ADVANCING THEORY FOR KINETICS AND DYNAMICS OF COMPLEX, MANY-DIMENSIONAL SYSTEMS: CLUSTERS AND PROTEINS

ADVANCES IN CHEMICAL PHYSICS, VOLUME 145

Edited by

TAMIKI KOMATSUZAKI, R. STEPHEN BERRY, DAVID M. LEITNER

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INTRODUCTION

Few of us can any longer keep up with the flood of scientific literature, even in specialized subfields. Any attempt to do more and be broadly educated with respect to a large domain of science has the appearance of tilting at windmills. Yet the synthesis of ideas drawn from different subjects into new, powerful, general concepts is as valuable as ever, and the desire to remain educated persists in all scientists. This series, *Advances in Chemical Physics*, is devoted to helping the reader obtain general information about a wide variety of topics in chemical physics, a field that we interpret very broadly. Our intent is to have experts present comprehensive analyses of subjects of interest and to encourage the expression of individual points of view. We hope that this approach to the presentation of an overview of a subject will both stimulate new research and serve as a personalized learning text for beginners in a field.

STUART A. RICE

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PREFACE

The simple descriptions of molecular dynamics that we envision for small molecules, and apply to other areas of chemical physics, such as chemical kinetics, are often incomplete or even inappropriate when carried over to large, complex molecules, such as those encountered in biology or nanoscale materials. New tools are needed to sort through the dynamics on the energy landscape that underlie the functional motion of biological molecules and energy transport within them. The aim of this volume is to present some of the theoretical and computational methods that have been developed recently to address this challenge. The following chapters provide a summary of topics presented by the authors at several recent workshops in Japan and the United States.

The first two chapters address dynamics and energy flow in biological molecules. Chapter 1 focuses on fast motions and energy transfer in biomolecules, mainly proteins, on the pico- to nanosecond timescale. Besides providing a general introduction to the field, this chapter presents a review of a non-Markovian theory for calculating vibrational energy transfer rates and provides a number of examples. Chapter 2 addresses functional motions of proteins, which can span a wide range of timescales, from nanoseconds to seconds. This chapter provides a review of general concepts and recent computational tools that have been put forth to elucidate functional motions.

Chapter 3 addresses dynamics and energy flow within basins on the energy landscape. While developing kinetic models for transitions between such basins is relatively simple if the dynamics within a basin is ergodic, the situation is much more complex when the assumptions of ergodicity break down. This chapter summarizes our understanding of the nature of nonergodic dynamics and the corresponding mixed phase space from a classical perspective, and reviews a quantum mechanical theory for corresponding systems with a mixed vibrational state space. The latter is also used to correct Rice–Ramsperger–Kassel–Marcus (RRKM) theory predictions of the unimolecular reaction rate when dynamics of the reactant is nonergodic. Continuing along these lines, Chapter 4 presents a review of recent work on non-RRKM kinetics from a classical phase space geometrical perspective. Finally, ergodicity in biological systems is further explored in Chapter 5, where local measures of ergodic and chaotic behavior are related to the topography of the energy landscape.

The chapters of this volume summarize important areas in our current understanding of dynamics and configurational changes of biological molecules and other many-dimensional systems. We hope that the material presented here will contribute further to the rapid development in the theory of these complex processes.

TAMIKI KOMATSUZAKI
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Guest Editors

NON-MARKOVIAN THEORY OF VIBRATIONAL ENERGY RELAXATION AND ITS APPLICATIONS TO BIOMOLECULAR SYSTEMS

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CONTENTS

Advancing Theory for Kinetics and Dynamics of Complex, Many-Dimensional Systems: Clusters and Proteins, Advances in Chemical Physics, Volume 145, Edited by Tamiki Komatsuzaki, R. Stephen Berry, and David M. Leitner.

I. INTRODUCTION

Energy transfer (relaxation) phenomena are ubiquitous in nature. At a macroscopic level, the phenomenological theory of heat (Fourier law) successfully describes heat transfer and energy flow. However, its microscopic origin is still under debate. This is because the phenomena can contain many-body, multiscale, nonequilibrium, and even quantum mechanical aspects, which present significant challenges to theories addressing energy transfer phenomena in physics, chemistry, and biology [1]. For example, heat generation and transfer in nanodevices is a critical problem in the design of nanotechnology. In molecular physics, it is well known that vibrational energy relaxation (VER) is an essential aspect of any quantitative description of chemical reactions [2]. In the celebrated RRKM theory of an absolute reaction rate for isolated molecules, it is assumed that the intramolecular vibrational energy relaxation (IVR) is much faster than the reaction itself. Under certain statistical assumptions, the reaction rate can be derived [3]. For chemical reactions in solutions, the transition state theory and its extension such as Kramer's theory and the Grote–Hynes theory have been developed [4, 5] and applied to a variety of chemical systems including biomolecular systems [6]. However, one cannot always assume separation of timescales. It has been shown that a conformational transition (or reaction) rate can be modulated by the IVR rate [7]. As this brief survey demonstrates, a detailed understanding of IVR or VER is essential to study the chemical reaction and conformation change of molecules.

