Vibrational energy relaxation in proteins

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Abstract

An overview of theories related to vibrational energy relaxation (VER) in proteins is presented. VER of a selected mode in cytochrome c is studied using two theoretical approaches. One is the equilibrium simulation approach with quantum correction factors, and the other is the reduced model approach which describes the protein as an ensemble of normal modes interacting through nonlinear coupling elements. Both methods result in estimates of the VER time (sub ps) for a CD stretching mode in the protein at room temperature. The theoretical predictions are in accord with the experimental data of Romesberg’s group. A perspective on future directions for the detailed study of time scales and mechanisms for VER in proteins is presented.

Classification: Physical Science, Biophysics.

Abbreviations: VER, vibrational energy relaxation; LTZ, Landau-Teller-Zwanzig; Mb, myoglobin; cyt c, cytochrome c; QCF, quantum correction factor.

1 Introduction

When a protein is excited by ligand binding, ATP attachment, or laser excitation there occurs vibrational energy relaxation (VER). Energy initially “injected” into a localized region flows to the rest of the protein and surrounding solvent. VER in large molecules (including proteins) itself is an important problem for chemical physics [1, 2]. Even more significant is the challenge to relate VER to fundamental reaction processes, such as a conformational change or electron transfer of a protein, associated with protein function. The development of a accurate understanding of VER in proteins is an essential step toward the goal of controlling protein dynamics [3].

Due to the advance of laser technology, there have been many experimental studies of VER in proteins [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17]. These experimental works are impressive but it is difficult to derive detailed information from the experimental data alone. Theoretical approaches including atomic-scale simulations can provide more detailed information. In turn, experimental data can be used to refine simulation methods and empirical force fields. This combination of experimental and theoretical studies of for protein structures and dynamics has begun to blossom. As experimental methods develop further and theoretical approaches grow in accuracy, the relationship will become fruitful.

There have been many theoretical tools (Sec. 2) developed to analyze VER in proteins. Some aspects of VER in proteins can be explained by perturbative formulas based on the equilibrium condition of the bath (Sec. 3), but the use of the perturbative formulas may be too restrictive to generally describe protein dynamics at room temperature. In this paper, we...
not only discuss the success of such established methods but also present a perspective on the future study of VER in proteins.

2 Theories

In this section, we present a selective overview of theories appropriate for the study of VER in proteins. For the most part, these theories have been developed to deal with VER in liquids, solids, or glasses. The reader is referred to a number of recent reviews [18, 19, 20]. We refer to two distinct categories: one based on equilibrium dynamics and Fermi’s golden rule, while the other is based on nonequilibrium dynamical models.

2.1 Fermi’s golden rule

If (a) there is a clear separation between the system and bath, (b) the coupling between them is weak enough, and (c) the bath is assumed to be at thermal equilibrium, we can use quantum mechanical perturbation theory to derive a vibrational population relaxation rate through Fermi’s golden rule [19, 20]

\[
\frac{1}{T_1} = \frac{\tanh(\beta \hbar \omega_S/2)}{\beta \hbar \omega_S/2} \int_0^\infty dt \cos(\omega_st) \zeta_{qm}(t)
\]

where the force-force correlation function \( \zeta_{qm}(t) \) is defined as

\[
\zeta_{qm}(t) = \frac{\beta}{2m_S} \langle F(t)F(0) + F(0)F(t) \rangle_{qm},
\]

\( F(t) \) is the quantum mechanical force applied to the relaxing bond (system) considered, \( m_S \) is the system mass, \( \omega_S \) is the system frequency, \( \beta \) is an inverse temperature, and the above bracket indicates a quantum mechanical average.

However, this time correlation function is very hard to numerically calculate. As a result, many approximate schemes have been proposed to address this limitation. A number of the most successful approaches is mentioned below.

2.1.1 Landau-Teller-Zwanzig formula

The most simple approximation is to take the classical limit (\( \hbar \to 0 \)) of Eq. (1)

\[
\frac{1}{T_{1cl}} = \frac{\beta}{m_S} \int_0^\infty dt \cos(\omega_st) \langle F(t)F(0) \rangle_{cl}.
\]

(3)

Here the bracket denotes a classical ensemble average. This is called the Landau-Teller-Zwanzig (LTZ) formula, which has been applied to the study of VER in liquids [21]. This strategy was used by Sagnella and Straub to discuss the VER of CO in Mb*CO [22]. This approximation should be good for low frequency modes, but it becomes questionable for high frequency modes due to quantum effects. As such, advanced methods have been proposed to address this deficiency of the LTZ formula.

