large fluctuations.
in the coupling. Two main differences are the smaller fluctuation amplitude of the amide I mode, and the presence of correlation between the coupling and the amide I frequency in the NMA-d7 molecule.

The calculated linear spectrum, obtained by propagating the Schrödinger equation with the time-dependent Hamiltonian given in Eqs. 6.1 and 6.2, is shown in Figure 6.3, together with the experimental spectrum from DeFlores et al. [2006]. The line shape of the amide I mode is predicted well by the calculations. In the amide II region, the agreement is not as good. The ratio between the integrated amide II and amide I intensities (0.4 in the calculation, 0.3 in experiment), and thus between the dipoles, is too large in the calculation. Secondly, the amide II peak is too narrow, indicating that the calculation underestimates the time scale or the amplitude of the fluctuations.

6.3.2 Dipeptide
The bilinear coupling terms $J$ in the peptide Hamiltonian (Eq. 6.1) were modeled by (electrodynamic) transition charge coupling [Hamm and Woutersen 2002; Jansen et al. 2006]. For interactions between amide groups that are linked by covalent bonds, the TCC model is not applicable, because mechanical coupling caused by movements of the in-between atoms (through-bond coupling) is important. Such through-bond couplings have been taken into account in models of amide I vibrations in peptides by performing DFT calculations on dipeptides or polypeptides [Torii and Tasumi 1998; Hamm and Woutersen 2002; Choi et al. 2003; Gorbunov et al. 2005; Watson and Hirst 2005; Jansen et al. 2006]. Here, we extend these methods to include the amide II mode. The goal of this procedure is to write the eigenmodes in a dipeptide as a linear superposition of the eigenmodes in two NMA-d7 molecules. If the dipeptide eigenmodes are denoted $|\psi\rangle$ and the NMA-d7 eigenmodes as $|\phi\rangle$, the required transformation can be expressed as a 4x4 matrix $T$ which satisfies $|\psi\rangle = T|\phi\rangle$. This is achieved by expressing the dipeptide eigenstates and the NMA-d7 eigenstates in the same basis set of stretch and bend vibrations, and then using a matrix reconstruction method to find the transformation between the two sets of eigenmodes.
Maps for amide I and amide II site frequencies, and the couplings, as a function of the dihedral angles (See Figure 6.1) were calculated in this way. The local basis used in the NMA-d$_7$ molecule was introduced in Section 6.3.1. Here, we denote the set of the basis states on the two sides of the dipeptide as \{\ket{n}\}. There are a total of 16 basis states, resulting from 4 stretching and 4 bending vibrations on each side of the dipeptide. The expansion of the dipeptide eigenmodes, \ket{\psi} = \sum_n \langle n | \psi \rangle \ket{n} and of the NMA-d$_7$ eigenmodes, \ket{\phi} = \sum_n \langle n | \phi \rangle \ket{n} are known. The transformation matrix $T$ is found by solving the system $\langle n | \psi \rangle = \sum_m T_{nm} \langle m | \phi \rangle$.

Because the system is overdetermined (64 equations for 16 unknowns), the transformation from the basis of dimer eigenstates to the direct product basis of NMA eigenstates is then found by a least square solution. Finally, the Hamiltonian in the required basis is obtained by transforming the (diagonal) Hamiltonian in the basis of dipeptide eigenstates, $H = T^\dagger E_{\text{dipeptide}} T$. The least squares procedure gives a transformation matrix that is not unitary, which results in a Hamiltonian in the basis of NMA states which is not exactly symmetric. We therefore explicitly symmetrize the Hamiltonian. This leads only to small corrections of the couplings, as we have checked by comparing to a minimization procedure that explicitly constrains the transformation matrix to be unitary. In that procedure, we minimize the difference between the known dipeptide normal modes and the transformation matrix times the NMA normal modes. Minimization is done with respect to the Frobenius norm (least squares), and is constrained to a unitary transformation matrix. The matrix elements reconstructed in this way differ from the ones obtained after symmetrization by less than 0.32 cm$^{-1}$.