A relatively well-understood class of VER is a single vibrational mode embedded in (vibrational) bath modes. If the coupling between the system and the bath modes is weak (or assumed to be weak), a Fermi's-golden-rule style formula derived using second-order perturbation theory [8–10] may be used to estimate the VER rate. However, the application of such theories to real molecular systems poses several (technical) challenges, including how to choose force fields, how to separate quantum and classical degrees of freedom, or how to treat the separation of timescales between system and bath modes. Multiple solutions have been proposed to meet those challenges leading to a variety of theoretical approaches to the treatment of VER [11–16]. These works using Fermi's golden rule are based on quantum mechanics and are suitable for the description of high-frequency modes (more than thermal energy $\simeq$200 cm^{-1}), on which nonlinear spectroscopy has recently focused [17–20].

In this chapter, we summarize our recent work on VER of high-frequency modes in biomolecular systems. In our previous work, we have concentrated on the VER rate and mechanisms for proteins [21]. Here we shall focus on the time course of the VER dynamics. We extend our previous Markovian theory of VER to a non-Markovian theory applicable to a broader range of chemical systems [22, 23]. Recent time-resolved spectroscopy can detect the time course of VER dynamics (with femtosecond resolution), which may not be accurately described by a single

timescale. We derive new formulas for VER dynamics and apply them to several interesting cases, where comparison to experimental data is available.

This chapter is organized as follows: In Section II, we briefly summarize the normal mode concepts in protein dynamics simulations, on which we build our non-Markovian VER theory. In Section III, we derive VER formulas under several assumptions and discuss the limitations of our formulas. In Section IV, we apply the VER formulas to several situations: the amide I modes in isolated and solvated *N*-methylacetamide and cytochrome *c*, and two in-plane modes (ν_4 and ν_7 modes) in a porphyrin ligated to imidazole. We employ a number of approximations in describing the potential energy surface (PES) on which the dynamics takes place, including the empirical CHARMM [24] force-field and density functional calculations [25] for the small parts of the system (*N*-methylacetamide and porphyrin). We compare our theoretical results with experiment when available, and find good agreement. We can deduce the VER mechanism based on our theory for each case. In Section V, we summarize and discuss the further aspects of VER in biomolecules and in nanotechnology (molecular devices).

II. NORMAL MODE CONCEPTS APPLIED TO PROTEIN DYNAMICS

Normal mode provides a powerful tool in exploring molecular vibrational dynamics [26] and may be applied to biomolecules as well [27]. The first normal mode calculations for a protein were performed for BPTI protein [28]. Most biomolecular simulation softwares support the calculation of normal modes [24, 29, 30]. However, the calculation of a mass-weighted Hessian K_{ij}, which requires the second derivatives of the potential energy surface, with elements defined as

$$K_{ij} = \frac{1}{\sqrt{m_i m_j}} \frac{\partial^2 V}{\partial x_i \partial x_j} \tag{1}$$

can be computationally demanding. Here m_i is the mass, x_i is the coordinate, and V is the potential energy of the system. Efficient methods have been devised including torsional angle normal mode [31], block normal mode [32], and the iterative mixed-basis diagonalization (DIMB) methods [33], among others. An alternative direction for efficient calculation of a Hessian is to use coarse-grained models such as elastic [34] or Gaussian network [35] models. From normal mode analysis (or instantaneous normal mode analysis [36]), the frequencies, the density of states, and the normal mode vectors can be calculated. In particular, the last quantity is important because it is known that the lowest eigenvectors may describe the functionally important motions such as large-scale conformational change, a subject that is the focus of another chapter of this volume [37].

