

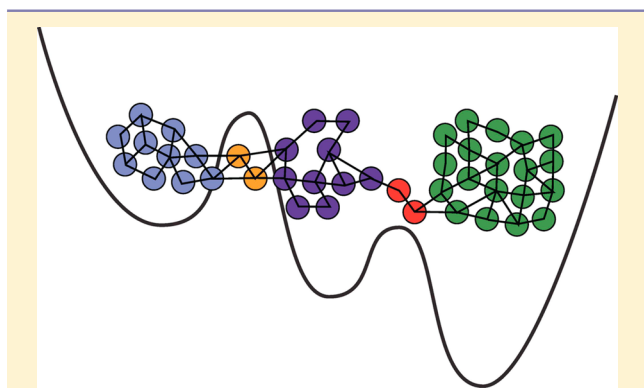
# Chemical Kinetics and Mechanisms of Complex Systems: A Perspective on Recent Theoretical Advances

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**ABSTRACT:** This Perspective presents a personal overview of the current status of the theory of chemical kinetics and mechanisms for complex processes. We attempt to assess the status of the field for reactions in the gas phase, at gas–solid interfaces, in liquid solutions, in enzymes, and for protein folding. Some unifying concepts such as potential energy surfaces, free energy, master equations, and reaction coordinates occur in more than one area. We hope this Perspective will be useful for highlighting recent advances and for identifying important areas for future research.

## 1. INTRODUCTION

Chemical kinetics is one of the oldest branches of physical chemistry, and its study is intrinsically tied to understanding mechanisms and assigning specific rate constants to individual mechanistic steps.<sup>1</sup> Some landmarks in the history of chemical kinetics are associated with making mechanisms more realistic: the steady-state approximation of Bodenstein and Lind,<sup>2</sup> the Lindemann mechanism involving activated molecules for unimolecular dissociation,<sup>3</sup> and the Michaelis–Menten multi-step mechanism for enzyme kinetics<sup>4</sup> are three examples.

Progress in theoretical kinetics involves not only sorting out the individual steps but also calculating the specific rate constants, and again we have landmarks such as transition state theory (TST) for pressure-independent thermal rate constants,<sup>5</sup> Rice–Ramsperger–Kassel–Marcus theory for microcanonical and pressure-dependent rate constants,<sup>6</sup> and the Marcus expression for electron transfer rates.<sup>7</sup> For simple reactions one can even calculate rate constants for individual reaction steps by accurate solution of the Schrödinger equation

using scattering theory.<sup>8,9</sup> The calculation of rate constants often involves two separate steps: (1) calculation of the potential energy surface (PES) for electronically adiabatic processes (sometimes called Born–Oppenheimer reactions) or calculation of multiple PESs and their couplings for electronically non-adiabatic reactions (sometimes called non-Born–Oppenheimer reactions, e.g., photochemical reactions induced by visible or UV radiation) and (2) calculation of the dynamics per se. Traditionally the interface between steps 1 and 2 has been analytic representations of the PESs<sup>10–20</sup> of step 1 for use in step 2, although more and more we are seeing the use of direct dynamics, in which, instead of using predefined potential surfaces, “all required energies and forces for each geometry that is important for evaluating dynamical properties are obtained directly from electronic structure calculations.”<sup>21</sup> When one studies the rates of physical processes, i.e., those in which no bonds are made or broken, and if one excludes electronically non-adiabatic processes, step 1 is relatively simple, and one can often use generally parametrized classical mechanical potential energy functions called molecular mechanics.<sup>22,23</sup> But for chemical reactions, i.e., processes in which bonds are formed, broken, or rearranged, PESs are almost always system-specific and must be obtained from quantum mechanical electronic structure calculations, either by the intermediacy of fitting a potential energy function to those calculations or by direct dynamics.

Thus the study of kinetics involves an inextricable mix of dynamics, mechanism, and electronic structure, and this Perspective will include all three. But the emphasis is on the kinetics of rate processes, not on dynamics as exemplified in state-to-state dynamics—covering the exciting progress in the latter on its own turf would at least double the length of this publication.

A key theme running through the progress in theoretical chemical kinetics is complexity. Mechanisms can have many steps, including nonequilibrated intermediates, and methods have been developed for including this.<sup>24</sup> However, in many cases in liquids and disordered solids, one cannot even develop a catalog of well-defined individual steps. Thus we must study complex processes that are too complicated to be broken into a countable number of individual kinds of steps. When one considers the overall mechanism, one has a related question: Is there a single pathway, or are there multiple parallel pathways

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giving rise to network effects?<sup>25,26</sup> Such questions were first addressed in determining the state-specific energy flow bottlenecks of gas-phase dissociation mechanisms of small molecules, but we will see that they also arise in various forms for reaction mechanisms of complex molecules.