The joint matrix reconstruction for the two vibrational modes gives values for the amide I and II frequencies at the C and the N side of the dipeptide, the intra-site...
Several previous maps of the amide I frequencies and coupling have been presented. Couplings were calculated as a finite difference of the energy [Torii and Tasumi 1998; Hamm and Woutersen 2002], or by matrix reconstruction methods [Choi et al. 2003; Gorbunov et al. 2005; Watson and Hirst 2005; Jansen et al. 2006]. Our results, which are found using joint inversion of the amide I and amide II modes, give qualitatively the same results as these works. All maps find a negative coupling along the anti-diagonal ($\psi = -\phi$) and positive couplings in the remaining corners. However, quantitative differences between the maps are significant. In the Torii and Tasumi map, the coupling varies between -9.5 and 32.7 cm\(^{-1}\) [Torii and Tasumi 1998]. This asymmetry between positive and negative amplitude is also found in our present result, while the amplitudes are almost equal in the work by Jansen et al. [2006] and Hayashi and Mukamel [2007]. The couplings between amide I units seem to be rather robust, but values for the frequency shifts strongly depend on the DFT method used [Gorbunov et al. 2005].

Calculations on the amide I, II, III and A modes in NMA-h7 have also been re-
Figure 6.5: Map for the couplings between the two sites. Contours were plotted every 2.5 \( \text{cm}^{-1} \). Contours in I-I are from -7.5 to 17.5 \( \text{cm}^{-1} \), in II-II from -10 to 0 \( \text{cm}^{-1} \), CI-NII from -12.5 to -2.5 \( \text{cm}^{-1} \), NI-CII from -5 to +5 \( \text{cm}^{-1} \).
6.3: Parametrization of the model

<table>
<thead>
<tr>
<th></th>
<th>( n + 1 )</th>
<th>( n + 2 )</th>
<th>( n + 3 )</th>
<th>( n + 4 )</th>
<th>( n + 5 )</th>
<th>( n + 6 )</th>
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<td>am I - am I</td>
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<td>-3.7</td>
<td>-6.8</td>
<td>-2.3</td>
<td>-0.8</td>
<td>-0.6</td>
</tr>
<tr>
<td>am II - am II</td>
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<td>-4.7</td>
<td>-0.1</td>
<td>1.4</td>
<td>-0.6</td>
<td>-0.3</td>
</tr>
<tr>
<td>am II - am I</td>
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<td>-1.1</td>
<td>0.2</td>
<td>0.0</td>
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<tr>
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<td>-9.5</td>
<td>3.3</td>
<td>-0.7</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

**Table 6.2**: Inter-site coupling constants in a model \( \alpha \)-helix in cm\(^{-1} \), obtained from a combination of the TCC model with the nearest neighbor coupling map. The amide groups are indexed from the N terminal to the C terminal.

lengths and angles [Lehninger 1975], and took all pairs of dihedral angles to be \((\phi, \psi) = (-57^\circ, -47^\circ)\).

The fluctuations in amide I and II site energies and in the coupling between them are parametrized from our NMA-d\(_7\) results. With the assumption that the fluctuations are Gaussian, all information is contained in the six auto- and cross correlation functions \(C(t)\), shown in Figure 6.2. Cross correlations between the two frequencies on the same group and the intragroup coupling are included, but we assume that the fluctuations in different groups are uncorrelated. Such correlations might be present, especially between the amide II and amide I vibrations in amide groups connected through a hydrogen bond. Detailed tests would require the combination of our map with MD simulations of peptide fragments, which is beyond the scope of this work. Assuming no inter-group correlations, a fluctuating Hamiltonian for a helix with \( N \) amide groups can be generated from the NMA-d\(_7\) correlation functions.

In this model we make the usual assumption that the intergroup couplings are constant in time. This can be rationalized from the origin of these couplings as electrodynamic or through-bond interactions, which are not expected to exhibit large fluctuations [Ham et al. 2004; Kobus et al. 2008]. Coupling constants in the helix, obtained from the transition charge coupling model combined with the dipeptide DFT map, are given in Table 6.2. The parameters for the TCC model, obtained in the same way as the amide I parameters by Jansen et al. [2006], are given in Table 6.3. In the helix, large couplings are found between the amide I modes that are connected along the backbone and through intramolecular hydrogen bonds. These interactions are quantitatively similar, in agreement with earlier work [Ham et al. 2004; Choi et al. 2005]. The couplings in the amide I band that we find are also in reasonable agreement with experimental results, where \( J_{12}^I = 8.5 \pm 1.8 \) cm\(^{-1} \), \( J_{13}^I = -5.4 \pm 1.0 \) cm\(^{-1} \) and \( J_{14}^I = -6.6 \pm 0.8 \) cm\(^{-1} \) [Fang et al. 2004]. While the couplings in the amide I band are rather well known, much less information is available for the amide II modes. One model included an amide II - amide II nearest neighbor coupling of -8.7 cm\(^{-1} \) [DeFlores et al. 2009]. This is inconsistent with the coupling constants found in our calculation, which are shown in Table 6.2. Perhaps surprisingly, the largest interaction between amide II modes skips one peptide unit along the backbone. The CN bonds in these units make an angle of only 13 degrees, which rationalizes the large coupling. Calculations on the couplings between amide II modes were performed by Hayashi and Mukamel [2007]. The trend of the couplings agrees with our results, \( J_{n,n+1}^{II} \) and \( J_{n,n+3}^{II} \) are small, the largest coupling is \( J_{n,n+2}^{II} \), which is negative and \( J_{n,n+4}^{II} \).
Simulation of vibrational dynamics in the amide I and II bands of an \( \alpha \)-helix