There is no doubt as to the usefulness of normal mode concepts. However, for molecular systems, it is always an approximate model as higher order nonlinear

coupling and intrinsic anharmonicity become essential. To describe energy transfer (or relaxation) phenomena in a protein, Moritsugu, Miyashita, and Kidera (MMK) introduced a reduced model using normal modes with third- and fourth-order anharmonicity [38], $C^{(3)}_{klm}$ and $C^{(4)}_{klmn}$, respectively,

$$V(\{q_k\}) = \sum_k \frac{\omega_k^2}{2} q_k^2 + \frac{1}{3!} \sum_{klm} C^{(3)}_{klm} q_k q_l q_m + \frac{1}{4!} \sum_{klmn} C^{(4)}_{klmn} q_k q_l q_m q_n \qquad (2)$$

with

$$C^{(3)}_{klm} \equiv \frac{\partial^3 V}{\partial q_k \partial q_l \partial q_m} \qquad (3)$$

$$C^{(4)}_{klmn} \equiv \frac{\partial^4 V}{\partial q_k \partial q_l \partial q_m \partial q_n} \qquad (4)$$

where q_k denotes the normal mode calculated by the Hessian K_{ij} and ω_k is the normal mode frequency. Classical (and harmonic) Fermi resonance [39] is a key ingredient in the MMK theory of energy transfer derived from observations of all-atom simulations of myoglobin at zero temperature (see Fig. 1).

At finite temperature, nonresonant effects become important and clear interpretation of the numerical results becomes difficult within the classical approximation. Nagaoka and coworkers [40] identified essential vibrational modes in vacuum simulations of myoglobin and connected these modes to the mechanism of "heme cooling" explored experimentally by Mizutani and Kitagawa [18]. Contemporaneously, nonequilibrium MD simulations of solvated myoglobin carried out by Sagnella and Straub provided the first detailed and accurate simulation of heme cooling dynamics [41]. That work supported the conjecture that the motion

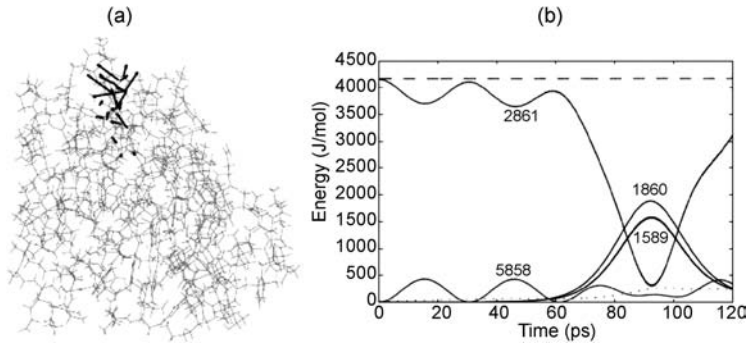

Figure 1. (**a**) The excited eigenvector depicted by arrows in myoglobin. (**b**) Classical simulation of mode-specific energy transfer in myoglobin at zero temperature. (Reproduced with permission from Ref. 38. Copyright 2009 by the American Physical Society.)

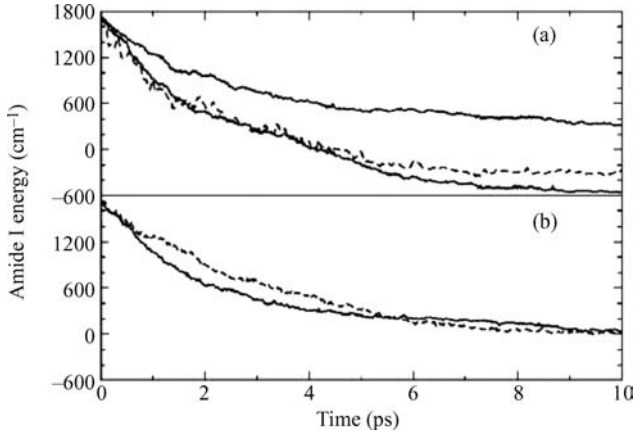

Figure 2. Nonequilibrium MD simulation of energy flow from the excited amide I mode in *N*-methylacetamide in heavy water. See also Fig. 3. (Reproduced with permission from Ref. 42. Copyright 2009 by the American Institute of Physics.)

similar to those modes identified by Nagaoka plays an important role in energy flow pathways.

Nguyen and Stock explored the vibrational dynamics of the small molecule, *N*-methylacetamide (NMA) often used as a model of the peptide backbone [42]. Using nonequilibrium MD simulations of NMA in heavy water, VER was observed to occur on a picosecond timescale for the amide I vibrational mode (see Fig. 2). They used the instantaneous normal mode concept [36] to interpret their result and noted the essential role of anharmonic coupling. Leitner also used the normal mode concept to describe energy diffusion in a protein and found an interesting link between the anomalous heat diffusion and the geometrical properties of a protein [43].

In terms of vibrational spectroscopy, Gerber and coworkers calculated the anharmonic frequencies in BPTI, within the VSCF level of theory [44], using the reduced model [Eq. (2)]. Yagi, et al. refined this type of anharmonic frequency calculation for large molecular systems with more efficient methods [45], appropriate for applications to biomolecules such as DNA base pair [46]. Based on the reduced model [Eq. (2)] with higher order nonlinear coupling, Leitner also studied quantum mechanical aspects of VER in proteins, by employing the Maradudin–Fein theory based on Fermi's golden rule [12]. Using the same model, Fujisaki, Zhang, and Straub focused on more detailed aspects of VER in biomolecular systems and calculated the VER rate, mechanisms, or pathways, using their non-Markovian perturbative formulas (described in Section III).