2.1.2 Quantum correction factor

The first alternative to the LTZ formula is the quantum correction factor (QCF) method. The basic idea of the QCF method is to relate a quantum mechanical correlation function with its classical analog [23]. When this is done for the force autocorrelation function in Eq. (1), the final expression for the VER rate \( 1/T_1^{QCF} \) is

\[
\frac{1}{T_1^{QCF}} \simeq \frac{Q(\omega_S)}{Q_H(\omega_S)} \frac{1}{T_{1cl}}
\]

(4)
where \( Q(\omega_S) \) is the QCF for the VER process considered and \( Q_H(\omega_S) \) is the QCF for a one phonon relaxation process (harmonic QCF)

\[
Q_H(\omega) = \frac{\beta \hbar \omega}{1 - e^{-\beta \hbar \omega}}.
\] (5)

In the previous work [19, 20], this result was expressed as \( T_1^{\text{QCF}} \simeq \left[ \beta \hbar \omega_S / Q(\omega_S) \right] T_1^{\text{cl}} \) which is correct in the limit \( \beta \hbar \omega_S \gg 1 \), as was appropriate for those studies.

If the relaxation process is the linear resonance (1:1 Fermi resonance), then \( Q(\omega_S) = Q_H(\omega_S) \), i.e., \( T_1^{\text{QCF}} = T_1^{\text{cl}} \) [24]. Skinner and coworkers have provided a theoretical framework for organizing and expanding on a variety of QCFs appropriate for specific dynamical processes, dependent upon the underlying mechanism of VER. Though this strategy has been criticized [25, 26, 27], it is known that the QCF method works rather well for specific problems [28, 19, 20].

2.1.3 Reduced model approach

An alternative approach to address the shortcomings of the LTZ formula is to use the reduced model approach [18, 19, 20], which exploits a normal mode picture of the protein. By representing the Hamiltonian in terms of system, bath, and interaction terms

\[
H = H_S + H_B + V_3 + V_4 + \cdots,
\] (6)

\[
H_S = \frac{p^2_S}{2} + \frac{\omega^2_S}{2} q^2_S,
\] (7)

\[
H_B = \sum_k \left( \frac{p^2_k}{2} + \frac{\omega^2_k}{2} q^2_k \right),
\] (8)

the residual interaction term may be expanded perturbatively as

\[
V_3 = \frac{1}{3} \sum_{k,l,m} G_{k,l,m} q_k q_l q_m,
\] (9)

\[
V_4 = \frac{1}{4} \sum_{k,l,m,n} H_{k,l,m,n} q_k q_l q_m q_n.
\] (10)

Calculating the force from this Hamiltonian, and substituting it into Fermi’s golden rule Eq. (1), we can derive a lowest order VER rate as [19, 20]

\[
\frac{1}{T_1} \simeq \frac{\tanh(\beta \hbar \omega_S/2)}{\hbar \omega_S} \sum_{k,l} \left[ \gamma^{(+)}_{k,l} \left( \frac{\zeta^{(+)}_{k,l}}{\gamma^2 + (\omega_k + \omega_l - \omega_S)^2} \right) + \frac{\gamma^{(-)}_{k,l}}{\gamma^2 + (\omega_k + \omega_l + \omega_S)^2} \right]
\]

\[
+ \left[ \frac{\gamma^{(-)}_{k,l}}{\gamma^2 + (\omega_k - \omega_l + \omega_S)^2} + \frac{\gamma^{(-)}_{k,l}}{\gamma^2 + (\omega_k - \omega_l - \omega_S)^2} \right]
\] (11)

where

\[
\zeta^{(+)}_{k,l} = \frac{h^2 (G_{S,k,l})^2}{2 \omega_k \omega_l} (1 + n_k + n_l + 2n_k n_l),
\] (12)

\[
\zeta^{(-)}_{k,l} = \frac{h^2 (G_{S,k,l})^2}{2 \omega_k \omega_l} (n_k + n_l + 2n_k n_l),
\] (13)

\[
n_k = 1/(e^{\beta \hbar \omega_k} - 1).
\] (14)

and in previous papers [19, 20], \( m_S \) in the perturbative formulas should read \( m_S = 1 \) as mass-weighted coordinates were employed.
The original formula contains delta functions, and we have included a width parameter $\gamma$ to broaden the delta functions for numerical calculations. There exists another well known formula to describe the VER rate, the Maradudin-Fein formula \cite{29, 18},