<table>
<thead>
<tr>
<th></th>
<th>( C_\alpha )</th>
<th>C</th>
<th>O</th>
<th>N</th>
<th>D</th>
<th>( C_\alpha )</th>
</tr>
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<td>( q )</td>
<td>0.11337</td>
<td>0.36621</td>
<td>-0.53731</td>
<td>-0.48052</td>
<td>0.24280</td>
<td>0.29545</td>
</tr>
<tr>
<td>( dq_1 )</td>
<td>0.01689</td>
<td>-0.02838</td>
<td>-0.01569</td>
<td>0.01729</td>
<td>0.00002</td>
<td>0.00986</td>
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<tr>
<td>( \nu_{1x} )</td>
<td>0.00705</td>
<td>0.02179</td>
<td>-0.00695</td>
<td>-0.02782</td>
<td>-0.12236</td>
<td>-0.00542</td>
</tr>
<tr>
<td>( \nu_{1y} )</td>
<td>-0.05670</td>
<td>0.82436</td>
<td>-0.50410</td>
<td>-0.07861</td>
<td>-0.08970</td>
<td>0.00772</td>
</tr>
<tr>
<td>( dq_2 )</td>
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<td>0.00778</td>
<td>-0.00734</td>
<td>0.00686</td>
<td>0.01117</td>
<td>-0.00289</td>
</tr>
<tr>
<td>( \nu_{2x} )</td>
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<td>0.57803</td>
<td>-0.05830</td>
<td>-0.53197</td>
<td>0.51119</td>
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</tr>
<tr>
<td>( \nu_{2y} )</td>
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<td>0.01505</td>
<td>0.05996</td>
<td>-0.0065</td>
<td>-0.04563</td>
<td>-0.02573</td>
</tr>
</tbody>
</table>

Table 6.3: Parameters of the TCC model for the amide I and amide II modes as obtained from quantum chemical calculations on a NMA-d\(_7\) molecule. The charges \( q \) and charge derivatives \( dq \) on the methyl groups have been summed into the values listed as \( C_\alpha \). The displacements \( \nu \) are given as a fraction of the oscillator amplitude, which is 0.028811 Å for the amide I mode and 0.037201 Å for the amide II mode. Charges are in units of \( e \). The coordinate system is defined as in Figure 6.1 in the main text.

Apart from the first and the last groups, each amide group in the helix has two neighbors. The presence of these neighbors shifts the frequencies and the intragroup coupling. From the dipeptide DFT map, these shifts can be determined, and their values in the \( \alpha \)-helix geometry are given in Table 6.4. For a group in the middle of a helix, the shifts from right and left neighbors must be added [Gorbunov and Stock 2007; Jansen et al. 2006]. We assume that the average frequency in each group is the same, which is only correct for groups in the middle of a long helix [Ham et al. 2004; Fang and Hochstrasser 2005; Mukherjee et al. 2006a].