As this brief survey demonstrates, the normal mode concept is a powerful tool that provides significant insight into mode-specific vibrational dynamics and energy transfer in proteins, when anharmonicity of the potential energy surface is taken into account.

III. DERIVATION OF NON-MARKOVIAN VER FORMULAS

We have derived a VER formula for the simplest situation, a one-dimensional relaxing oscillator coupled to a "static" bath [22]. Here we extend this treatment to two more general directions: (a) multidimensional relaxing modes coupled to a "static" bath and (b) a one-dimensional relaxing mode coupled to a "fluctuating" bath [47].

A. Multidimensional Relaxing Mode Coupled to a Static Bath

We take the following time-independent Hamiltonian:

$$\mathcal{H} = \mathcal{H}_S^0 + \mathcal{H}_B + \mathcal{V}^0 \tag{5}$$

$$= \mathcal{H}_S^0 + \langle \mathcal{V} \rangle_B + \mathcal{H}_B + \mathcal{V}^0 - \langle \mathcal{V} \rangle_B \tag{6}$$

$$= \mathcal{H}_S + \mathcal{H}_B + \mathcal{V} \tag{7}$$

where

$$\mathcal{H}_S \equiv \mathcal{H}_S^0 + \langle \mathcal{V} \rangle_B \tag{8}$$

$$\mathcal{V} \equiv \mathcal{V}^0 - \langle \mathcal{V} \rangle_B \tag{9}$$

In previous work [22], we have considered only a single one-dimensional oscillator as the system. Here we extend that treatment to the case of an N_S-dimensional oscillator system. That is,

$$\mathcal{H}_S = \sum_{i=1}^{N_S} \left(\frac{p_i^2}{2} + \frac{\omega_i^2}{2} q_i^2 \right) + V(\{q_i\}) \tag{10}$$

$$\mathcal{H}_B = \sum_{\alpha=1}^{N_B} \left(\frac{p_\alpha^2}{2} + \frac{\omega_\alpha^2}{2} q_\alpha^2 \right) \tag{11}$$

$$\mathcal{V} = -\sum_{i=1}^{N_S} q_i \delta \mathcal{F}_i(\{q_\alpha\}) \tag{12}$$

where $V(\{q_i\})$ is the interaction potential function between N_S system modes that can be described by, for example, the reduced model, Eq. (2). The simplest case

$V(\{q_i\}) = 0$ is trivial as each system mode may be treated separately within the perturbation approximation for $\mathcal{V}$.

We assume that $|k\rangle$ is a certain state in the Hilbert space spanned by $\mathcal{H}_S$. Then the reduced density matrix is

$$(\rho_S)_{mn}(t) = \langle m|e^{-i\mathcal{H}_S t/\hbar}\mathrm{Tr}_B\{\tilde{\rho}(t)\}e^{i\mathcal{H}_S t/\hbar}|n\rangle \tag{13}$$

where the tilde denotes the interaction picture. Substituting the time-dependent perturbation expansion

$$\begin{aligned}\tilde{\rho}(t) = \rho(0) &+ \frac{1}{i\hbar}\int_0^t dt'[\tilde{\mathcal{V}}(t'), \rho(0)] \\ &+ \frac{1}{(i\hbar)^2}\int_0^t dt' \int_0^{t'} dt''[\tilde{\mathcal{V}}(t'), [\tilde{\mathcal{V}}(t''), \rho(0)]] + \cdots\end{aligned} \tag{14}$$

into the above, we find

$$(\rho_S)_{mn}(t) \simeq (\rho_S)^{(0)}_{mn}(t) + (\rho_S)^{(1)}_{mn}(t) + (\rho_S)^{(2)}_{mn}(t) + \cdots \tag{15}$$

where

$$\begin{aligned}(\rho_S)^{(0)}_{mn}(t) &= \langle m|e^{-i\mathcal{H}_S t/\hbar}\rho_S(0)e^{i\mathcal{H}_S t/\hbar}|n\rangle, \\ &= \langle m(-t)|\rho_S(0)|n(-t)\rangle = \langle m|\rho_S(t)|n\rangle\end{aligned} \tag{16}$$