\begin{align}
W &= W_{\text{decay}} + W_{\text{coll}}, \\
W_{\text{decay}} &= \frac{\hbar}{2\omega_S} \sum_{k,l} \frac{(G_{S,k,l})^2}{\omega_k \omega_l} \left(1 + n_k + n_l\right) \frac{\gamma}{\gamma^2 + (\omega_S - \omega_k - \omega_l)^2}, \\
W_{\text{coll}} &= \frac{\hbar}{\omega_S} \sum_{k,l} \frac{(G_{S,k,l})^2}{\omega_k \omega_l} \left(n_k - n_l\right) \frac{\gamma}{\gamma^2 + (\omega_S + \omega_k - \omega_l)^2}
\end{align}

with a width parameter $\gamma$. These two formulas are numerically similar for small $\gamma$, and equivalent for the limit of $\gamma \to 0$ \cite{30}. This is a quantum mechanically exact treatment given the approximate truncated form of the interaction Hamiltonian. We have found that the truncation error (the contribution from higher order terms) can be a serious problem, especially for proteins. For a more accurate treatment of VER, we must appeal to more advanced methods, described below.

### 2.1.4 Other (advanced) approaches

Methods that complement the above three methods involve calculating the force auto correlation function $\zeta(t)$ appearing in Fermi’s golden rule using different levels of approximations. Shi and Geva \cite{27} used a semiclassical approximation \cite{31} for $\zeta(t)$, and showed that even the slow relaxation of neat liquid oxygen (at 77K) can be well reproduced by their method. From their study, it was shown that the short time dynamics of $\zeta(t)$ is important to predict the correct VER rate. This implies that the short time approximation may be adequate for an accurate estimate of $\zeta(t)$. Various time-dependent self-consistent field methods \cite{32} or path integral methods \cite{33} should be applicable to calculate $\zeta(t)$. For other methods, the reader is referred to additional works \cite{34, 35, 36}.

To derive Fermi’s golden rule, we have used the Bader-Berne correction \cite{24}, which holds only for harmonic systems. Bader, Berne, Pollak, and Hänggi extended this to an anharmonic system within a classical framework \cite{37}, and found that the VER of such a system can be nonexponential in time and is significantly affected by the character of the bath. This consideration will be important when one studies the VER of CO in Mb, especially for the VER of a highly excited CO bond.

### 2.2 Nonequilibrium simulation

The above equilibrium simulation methods based on Fermi’s golden rule invoke several assumptions as described above. These assumptions might be invalid in some cases. As VER is a nonequilibrium phenomenon, the appeal of nonequilibrium approaches is quite natural.

#### 2.2.1 Classical approaches

Classical nonequilibrium simulations to investigate VER in proteins were first conducted by Henry, Eaton and Hochstrasser \cite{38}. In conjunction with their experimental studies, they employed classical molecular dynamics simulations of heme cooling in Mb and cyt c in vacuum and found that heme cooling occurred on two time scales: short (1-4 ps) and long (20 ps for Mb and 40 ps for cyt c). Nagaoka and coworkers carried out the similar simulations for Mb in vacuum and obtained similar time scales \cite{39}. Importantly, they found that the normal mode frequencies localized in the propionate side chains of the heme are resonant with the water vibrational frequencies.
and Straub showed that the VER for Mb in water can be described by a single exponential with a few ps VER time [40]. Furthermore, they suggested that the main doorway of VER is due to the coupling between the propionate side chains and water, which is in accord with Nagaoka’s and Hochstrasser’s observations. Bu and Straub supported this view through simulations of mutant Mb’s and Mb variants having structurally modified heme groups [41]. They also investigated VER of cyt c in water, and found that the VER presents a biphasic exponential decay with two VER times: fast (a few ps) and slow (tens of ps) [42].

Kidera’s group studied VER in proteins from a different perspective [43]. They excited a single normal mode in Mb, and examined the vibrational energy transfer (VET) between normal modes. As is well known, VET is caused by (nonlinear) Fermi resonance: if the frequency matching is good, and the coupling between normal modes is strong enough, there will be VET. This picture is very useful to characterize VET at low temperatures. However, at high temperature there occurs non-resonant VET. They numerically found that the amount of VET is proportional to a reduced model energy including up to third order coupling elements (see also Sec. 2.1.3).

2.2.2 Quantum approaches

For all but the simplest systems, quantum approaches for nonequilibrium simulations are approximate and time-consuming. Nevertheless, these methods can overcome problems inherent to classical simulations. There are two categories: vibrationally quantum methods, and electronically quantum ones.