### 6.4 Results and discussion

#### 6.4.1 Nature of modes and linear spectrum

The nature of the vibrational modes in the helix is determined by the competition between coherent couplings and environment-induced fluctuations. The coherent couplings lead to three collective modes, the A mode (polarized along the helix axis) and two degenerate E modes (polarized perpendicular to the helix axis) [Miyazawa 1960]. In our model, due to finite size effects and the coupling with the amide II mode, the E modes are no longer degenerate. Furthermore, the coupling with the

<table>
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<th>N-site</th>
<th>C-site</th>
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<tr>
<td>amide I frequency</td>
<td>16.9</td>
<td>12.7</td>
<td>29.6</td>
</tr>
<tr>
<td>amide II frequency</td>
<td>-9.2</td>
<td>-26.4</td>
<td>-35.6</td>
</tr>
<tr>
<td>on-site coupling</td>
<td>13.9</td>
<td>-6.2</td>
<td>7.7</td>
</tr>
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</table>

Table 6.4: Shifts in the frequencies and in the on-site coupling obtained from the DFT map for the \( \alpha \)-helix configuration, in cm\(^{-1}\).
Figure 6.6: Stick spectrum (a) and Linear absorption (b) of a model α-helix with 10 amide units. The stick spectrum in panel (a) was calculated from the average frequencies and couplings. The contributions to the intensity from dipoles in the \( x \), \( y \), and \( z \) directions are given in white, black and gray, respectively. Frequency shifts from the nearest neighbour coupling map are included.

amide II mode causes a Davydov splitting of each of the E-modes. As a result, a total of four modes polarized perpendicular to the helix axis are observed in the stick spectrum (Figure 6.6 a) of a non-fluctuating helix. On average, this splitting increases the distance between the A and E peaks, and a shoulder becomes visible in the calculated linear spectrum shown in Figure 6.6 b. Because such a shoulder is not found in experiment, we are led to believe that we have overestimated the magnitude of the amide I - amide II coupling (see below).

The interaction with the environment leads to fluctuations in the peptide Hamiltonian, and the eigenstates are short-lived. Eigenstates at a fixed moment in time - instantaneous normal modes - are defined as the solution of \( H(t)\psi_u(t) = E_u(t)\psi_u(t) \) at a fixed time \( t \). They are partially localized by the fluctuations. Because of rapid

Figure 6.7: Density of instantaneous normal modes (left panel) and inverse participation ratio spectrum (right panel) for a length 10 helix.
crossing of eigenstates in the amide I band, the adiabatic approximation is not valid. This makes it hard to identify states at different times. Localization properties of the fluctuating system must be studied in an average way. A measure of the localization is given by the inverse participation ratio (IPR) of the instantaneous normal modes as a function of their energy [Ham et al. 2004]. It is given by

$$R(\omega) = \left\langle \left( \sum_n \frac{\psi_n^4(t)}{\delta(\omega - E_u(t))} \right) \right\rangle / \text{DOS}(\omega).$$  

The IPR spectrum is normalized by the density of instantaneous normal modes, defined as $\text{DOS}(\omega) = \left\langle \sum_u \delta(\omega - E_u(t)) \right\rangle$. The averages $\langle \cdots \rangle_C$ are over time (and over trajectories if the system is not ergodic in the simulation time). The density of states and the IPR spectrum are plotted in Figure 6.7. Due to smaller couplings, the density of states in the amide II band is much larger than in the amide I band. There is a clear gap between the two peaks in the density of states, so that one can speak of two different modes. However, as expected from the coupling, examination of the eigenstates themselves shows that the solvent induces some mixing between the gas phase amide I and II modes. The IPR spectrum is found to depend strongly on frequency. It suggests a localization length of almost four oscillators in the amide I band, while amide II modes are slightly more localized. The IPR results for the amide I mode are similar to the $\alpha$-helix calculations by Ham et al. [2004], where the maximum IPR is just below five. Similar localization sizes have been found in experimental work on $\beta_{10}$ helices [Maekawa et al. 2008]. The measured 2DIR spectra of the helices are found to be strongly dependent on the helix length for short helices, while spectra for helices longer than 5 amide groups appear similar. Although this suggests that the size of the excitations in $\alpha$ and $\beta_{10}$ helices are similar, the delocalization pattern might be different in both cases.

In the peptide Hamiltonian, we have included the frequency shifts found from the dipeptide map (given for the $\alpha$-helix geometry in Table 6.4). Because of the blueshift of the amide I frequency, the redshift of the amide II frequency and the positive shift in the coupling, the frequency gap between the two bands is bigger than in NMA-d$_7$. This is in agreement with experiment, as can be seen by comparing the calculated and the measured linear spectra. In our length 10 helix (including end effects), the maximum of the amide I peak in the linear spectrum occurs at 1612 cm$^{-1}$, the maximum of the amide II peak is found at 1467 cm$^{-1}$. In $\alpha$-helix forming polylysine, the peak maxima are near 1650 cm$^{-1}$ and 1425-1445 cm$^{-1}$ [DeFlores et al. 2009]. Our calculated increase in the frequency gap, when compared to NMA-d$_7$, turns out to be smaller than the experimental value, but the agreement is rather good.