$$\begin{aligned}(\rho_S)^{(2)}_{mn}(t) &= \frac{1}{(i\hbar)^2}\int_0^t dt' \int_0^{t'} dt''\langle m|e^{-i\mathcal{H}_S t/\hbar}\mathrm{Tr}_B\{[\tilde{\mathcal{V}}(t'), [\tilde{\mathcal{V}}(t''), \rho(0)]]\}e^{i\mathcal{H}_S t/\hbar}|n\rangle \\ &= \frac{1}{(i\hbar)^2}\int_0^t dt' \int_0^{t'} dt'' \sum_{i,j}\langle m(-t)|[q_i(t')q_j(t'')\rho_S(0) \\ &\quad - q_j(t'')\rho_S(0)q_i(t')]|n(-t)\rangle\langle\delta\mathcal{F}_i(t')\delta\mathcal{F}_j(t'')\rangle_B \\ &\quad + \frac{1}{(i\hbar)^2}\int_0^t dt' \int_0^{t'} dt'' \sum_{i,j}\langle m(-t)|[\rho_S(0)q_j(t'')q_i(t') \\ &\quad - q_i(t')\rho_S(0)q_j(t'')]|n(-t)\rangle\langle\delta\mathcal{F}_j(t'')\delta\mathcal{F}_i(t')\rangle_B\end{aligned} \tag{17}$$

Here we have defined $|m(t)\rangle = e^{-i\mathcal{H}_S t/\hbar}|m\rangle$ and taken $(\rho_S)^{(1)}_{mn}(t) = 0$. Recognizing that we must evaluate expressions of the form

$$\begin{aligned}R_{mn;ij}(t; t', t'') &= \langle m(-t)|[q_i(t')q_j(t'')\rho_S(0)|n(-t)\rangle, \\ &\quad -\langle m(-t)|q_j(t'')\rho_S(0)q_i(t')]|n(-t)\rangle\end{aligned} \tag{18}$$

$$C_{ij}(t', t'') = \langle\delta\mathcal{F}_i(t')\delta\mathcal{F}_j(t'')\rangle_B \tag{19}$$

and their complex conjugates, $R^*_{nm;ij}(t;t',t'')$, $C^*_{ij}(t',t'')$, the second-order contribution can be written as

$$(\rho_S)^{(2)}_{mn}(t) = \frac{1}{(i\hbar)^2}\int_0^t dt' \int_0^{t'} dt'' \sum_{i,j}[R_{mn;ij}(t;t',t'')C_{ij}(t',t'') + R^*_{nm;ij}(t;t',t'')C^*_{ij}(t',t'')] \tag{20}$$

We can separately treat the two terms. Assuming that we can solve $\mathcal{H}_S|a\rangle = E_a|a\rangle$, we find

$$\begin{aligned} R_{mn;ij}(t;t',t'') = &\sum_{abcd}\langle m|a\rangle(q_i)_{ab}(q_j)_{bc}(\rho_S)_{cd}\langle d|n\rangle \\ &\times e^{-i(E_a-E_d)t-i(E_b-E_a)t'-i(E_c-E_b)t''} \\ &-\sum_{abcd}\langle m|a\rangle(q_j)_{ab}(\rho_S)_{bc}(q_i)_{cd}\langle d|n\rangle \\ &\times e^{-i(E_a-E_d)t-i(E_d-E_c)t'-i(E_b-E_a)t''} \end{aligned} \tag{21}$$

For the bath-averaged term, we assume the following force due to third-order nonlinear coupling of system mode i to the normal modes, α and β, of the bath [21]:

$$\delta\mathcal{F}_i(\{q_\alpha\}) = \sum_{\alpha,\beta} C_{i\alpha\beta}(q_\alpha q_\beta - \langle q_\alpha q_\beta\rangle) \tag{22}$$

and we have [21]

$$C_{ij}(t',t'') = R^{--}_{ij}(t',t'') + R^{++}_{ij}(t',t'') + R^{+-}_{ij}(t',t'') \tag{23}$$

with

$$R^{--}_{ij}(t',t'') = \frac{\hbar^2}{2}\sum_{\alpha,\beta} D_{\alpha\beta;ij}(1+n_\alpha)(1+n_\beta)e^{-i(\omega_\alpha+\omega_\beta)(t'-t'')} \tag{24}$$

$$R^{++}_{ij}(t',t'') = \frac{\hbar^2}{2}\sum_{\alpha,\beta} D_{\alpha\beta;ij}n_\alpha n_\beta e^{i(\omega_\alpha+\omega_\beta)(t'-t'')} \tag{25}$$

$$R^{+-}_{ij}(t',t'') = \hbar^2\sum_{\alpha,\beta} D_{\alpha\beta;ij}(1+n_\alpha)n_\beta e^{-i(\omega_\alpha-\omega_\beta)(t'-t'')} \tag{26}$$

where

$$D_{\alpha\beta;ij} = \frac{C_{i\alpha\beta}C_{j\alpha\beta}}{\omega_\alpha\omega_\beta} \tag{27}$$

and n_α is the thermal population of the bath mode α.