Hahn and Stock used a reduced model (consisting of the retinal rotation and other environmental degrees of freedom) to describe the pump-probe spectroscopy for the retinal chromophore in rhodopsin [44]. Flores and Batista, employing the same model, suggested the possibility to control the retinal rotation by two (chirped) laser pulses [45]. To solve the quantum dynamics for the large system, they employed time-dependent self-consistent field (TD-SCF) methods [32]. Notably, vibrational SCF methods have been used to calculate vibrational energy levels for a small protein (BPTI) [46].

The combination of classical simulations for vibrational motions and quantum calculations for electronic structure, in some portion of the molecule, has been widely used for the calculations of up to moderate-sized molecules. One cutting edge application to a large system is the calculation of bacteriorhodopsin’s photoisomerization in the excited chromophore state by Hayashi, Tajkhorshid, and Schulten [47]. In their treatment, a portion of the retinal chromophore including three double bonds was treated as the quantum mechanical region, and the complement, including the protein and water, as the molecular mechanical region. During the simulations, there occurs nonadiabatic transitions between two electronic states (S_0 and S_1) which was treated semiclassically. They numerically showed that only one bond (C_{13}=C_{14}) rotates unidirectionally due to the coupling with the protein, and found that several other bonds can twist in any direction if there is no protein.

3 Cytochrome c

In this section, we shall focus on one protein, cytochrome c (cyt c), and review the recent theoretical studies about this protein. There are several reasons to select this protein as a prototypical one: (a) Cyt c is a relatively small protein with 1745 atoms. Other proteins of similar scale are Mb, BPTI, and human lysozyme. (b) The detailed X-ray structure is known for cyt c. (c) Cyt c has a function of electron transfer. The basic theoretical and computational works on cyt c were summarized by Wolynes and coworkers [48]. Wang, Wong, and Rabitz studied VER in cyt c using their hydrodynamical method [49]. Garcia and Hummer
describe the results of our studies on the VER of cyt c using two different methods (the QCF method in Sec. 2.1.2 and the reduced model approach in Sec. 2.1.3) and compare them with the experimental results of Romesberg’s group [12, 13, 17].

3.1 Quantum correction factor approach for cyt c

Bu and Straub [52] employed the QCF approach (Sec. 2.1.2) to estimate the VER rate of a CD bond in the terminal methyl group of Met80 in cyt c (see Fig. 1). Their calculations were carried out using the program CHARMM [53], and cyt c was surrounded by water molecules at 300K. In Fig. 2 we show the force autocorrelation function and its power spectrum. With the CD bond frequency \( \omega_S = 2133 \text{ cm}^{-1} \), we find \( 1/T_1^1 = \tilde{\zeta}_c(\omega_S) \simeq 0.4 \sim 1.0 \text{ ps}^{-1} \), so that the classical VER time is \( 1.0 \sim 2.5 \text{ ps} \).

Figure 2: Left: Averaged force autocorrelation function for four trajectories at 300K. Right: Fourier spectrum for the four correlation functions with error bars.

Since the CD bond frequency is located in a transparent region of the vibrational density of states, with no other state overlapping with this frequency [52], it is concluded that there is no linear resonance (1:1 resonance). To use the QCF method, we thus need to assume nonlinear resonances corresponding to multiphonon VER processes. If the VER process assumes that
The VER time becomes

$$Q_{HH}(\omega_S) = Q_H(\omega_A)Q_H(\omega_S - \omega_A).$$

Alternatively, if the VER process is one that leads to the excitation of one bath vibrational mode of frequency $\omega_A$, with the remaining energy $\hbar(\omega_S - \omega_A)$ being transferred to lower frequency bath rotational and translational modes, the appropriate QCF (harmonic-harmonic-Schofield QCF) is

$$Q_{H-HS}(\omega_S) = Q_H(\omega_A)\sqrt{Q_H(\omega_S - \omega_A)e^{\beta \hbar(\omega_S - \omega_A)/4}}.$$  \hfill (19)