### 6.4.2 Vibrational dynamics

In our model, there is no mechanism by which the environment refocuses an amide I excitation, and solitonic transport [Davydov 1985; Tsivlin and May 2007] does not occur. It is, however, interesting to study the excitation transport along a helix and to
distinguish between transport along the backbone, through hydrogen bonds, and to the amide II mode. The populations of amide I and amide II modes in the site basis are shown in Figure 6.8 for various waiting times. These populations were obtained after averaging over 10,000 trajectories, leaving out the relaxation to modes outside the amide I and II bands. As the initial condition, we put an excitation on the first amide I oscillator at \( t = 0 \). The amide I population on group 4, which is hydrogen bonded to group 1, rises quickly, illustrating the transport along the hydrogen bond. On the same timescale, on-site relaxation to the amide II mode on group 1 takes place. Within 1 ps, the excitations have traveled through a large part of the helix.

To quantify the dynamics, we have plotted the average distance \( d \) traveled by an excitation as a function of time in Figure 6.9. The distance was defined in terms of the components of the density matrix in the site basis as \( d(t) = \sum_n (n-1) \langle \rho_{nn}(t) \rangle_C = \sum_n (n-1) \langle (U(t; t_0) \rho(t_0) U^\dagger(t; t_0))_{nn} \rangle_C \). In panel (a) of the figure, the initial excitation was on the first amide I oscillator in the helix, and we follow its average position in the amide I band. In the first 500 fs, as a consequence of the partial delocalization of excitations, we observe ballistic transport with a rate of 4 peptide units per ps \( (d = t/0.22 \text{ ps} - 0.4) \). Here, the offset \(-0.4\) reflects the nonlinear behavior of \( d \) with \( t \) at very early times, which is a consequence of the initial accelerated vibron motion. After approximately 500 fs, the excitation transport can be characterized as diffusive, with a one-dimensional diffusion constant\(^1\) \( (d^2 = 2Dt) \) of 11 peptide units squared.

\(^1\)The diffusion constant is usually defined by considering the average value of the squared displace-
Simulation of vibrational dynamics in the amide I and II bands of an $\alpha$-helix

Figure 6.9: Average distance traveled by an (a) amide I and (b) amide II excitation in an $\alpha$-helix. The solid line is the result of our calculation. A ballistic fit at short times and a diffusive fit at longer times are indicated by open circles and squares, respectively.

per picosecond. A similar picture emerges for the amide II dynamics, although the dynamics is a few times slower. In Figure 6.9 b the position in the amide II band is plotted after initial excitation of an amide II oscillator. The ballistic transport takes place with a time constant of 0.9 ps ($d = t/0.94 \text{ ps} - 0.4$). The diffusion constant is $4 \text{ peptide units squared per picosecond}$.

In addition to intraband dynamics in the amide I band, relaxation between the two bands takes place. This process can be followed by plotting the total amide I population after initial amide I excitation as a function of waiting time. In the first few hundred femtoseconds, coherent oscillations are observed. After longer waiting times, the amide I population decays exponentially, with a decay constant of $2.12 \pm 0.01 \text{ ps}$. This decay is much slower than in NMA-d [Bloem et al. 2008]. The decrease in the intraband relaxation time can, however, be attributed almost entirely to the frequency shifts induced by the surrounding peptide units and the smaller fluctuations. The shifts increase the gap between the amide I and amide II mode, thereby making the transfer between these two modes slower. It is easily checked that the transfer time in a single peptide unit, taking into account the frequency shifts, is also 2.1 ps.