This formula reduces to our previous result for a one-dimensional system oscillator [22] when $N_S = 1$ and all indices (i, j) are suppressed. Importantly, this formula can be applied to situations where it is difficult to define a "good" normal mode to serve as a one-dimensional relaxing mode, as in the case of the CH stretching modes of a methyl group [21]. However, expanding to an N_S-dimensional system adds the burden of solving the multidimensional Schrödinger equation $\mathcal{H}_S|a\rangle = E_a|a\rangle$. To address this challenge, we may employ vibrational self-consistent field (VSCF) theory and its extensions developed by Bowman and coworkers [48] implemented in MULTIMODE program of Carter and Bowman [49] or in the SINDO program of Yagi and coworkers [50]. As in the case of our previous theory of a one-dimensional system mode, we must calculate N_S-tiple third-order coupling constants $C_{i\alpha\beta}(i = 1, 2, ..., N_S)$ for all bath modes α and β.

B. One-Dimensional Relaxing Mode Coupled to a Fluctuating Bath

We start from the following time-dependent Hamiltonian:

$$\mathcal{H}(t) = \mathcal{H}_S^0(t) + \mathcal{H}_B(t) + \mathcal{V}^0(t) \tag{28}$$

$$= \mathcal{H}_S^0(t) + \langle \mathcal{V}(t) \rangle_B + \mathcal{H}_B(t) + \mathcal{V}^0(t) - \langle \mathcal{V}(t) \rangle_B \tag{29}$$

$$= \mathcal{H}_S(t) + \mathcal{H}_B(t) + \mathcal{V}(t) \tag{30}$$

where

$$\mathcal{H}_S(t) \equiv \mathcal{H}_S^0(t) + \langle \mathcal{V}(t) \rangle_B \tag{31}$$

$$\mathcal{V}(t) \equiv \mathcal{V}^0(t) - \langle \mathcal{V}(t) \rangle_B \tag{32}$$

with the goal of solving the time-dependent Schrödinger equation

$$i\hbar \frac{\partial |\Psi(t)\rangle}{\partial t} = [\mathcal{H}_S(t) + \mathcal{H}_B(t) + \mathcal{V}(t)]|\Psi(t)\rangle = [\mathcal{H}_0(t) + \mathcal{V}(t)]|\Psi(t)\rangle \tag{33}$$

By introducing a unitary operator $U_0(t) = U_S(t)U_B(t)$

$$i\hbar \frac{d}{dt} U_0(t) = \mathcal{H}_0(t) U_0(t) \tag{34}$$

$$i\hbar \frac{d}{dt} U_S(t) = \mathcal{H}_S(t) U_S(t) \tag{35}$$

$$i\hbar \frac{d}{dt} U_B(t) = \mathcal{H}_B(t) U_B(t) \tag{36}$$

we can derive an "interaction picture" von Neumann equation

$$i\hbar \frac{d}{dt} \tilde{\rho}(t) = [\tilde{\mathcal{V}}(t), \tilde{\rho}(t)] \tag{37}$$

where

$$\tilde{\mathcal{V}}(t) = U_0^\dagger(t)\mathcal{V}(t)U_0(t) \tag{38}$$

$$\tilde{\rho}(t) = U_0^\dagger(t)\rho(t)U_0(t) \tag{39}$$

We assume the simple form of a harmonic system and bath, but allow fluctuations in the system and bath modes modeled by time-dependent frequencies

$$\mathcal{H}_S(t) = \hbar\omega_S(t)(a_S^\dagger a_S + 1/2) \tag{40}$$

$$\mathcal{H}_B(t) = \sum_\alpha \hbar\omega_\alpha(t)(a_\alpha^\dagger a_\alpha + 1/2) \tag{41}$$

The unitary operators generated by these Hamiltonians are

$$U_S(t) = e^{-i\int_0^t d\tau\omega_S(\tau)(a_S^\dagger a_S+1/2)} \tag{42}$$

$$U_B(t) = e^{-i\int_0^t d\tau\sum_\alpha \omega_\alpha(\tau)(a_\alpha^\dagger a_\alpha+1/2)} \tag{43}$$

and the time evolution of the annihilation operators is given by

$$U_S^\dagger(t)a_S U_S(t) = a_S e^{-i\int_0^t d\tau\omega_S(\tau)} \tag{44}$$

$$U_B^\dagger(t)a_\alpha U_B(t) = a_\alpha e^{-i\int_0^t d\tau\omega_\alpha(\tau)} \tag{45}$$