We need to determine the value of $\omega_A$ to use these formulas. From the normal mode and anharmonic coefficient calculations carried out in Sec. 3.2, we have found that the CD mode is strongly resonant with two lower frequency modes, $\omega_{1655} = 685.48 \text{ cm}^{-1}$ and $\omega_{3823} = 1443.54 \text{ cm}^{-1}$, where $|\omega_S - \omega_{1655} - \omega_{3823}| = 0.03 \text{ cm}^{-1}$ for the standard parameters of CHARMM. We might be able to choose $\omega_A = 1443.54 \pm 685.48 \text{ cm}^{-1}$ or 685.48 cm$^{-1}$ at 300K, $T_1^QCF / T_1^{QCF} = Q_{HH}(\omega_S)/Q_H(\omega_S) = 2.3$ for the harmonic-harmonic QCF and $T_1^QCF / T_1^{QCF} = Q_{H-HS}(\omega_S)/Q_H(\omega_S) = 2.8$ for the harmonic-harmonic-Schofield QCF. Thus we find $T_1^{QCF} = T_1^QCF / (2.3 \sim 2.8) \approx 0.3 \sim 1.0 \text{ ps}$.

### 3.2 Reduced model approach for cyt c

Fujisaki, Bu, and Straub took the reduced model approach (Sec. 2.1.3) to investigate the VER for the same CD bond stretching in cyt c. However, in their calculation, all modes represent normal modes, so the CD “bond” turned out to be the CD “mode.” Using the formulas in Sec. 2.1.3, they calculated the VER rate for the CD mode ($\omega_{CD} = 2129.1 \text{ cm}^{-1}$) and other low frequency modes ($\omega_{3330} = 1330.9 \text{ cm}^{-1}$, $\omega_{1996} = 829.9 \text{ cm}^{-1}$, $\omega_{1655} = 685.5 \text{ cm}^{-1}$) as a function of the width parameter $\gamma$ (Fig. 3). To this end, they needed to calculate anharmonic coupling coefficients according to the formula

$$G_{S,k,l} = \frac{1}{2} \frac{\partial^2 V}{\partial q_S \partial q_k \partial q_l} \approx \frac{1}{2} \sum_{ij} U_{ik} U_{jl} \frac{K_{ij}(\Delta q_S) - K_{ij}(-\Delta q_S)}{2\Delta q_S}$$  \hfill (20)

where $U_{ik}$ is an orthogonal matrix that diagonalizes the (mass-weighted) hessian matrix at the mechanically stable structure $K_{ij}$, and $K_{ij}(\pm \Delta q_S)$ is a hessian matrix calculated at a shifted structure along the direction of a selected mode with a shift $\pm \Delta q_S$.

If we take $\gamma \approx \Delta \omega \sim 3 \text{ cm}^{-1}$, we have $T_1 \approx 0.1 \text{ ps}$, which agrees with the sub-picosecond time scale for relaxation predicted using the QCF method ($T_1^{QCF} = 0.3 \sim 1.0 \text{ ps}$). We also see that the low frequency modes have longer VER time, a few ps, which agrees with the similar calculations by Leitner’s group. In the right of Fig. 3 we show the temperature dependence of the VER rate. At low temperatures, the VER rate becomes flat as a function of temperature. At these lower temperatures, the VER is caused by the remaining quantum fluctuation associated with zero point energy.

### 3.3 Related experiment

Here we discuss the related experiment by Romeberg’s group. They measured the shifts and widths of the spectra for different forms of cyt c; the widths of the spectra (FWHM) were found to be $\Delta \omega_{FWHM} \approx 6.0 \sim 13.0 \text{ cm}^{-1}$. If we can neglect inhomogeneous effects, the estimate of the VER time becomes

$$T_1 \sim 5.3 / \Delta \omega_{FWHM} \text{ (ps)}$$  \hfill (21)
which corresponds to $T_1 \simeq 0.4 \sim 0.9$ ps. This estimate is similar to the QCF prediction using Eq. (11) ($\simeq 0.1 \sim 1.0$ ps) and larger than the estimate by the reduced model approach using Eq. (11) or (15) ($\simeq 0.1$ ps). This might be due to the strong resonance between the three modes (4357, 3823, 1655), which forms a peak near $\gamma \simeq 0.03$ cm$^{-1}$ in the left of Fig. 3. This resonance causes an increase in the VER rate, so we can say that this estimate of the VER rate is too large. On the other hand, there is no peak for the low frequency modes for $\gamma < 10$ cm$^{-1}$; the estimate of the VER rate does not seem to be affected by the resonances.

Note also that Romesberg’s group studied Met80-3D, methionine with three deuteriums on the terminal methyl group, while we have examined Met80-1D, with one deuterium. It is known that the CHARMM force field calculation does not give an accurate value of the absorption peak. On the other hand, the DFT calculation for the methionine leads to much better results (Matt Cremeens, private communication). Clearly, we must improve our force field parameters according to DFT calculations, and examine how further optimization of the parameters affects the resonance structures and the VER rate of the protein.