Vibrational dynamics can be characterized starting from initial excitation on a single oscillator in the site basis, as we did in this section. In an experiment with short laser pulses, however, multiple oscillators would be excited coherently. Excitation of a single site can be achieved when the site is special, for example when its excitation frequency differs from the rest of the chain. Such different excitation frequencies occur when atoms are replaced by heavier isotopes, or when the oscillator has a different chemical environment. This approach has been used in experimental studies of vibrational energy transport [Backus et al. 2008]. With an amide I frequency shift of $30 \text{ cm}^{-1}$, which is significantly larger than the coherent couplings,
one would expect the excitation to be localized. Furthermore, coherent hopping to neighboring oscillators would be suppressed. However, although the average frequency of the initially excited oscillator almost forbids mixing with other amide I modes, the environment-induced frequency fluctuations are large enough to make such mixing possible. With the help of the fluctuations, the excitations manages to escape from the initial site. The rate of the resulting intraband dynamics depends on the size of the initial frequency shift, the coherent couplings, and the size and time scale of the fluctuations. Because intraband dynamics competes with processes that reduce the total amide I population, it is not a priori clear if the intraband dynamics occurs at all. In our model, this issue can be clarified with the help of a direct calculation. In Figure 6.10, we plotted the total population on the fourth amide I oscillator, which is connected to the initially excited first site by a hydrogen bond. The figure demonstrates that significant subpicosecond intraband transfer is possible starting from an initial excitation with a frequency shifted by \(-30 \text{ cm}^{-1}\) from the center of the main band. However, the amplitude of the arriving population is roughly halved compared to the population transferred from an unshifted initial site. In our model, a shift of \(-30 \text{ cm}^{-1}\) in the frequency of the initially excited oscillator does not prohibit intraband vibrational energy transport. However, our model overestimates frequency fluctuations from interaction with the solvent, while neglecting fluctuations due to the peptide. If the resulting frequency fluctuations are considerably smaller than in the model employed here, transport will be further suppressed.

### 6.4.3 2DIR spectra

2DIR spectra of a helix with ten amide units were calculated for different polarization geometries in the rephasing and non-rephasing pathways. To make a connec-
Simulation of vibrational dynamics in the amide I and II bands of an α-helix

Figure 6.11: (a) integrated intensities of the upper amide II - amide I cross peak in a length 10 helix (non-rephasing spectrum) and (b) polarization anisotropy of the integrated amide I diagonal peak intensities (rephasing spectrum).

The polarization anisotropy of the integrated peak intensities is shown in Figure 6.11 b. For a single helix unit, the anisotropy of the amide I diagonal peak decays slowly, with an exponential time constant of 2.4 ps. The slow decay can be attributed to the mixing with the amide II mode, and the time constant corresponds to the decay to this mode. In a single peptide unit, intraband relaxation is not possible. In a longer helix, this mechanism leads to additional relaxation of the polarization anisotropy. In an eigenstate picture, the initial excitation will mainly populate the intense A modes of the helix. In an isotropic system, the polarization anisotropy at time zero would be 0.4 at zero waiting time. However, the diagonal amide I peak also contains a cross peak between A and E modes. As a consequence of the perpendicular orientation of these modes, the polarization anisotropy in this cross peak will be smaller than 0.4. This can be seen in the anisotropy spectra in Figure 6.12. Therefore, the anisotropy calculated from the intensities integrated over the whole amide I peak is slightly lower than 0.4 at zero waiting time. At longer waiting times, as a result of the fluctuations, the initially excited state relaxes, and the average dipole of the excitation is rotated. This is seen as a decay of the anisotropy. An exponential fit gives a decay time of 0.23 ± 0.04 ps, which corresponds to the ballistic transport time in the amide I band.

The cross peaks between the amide I and amide II modes are expected to increase with waiting time as a result of the vibrational relaxation between these two modes. However, the intraband relaxation leads to rotation of the dipole of the excitation. Therefore, in the parallel polarization, the cross peak intensity drops in the first 600
6.4: Results and discussion

Figure 6.12: Non-rephasing absolute value anisotropy spectra for two chain lengths and two waiting times (as indicated in the figure).

fs (Figure 6.11 a). The cross peak intensity normalized to the intensity of the amide I diagonal peak does increase with waiting time, and reflects the relaxation process between amide II and amide I modes. Because diagrams with a coherent superposition of exciton states contribute differently to the rephasing and non-rephasing spectra, we have plotted rephasing diagonal peak intensities and non-rephasing cross peak intensities in Figure 6.11. In an exciton model, these peak intensities are free of oscillating contributions from coherent superpositions of delocalized states.