To simplify the evaluation of the force autocorrelation function, we assume that the temperature is low or the system mode frequency is high as a justification for the approximation. Substituting the above result into the force autocorrelation function calculated by the force operator, Eq. (22), we find

$$\langle\delta\mathcal{F}(t')\delta\mathcal{F}(t'')\rangle \simeq \frac{\hbar^2}{2}\sum_{\alpha,\beta}\frac{C_{S\alpha\beta}(t')C_{S\alpha\beta}(t'')}{\sqrt{\omega_\alpha(t')\omega_\beta(t')\omega_\alpha(t'')\omega_\beta(t'')}} \times e^{-i[\Theta_{\alpha\beta}(t')-\Theta_{\alpha\beta}(t'')]} \tag{46}$$

where

$$\Theta_S(t) = \int_0^t d\tau\omega_S(\tau) \tag{47}$$

$$\Theta_{\alpha\beta}(t) = \int_0^t d\tau[\omega_\alpha(\tau) + \omega_\beta(\tau)] \tag{48}$$

Substituting this approximation into the perturbation expansion Eqs. (15), (16), (17), we obtain our final result:

$$(\rho_S)_{00}(t) \simeq \frac{\hbar}{2}\sum_{\alpha,\beta}\int_0^t dt' \int_0^{t'} dt'' \frac{C_{S\alpha\beta}(t')C_{S\alpha\beta}(t'')}{\sqrt{\omega_S(t')\omega_\alpha(t')\omega_\beta(t')\omega_S(t'')\omega_\alpha(t'')\omega_\beta(t'')}} \times \cos\left\{\Theta_S(t') - \Theta_{\alpha\beta}(t') - \Theta_S(t'') + \Theta_{\alpha\beta}(t'')\right\} \tag{49}$$

which provides a dynamic correction to the previous formula [22]. The time-dependent parameters $\omega_S(t)$, $\omega_\alpha(t)$, and $C_{S\alpha\beta}(t)$ may be computed from a running trajectory using instantaneous normal mode analysis [36]. This result was first derived by Fujisaki and Stock [47], and applied to the VER dynamics of *N*-methylacetamide as described below. This correction eliminates the assumption that the bath frequencies are static on the VER timescale.

For the case of a static bath, the frequency and coupling parameters are time-independent and this formula reduces to the previous one-dimensional formula (when the off-resonant terms are neglected) [22]:

$$(\rho_S)_{00}(t) \simeq \frac{\hbar}{2\omega_S}\sum_{\alpha,\beta}\frac{C_{S\alpha\beta}^2}{\omega_\alpha\omega_\beta}\frac{1-\cos[(\omega_S-\omega_\alpha-\omega_\beta)t]}{(\omega_S-\omega_\alpha-\omega_\beta)^2} \tag{50}$$

Note that Bakker derived a similar fluctuating Landau–Teller formula in a different manner [51]. It was successfully applied to molecular systems by Sibert and coworkers [52]. However, the above formula differs from Bakker's as (a) we use the instantaneous normal mode analysis to parameterize our expression and (b) we do not take the Markov limit. Our formula can describe both the time course of the density matrix and the VER rate.

Another point is that we use the cumulant-type approximation to calculate the dynamics. When we calculate an excited state probability, we use

$$(\rho_S)_{11}(t) = 1 - (\rho_S)_{00}(t) \simeq \exp\{-(\rho_S)_{00}(t)\} \tag{51}$$

Of course, this is valid for the initial process ($(\rho_S)_{00}(t) \ll 1$), but, at longer timescales, we take $(\rho_S)_{11}(t) \simeq \exp\{-(\rho_S)_{00}(t)\}$ because the naive formula $(\rho_S)_{11}(t) = 1 - (\rho_S)_{00}(t)$ can be negative, which is unphysical [47].

C. Limitations of the VER Formulas and Comments

There are several limitations to the VER formulas derived above. The most obvious is that they are second-order perturbative formulas and rely on a short-time approximation. As far as we know, however, there exists no nonperturbative quantum mechanical treatment of VER applicable to *large* molecular systems. It is prohibitive to treat the full molecular dynamics quantum mechanically [53] for large molecules. Moreover, while there exist several mixed quantum classical methods [11]

that may be applied to the study of VER, there is no guarantee that such approximate methods work better than the perturbative treatment [54].