## 4 Concluding Remarks

In this paper, we have described theoretical (Sec. 2) approaches to the study of VER in proteins. We have examined VER of a CD stretching bond (mode) in cytochrome c from the QCF approach (Sec. 2.1.2) and the reduced model approach (Sec. 2.1.3). For the CD mode in cyt c (in vacuum) at room temperature, both approaches yield similar results for the VER rate, which is also very similar to an estimate derived from an experiment by Romesberg’s group. Our work demonstrates both the feasibility and accuracy of a number of theoretical approaches to estimate VER rates of selected modes in proteins.

There are advantages and disadvantages of the (a) QCF approach and (b) reduced model approach to the prediction of VER rates in proteins. The QCF method is simple and applicable even for a large molecule like a protein. However, the VER mechanism may not be known a priori, and it must be supplemented by other methods such as anharmonic coefficient calculations. Furthermore, the method relies on the local mode picture, which is easily applicable for high frequency (localized) modes, but not for low frequency (delocalized) modes. The reduced model approach is quantum mechanically exact, and easily applicable for VER of low frequency modes. However, the anharmonic coefficient calculation is cumbersome even for the third order coupling terms in cyt c. Moreover, such a Taylor series expansion has not been
shown to converge at low order for general systems [26]. Our preliminary calculations show that the classical VER dynamics using an isolated methionine does not seem to be affected by including the fourth-order coupling elements (see the left of Fig. 4), but we need to examine this issue further with quantum mechanical approaches such as TD-SCF methods. There is also an unsolved problem of the width parameter. Actually, this problem is not peculiar to the reduced model approach. The introduction of the width corresponds to coarse-graining, which also appears in the QCF approach when one averages the power spectrum of the force auto-correlation function. The most “ab initio” approach to solve this problem is a rigorous quantum mechanical treatment of the tier structure of energy levels in the protein [54]. The other appealing way is to regard $\gamma$ as a hopping rate between conformational substates [55, 56], or a frequency correlation time, that may be derived from estimates of the frequency fluctuation [57, 58].

Since both the QCF and reduced model approaches are based on Fermi’s golden rule, there is a limitation for the strength of the interaction between the system and bath. There is a need to develop other methods without this deficiency. Promising approaches include nonequilibrium molecular dynamics methods [59], time-dependent self-consistent field methods [32], mixed quantum-classical methods [60], and semiclassical methods [27]. Another important issue is to calculate not only VER rates, but the physical observables related to the experiment data such as absorption spectrum or 2D-IR signals [61, 62]. In this case, we also need to deal with the effects of dephasing (decoherence) as well as VER.

The accuracy of the force field parameters is the most annoying problem. Our preliminary calculations show that the VER rate in cyt c can vary by two order of magnitude when we change the bond force constant by ten percent (see the right of Fig. 4). This situation is rather similar to that of the reaction rate calculation, where one must determine the activation energy accurately. Any inaccuracy in the activation energy causes an exponentially large deviation in the rate constant. This problem will be solved through ab initio quantum dynamics (Sec. 2.2.2) or the reparametrization of the force field using experimental data or accurate ab initio calculations. Given sufficient accuracy in the force field, we will be in a position to discuss the relation between the VER and function of a protein such as electron transfer in cyt c. As is well known, the dynamics of proteins related to function are well described by large amplitude (and low frequency) principal components [63, 64]. The connection between principal components and VER should be investigated. The ergodic measure [65] will be a good device to examine this issue. As suggested by experiments [4, 6], collective motions in proteins can be important for the fast VER in proteins. The collective motions near the protein surface including solvation dynamics of water [66, 67, 68, 69, 70] might be relevant for the VER and function. Cytochrome c and Mb remain excellent target proteins to investigate these fundamental issues of protein dynamics and its relation to function.

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Figure 4: Left: Classical nonequilibrium dynamics calculation for an isolated methionine using the reduced model (see Sec. 2.1.3). Initially the CD mode is excited to $\simeq 6$ kcal/mol. The other modes are excited according to the Boltzmann distribution at 300K. The quenched normal mode (QNM) energy for the CD mode (ten trajectory average) is shown for two cases: (a) only 3rd order coupling elements are included, and (b) both 3rd and 4th order coupling elements are included. Right: VER rate calculation for the Met80-3D case with different force field parameters. For the modified CHARMM parameters, the CD bond force constant was increased by ten percent in order to match with the absorption peak of the experiment by Romesberg’s group.

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