A further theme running through not just theoretical chemical kinetics but almost all of modern theoretical chemistry is the reliance on computation so that theoretical chemistry cannot proceed without computational chemistry. In fact sometimes computation proceeds without a theoretical model; that is, we do not use computation to evaluate specific rate constants or other well-defined theoretical constructs like diffusion coefficients, but we simulate a complex dynamical system globally in terms of basic physical laws (like Newton's equations of motion for step 2). An advantage of global simulation in addition to its applicability to processes not easily broken down into individual steps is that it eliminates the use of physical models, which often strip away nonlinear effects, use oversimplified boundary conditions, or in other ways eliminate details of the real-world global problems.<sup>27</sup> A disadvantage of global simulation is that real complex processes often involve length scales that are large compared to atomic dimensions and time scales that are long (microseconds, minutes, or years) compared to the time scales (sub-femtosecond) on which we can integrate the basic physical laws of atomic motion. This has created the new field of multiscale simulation.<sup>28–30</sup> Another advantage of global simulation is that by relating the output to the input, one can hope to understand the controlling variables. A challenge in global simulation is data extraction; a global simulation produces a myriad of time-ordered structures, but one must devise a way to extract useful information and understanding.<sup>31,32</sup>

A recurring construct in modern kinetics and simulation is the master equation. The master equation is so prominent in modern dynamical thinking and so missing in most dynamics and kinetics textbooks that it deserves some introduction. The master equation assumes that one has divided all possible states of the system into a discrete set; for example, the states could be the various chemical arrangements or chemical structures, they could be the vibrational–rotational states of a set of molecules, or they could be regions of phase space identified in various ways. Then the master equation is a set of differential equations governing the evolution of the system from one set of state probabilities to another with the key property that the probability distribution at time  $t + dt$  depends only on the probability distribution at a time  $t$  and on a set of state-to-state transition probabilities. This property is called the Markov property, and it is essentially equivalent to saying that the system has no memory of its past history—of how it got to the present point in time. If the states are chemical arrangements, the probabilities become the concentrations of various chemical species, and the state-to-state transition probabilities become chemical rate constants; if the states are vibrational–rotational quantum states of a molecule, the transition probabilities become state-to-state rate constants or inelastic cross sections; or the state specification could contain information about the site on a surface; etc. The master equation may be solved (exactly or approximately) by a variety of methods,<sup>26,33–45</sup> e.g., numerically integrating differential equations, Monte Carlo simulation, iterating to a steady-state solution, approximating steady-state solutions analytically, or eigenvalue analysis. A master equation is most amenable to analysis when it is linear, and some of these methods are valid only for linear master

equations or involve linearization; linear master equations arise when all processes are first-order or pseudo-first-order—nonlinear effects are still largely under explored.

The master equation sometimes seems obvious for simple model systems, like the coupled chemical rate equations of a reaction proceeding through thermally equilibrated reactants and products, but there are cases in which it is not obvious. One is a quantum system, where coherence effects mean that we cannot think entirely in terms of probabilities; for quantum systems, Pauli derived the conditions when a master equation would hold, and the master equation is sometimes called the Pauli master equation.<sup>46,47</sup> Of more relevance for the present Perspective is the case where states are not internally equilibrated; thus, two systems that we lump into the same state but that arrived there differently will have different probabilities for their future evolution. To resolve this we must use finer definitions of the states (but—and here are the challenges—not so fine that quantum coherence effects come into play and not so fine that the number of states becomes unmanageably large). For example, in a gas-phase combustion system, we might produce “hot” radicals R whose probabilities of various reactions depend, for example, on their energy. Then we cannot take the probability of being radical R (i.e., the concentration of R) as a state population, but we must consider the radicals with energy between  $E$  and  $E + \Delta E$  as being in one state, the radicals with energy between  $E + \Delta E$  and  $E + 2\Delta E$  as being in another state, and so forth. Further complications arise in relating the time dependence of these finely divided state populations, which arise from the numerical solution of the master equation, to the chemical rate equations required for global kinetic systems. For complex systems like proteins, it is not obvious how to divide up phase space so that the state evolution is Markovian, and when we fail to do this, we call the evolution non-Markovian. We shall return to this below.