In the calculated two-dimensional correlation spectra of helices (not shown), the E modes are clearly visible. The appearance of these modes is consistent with the observation of a shoulder in the amide I peak in the linear spectrum (Section 6.4.1). This is not the case in experiment, although the A and E structure can be observed by subtracting spectra in the parallel and perpendicular polarization geometry [Woutersen and Hamm 2001b]. The A-E peak distance in our model is influenced by the strength of the on-site amide I - amide II coupling. This coupling is modeled from MD simulations of the NMA-d_{7} molecule in D_{2}O. The fact that we overestimate the A-E splitting suggests that the amide I - amide II coupling in an actual helix is smaller than this value. The discrepancy can be understood from the origin of the coupling, which arises from mode mixing by the solvent. In a helix, the effect of the water on the amide frequencies [Mukherjee et al. 2006b] and, probably also on the on-site coupling, is reduced. This lowers the magnitude of the frequency fluctuations, as well as the average strength of the on-site coupling. An important other source of fluctu-
ations in the helix comes from structural fluctuations [Woutersen and Hamm 2001b; Gnanakaran et al. 2004], which would modulate the amide frequencies mainly by changing the intramolecular hydrogen bonds. The effect of this environment on the amide I frequency is smaller and slower than the water effect in NMA-d$_7$ [Ham et al. 2004; Mukherjee et al. 2006a].

6.5 Conclusions and outlook

In this chapter, we have presented dual mode 2DIR spectra of a model oligopeptide. We have deliberately chosen to build a helix from individual amide units. Each unit can be parametrized by considering the NMA-d$_7$ molecule. From DFT calculations combined with MD simulations, we have found the solvent-induced fluctuations in the amide I and amide II frequencies, as well as in the intermode coupling. Compared to earlier results on NMA-d [Bloem et al. 2008], the NMA-d$_7$ molecule turns out to be a better model system for the amide II mode in peptides, because the methyl groups move less. To account for interactions between the amide groups, we have created an electrodynamic TCC model and a nearest neighbor coupling map for both the amide I and II mode. The map is the result of a new and rigorous matrix reconstruction method which is used to find the coupling from knowledge of the vibrational eigenstates in a dipeptide.

Calculations of the vibrational dynamics in a model $\alpha$-helix show that energy transport over a few turns is possible within the lifetime of an amide excitation. It is possible to make a direct connection to the calculated 2DIR spectra, where the intraband transport shows as a decay of the diagonal peak anisotropy. The time scale of relaxation between the amide I and amide II modes is found to be 2.1 ps. This is much slower than the time scales we found earlier in NMA-d [Dijkstra et al. 2007; Bloem et al. 2008]. The difference can be attributed to the shift in oscillator frequencies caused by the neighboring peptide groups, which increases the gap between the two modes.

Future work should focus on a more precise parametrization of the model, including the effects of fluctuations from both the water and the peptides. All these effects can be parametrized from an MD simulation with the use of electrostatic maps. Furthermore, the system-bath interaction term in the Hamiltonian, Eq. 6.2, corresponds to a stochastic model for the interaction [Kubo et al. 1985]. Such a model is valid in the limit where the thermal energy is much larger than half the system bandwidth. In particular, after a long waiting time, all oscillators will have the same population, and a correct Boltzmann equilibrium is not found. In the combined amide I and amide II manifolds, the thermal energy is only around two times larger than half the bandwidth. In the case of linear coupling of the system to a bath of harmonic oscillators, the full quantum dynamics can be solved [Tanimura 2006]. This approach has been used to calculate 2D spectra for arbitrary strengths of the system-bath interaction and arbitrary temperatures in the limit of independent dynamics during the three time evolution periods [Ishizaki and Tanimura 2008]. Alternatively, an exact equation of motion can be derived for the reduced density matrix as a stochastic Schrödinger equation [Stockburger and Grabert 2002; Stockburger 2004; Weiss 2008].
It would be of interest to develop models for 2DIR spectroscopy from these stochastic equations. We will come back to this approach in Chapter 8.

Finally, we comment on the similarity of our approach to models of solitonic energy transport in $\alpha$-helices. These models often start with a Fröhlich-type Hamiltonian [Ivić 1998; Falvo and Pouthier 2005]. This differs from our model in the nature of the low frequency modes. While we assumed frequency fluctuations arising from changes in the local environment close to each peptide unit, the soliton model involves acoustic phonons in the helix. Such phonons lead to correlated fluctuations in the frequencies of all amide oscillators in the helix, which can be included in our approach. It would be of interest to study the nature of the correlations predicted by molecular dynamics simulations.