Another important limitation is the adaptation of a normal mode basis set, a natural choice for molecular vibrations. Because of the normal mode analysis, the computation can be burdensome. When we employ instantaneous normal mode analysis [36], there is a concern about the imaginary frequency modes. For the study of high-frequency modes, this may not be significant. However, for the study of low-frequency modes, the divergence of quantum (or classical) dynamics due to the presence of such imaginary frequency modes is a significant concern. For the study of low-frequency modes, it is more satisfactory to use other methods that do not rely on normal mode analysis such as semiclassical methods [55] or path integral methods [56].

We often use "empirical" force fields, with which quantum dynamics is calculated. However, it is well known that the force fields underestimate anharmonicity of molecular vibrations [57]. It is often desirable to use *ab initio* potential energy surfaces. However, such a rigorous approach is much more demanding. Lower levels of theory can fail to match the accuracy of some empirical potentials. As a compromise, approximate potentials of intermediate accuracy, such as QM/MM potentials [58], may be appropriate. We discuss this issue further in Sections IV.A and IV.C.

IV. APPLICATIONS OF THE VER FORMULAS TO VIBRATIONAL MODES IN BIOMOLECULES

We report our quantum dynamics studies of high-frequency modes in biomolecular systems using a variety of VER formulas described in Section III. The application of a variety of theoretical approaches to VER processes will allow for a relative comparison of theories and the absolute assessment of theoretical predictions compared with experimental observations. In doing so, we address a number of fundamental questions. What are the limitations of the static bath approximation for fast VER in biomolecular systems? Can the relaxation dynamics of a relaxing amide I vibration in a protein be accurately modeled as a one-dimensional system mode coupled to a harmonic bath? Can the "fluctuating bath" model accurately capture the system dynamics when the static picture of normal modes is not "good" on the timescale of the VER process? In Sections IV.A and IV.B, our main focus is the VER of excited amide I modes in peptides or proteins. In Section IV.C, we study some vibrational modes in porphyrin ligated to imidazole, which is a mimic of a heme molecule in heme proteins including myoglobin and hemoglobin.

A. *N*-Methylacetamide (NMA)

NMA is a well-studied small molecule (CH_3–CO–NH–CH_3) that serves as a convenient model of a peptide bond structure (–CO–NH–) in theory and experiment.

As in other amino acids, there is an amide I mode, localized on the CO bond stretch, which is a useful "reporter" of peptide structure and dynamics when probed by infrared spectroscopy. Many theoretical and experimental studies on amide I and other vibrational modes (amide II and amide III) have characterized how the mode frequencies depend on the local secondary structure of peptides or proteins [59, 60]. For the accurate description of frequencies and polarizability of these modes, see Refs. 15, 16 and 61–65. The main focus of these works is the frequency sensitivity of amide modes on the molecular configuration and environment. In this case, the amide mode frequencies are treated in a quantum mechanical way, but the configuration is treated classically. With a focus on interpreting mode frequency shifts due to configuration and environment, mode coupling between amide modes and other modes is often neglected. As we are mainly interested in VER or IVR dynamics of these modes, an accurate treatment of the mode coupling is essential.

Recent theoretical development of IVR dynamics in small molecules is summarized in Ref. 53. Leitner and Wolynes [7] utilized the concept of local random matrix to clarify the quantum aspects of such dynamics. The usefulness and applications of their approach are summarized both in Ref. 12 and in this volume [13]. However, these studies are focused on isolated molecules, whereas our main interest is in exploring quantum dynamics in a condensed phase. We take a step-by-step hierarchical approach. Starting from the isolated NMA molecule, we add several water molecules to form NMA–water clusters, and finally treat the condensed phase NMA–water system (see Fig. 3). With increasing complexity of our model, the accuracy of our theory, including the quality of the potential energy surface, and the accuracy of the quantum dynamics must diminish. As such, the principal focus of our account is a careful examination and validation of our procedures through comparison with accurate methods or experiments.

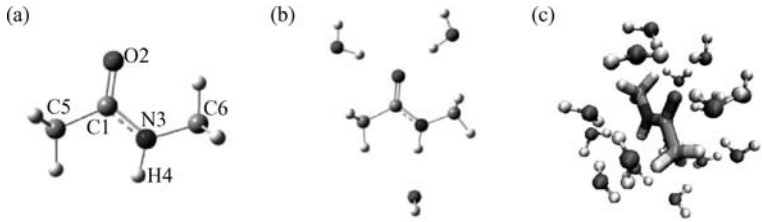

Figure 3. Representation of three models employed for the study of VER dynamics in *N*-methylacetamide. (**a**) NMA, (**b**) NMA with three solvating water, and (**c**) NMA with first solvation shell derived from simulations in bulk water. ((**a** and **b**) Reproduced with permission from Ref. 72. Copyright 2009 by the American Chemical Society. (**c**) Reproduced with permission from Ref. 47. Copyright 2009 by the American Institute of Physics.)