Not only does complexity increase the number of individual states and steps and blur the distinction between them, but it also adds complications to the treatment of individual steps, even if these are well defined. For example, a well-defined concerted reaction rate may involve an ensemble of reactant conformations, transition-state conformations, and reaction paths not centered on a single PES valley from reactants to products.<sup>48,49</sup>

With the above considerations as motivation, this Perspective will present some of the ways that have been developed and are being developed to model the chemical kinetics of complex systems. We emphasize that this Perspective does not attempt to provide a comprehensive review; it rather focuses on selected aspects of the current status and prospects that the authors want to emphasize to highlight key concepts and recent progress.

## 2. GAS-PHASE KINETICS

Theoretical kinetics provides a valuable means for improving the fidelity of chemical mechanisms for conditions that are difficult to explore experimentally, such as combustion,<sup>50</sup> atmospheric,<sup>51</sup> and interstellar chemistries. The most powerful framework is the master equation<sup>24,52</sup> (i.e., the set of coupled rate equations for all the steps in the mechanism) with rate constants based on TST, either conventional or variational. The conventional TST expression for the high-pressure limit thermal rate coefficient at a given temperature  $T$  is<sup>5</sup>

$$k = \kappa \frac{\tilde{k}T}{h} \frac{Q^\ddagger(T)}{Q^R(T)} \exp(-V^\ddagger/RT) \quad (1)$$

where  $V^\ddagger$  denotes the barrier height,  $Q^\ddagger$  and  $Q^R$  denote the canonical partition functions for the conventional transition state (located at a PES saddle point, also called a transition structure) and reactants, respectively;  $\kappa$  is the transmission coefficient that accounts for quantum effects on reaction-coordinate motion (tunneling and nonclassical reflection) and for classical recrossing of the conventional transition state;  $\tilde{k}$  and  $h$  are the Boltzmann and Planck constants, respectively; and  $R$  is the gas constant (used here because it is conventional to express  $V^\ddagger$  in molar units). In variational TST,<sup>53,54</sup>  $V^\ddagger$  and  $Q^\ddagger$  are replaced by analogous quantities referring to the generalized transition state with the maximum free energy of activation along the reaction path (whereas  $V^\ddagger$  and  $Q^\ddagger$  are calculated at the maximum of the potential energy along the reaction coordinate), and recrossing is thereby minimized ( $\kappa$  increased). A detailed derivation of the variational principle is given elsewhere;<sup>55</sup> it strictly holds only when nuclear motion is governed by classical mechanics, but it is assumed to hold approximately even when vibrations are quantized.<sup>56</sup> We use TST as an abbreviation for both conventional and variational transition state theory. TST calculations without tunneling may be called quasiclassical, where “quasi” refers to the very important fact that vibrations are quantized (as they should be, even at transition states<sup>57</sup>); TST calculations with tunneling may be called semiclassical (or quantal, if no semiclassical Wentzel–Kramers–Brillouin (WKB)-like approximations are made).

In modern work, the key PES properties that determine the barrier height and canonical partition functions are obtained from electronic structure theory, although sometimes the calculated barrier height is still partly empirical. The electronic structure calculations are often based on wave function theory for small and moderately sized systems, but almost exclusively on Kohn–Sham density functional theory<sup>58</sup> (DFT) for large systems. Importantly, this approach is readily applicable to complex polyatomic systems and the focus within TST on a limited region of the PES allows for the coupling with high-level electronic structure methods. The accuracy of DFT depends on the quality of the exchange–correlation functional used, and these are continually improving. The efficiency of DFT allows—when needed—for full examination of multiple conformations of reactants and transition states, for variational optimization of transition states, and for calculations of tunneling probabilities, to which we return below.

With careful application of the above approach, it is now often possible to predict rate constants accurately enough for useful mechanistic predictions, especially for temperatures of relevance to combustion (greater than about 800 K) and often for lower temperatures as well. In contrast, classical time-propagation-based methods (such as trajectory calculations, sometimes confusingly labeled molecular dynamics (MD) as if all MD calculations were classical) require a global PES, and anyway are inaccurate for rate calculations because of the lack of quantum effects, especially zero-point energy and tunneling. The neglect of such effects in classical trajectory simulations leads to problems in interpreting and predicting threshold behavior, which is critical for the magnitudes of rate constants. Fully quantum dynamical methods are generally too numerically intensive to be applicable to the study of complex polyatomic systems, although prototype fully converged

quantal dynamics calculations for small systems<sup>8,9</sup> provide a bedrock foundation for the theory. We focus here on a description of the recent progress and current limitations in the application of the TST and master equation approach to complex systems.

**Electronic Structure.** In the 1930s, Eyring called TST “absolute reaction rate theory” because of the hope that the combination of electronic structure theory and TST would lead to accurate rate constants; however, until very recently uncertainties in the prediction of the barrier heights prevented this dream from being realized. However, recent and continuing advances in electronic structure methodologies and computational capabilities have resulted in dramatically reduced uncertainties for such predictions.<sup>59</sup> For example, the Weizmann-4 (W4)<sup>60</sup> and “high accuracy extrapolated ab initio thermochemistry” (HEAT)<sup>61</sup> model chemistries yield predicted heats of formation that agree with the highest accuracy thermochemical data (e.g., as obtained from the “Active ThermoChemical Tables” approach<sup>62</sup>) to better than 0.2 kcal/mol ( $2\sigma$ ), and coupled cluster theory with single and double excitations and a quasiperturbative treatment of connected triple excitations [CCSD(T)] and an essentially complete basis set (CBS) is accurate to about 1.1 kcal/mol ( $2\sigma$ ) for reaction energies and barrier heights,<sup>63</sup> at least for systems where a single electronic configuration provides a good zero-order wave function. Notably, the inclusion of a bond additivity correction reduces the QCISD(T)/CBS uncertainties in the heat of formation to 0.6 kcal/mol ( $2\sigma$ ).<sup>64</sup> The W4 and HEAT model chemistries are readily applicable to systems containing up to 5 non-hydrogenic atoms, but slightly less accurate methods may be applied to systems with up to 10 non-hydrogenic atoms.

These high-level electronic structure methods are based on single-reference coupled cluster calculations, usually with connected excitations no higher than triple. Unfortunately, many transition states, such as those involved in radical–radical reactions, are not well described even at zero order by a single electronic configuration; such systems are called multireference systems to remind us that reliable practical correlated wave functions must be built from a multiconfigurational reference function. The CCSDT(2)<sub>Q</sub><sup>65</sup> and CCSDT(Q)<sup>66</sup> methods, which include connected excitations up to quadruple within coupled cluster theory, provide an effective approach for treating intrinsically multiconfigurational systems more accurately, but at higher (often unaffordable) cost. Efforts are currently underway to develop massively parallel implementations of such higher-order coupled cluster methods.<sup>67,68</sup>

Examples of multireference systems are ozone,<sup>69</sup> ethenol,<sup>70</sup> diradicals,<sup>71</sup> and many metal-containing systems.<sup>72</sup> For reactions involving multireference systems, electronic structure methods, such as second-order perturbation theory from a complete active space multireference wave function (CASPT2) or multireference configuration interaction including single and double excitations (MR-CISD), are often required.<sup>73</sup> Recent local versions of these methods are extending their range of applicability to fairly large systems.<sup>74</sup> Nevertheless, some systems, such as the recently studied zwitterionic water loss TS in  $O_2 + C_4H_9O$ , still present difficulties for these standard methods.<sup>75</sup> Multireference coupled cluster methods are often sought for such complications,<sup>76–78</sup> although they are not always satisfactory at their current state of development.<sup>71</sup>

For molecules with more than five non-hydrogenic atoms, CCSD(T) rovibrational analyses become problematic, but DFT



remains affordable up to at least  $O(10^2)$  atoms. The recently developed MN12 exchange-correlation functional provides high-accuracy properties that are appropriate across a wide range of chemical environments.<sup>79</sup> The earlier M06-2X<sup>80</sup> and M08-HX<sup>81</sup> functionals have proven to be of great utility for chemical kinetics studies, with the former (which is available in a greater number of software packages) often providing an effective replacement for the old standard of B3LYP. For moderately sized molecules (e.g., up to about 10 non-hydrogenic atoms), it can still be effective to evaluate higher level CCSD(T)-based energies at the DFT geometries, although for basis sets smaller than augmented correlation-consistent valence triple zeta, CCSD(T) gives less accurate barrier heights than the best exchange-correlation functionals.<sup>82</sup>

**Entropy.** For many reactions, the greatest uncertainties in the kinetic predictions are now related to the treatment of entropic effects, i.e., in the evaluation of the partition functions. Traditionally, the partition functions of gas-phase reactions have been evaluated on the basis of a single structure (single equilibrium structure or single transition structure) by the rigid-rotor harmonic oscillator approximation for all modes or for all but the torsional modes, with the latter commonly treated as decoupled one-dimensional hindered rotors.<sup>83,84</sup> We now know that this is often insufficient, and there is considerable current interest in developing more accurate methods.

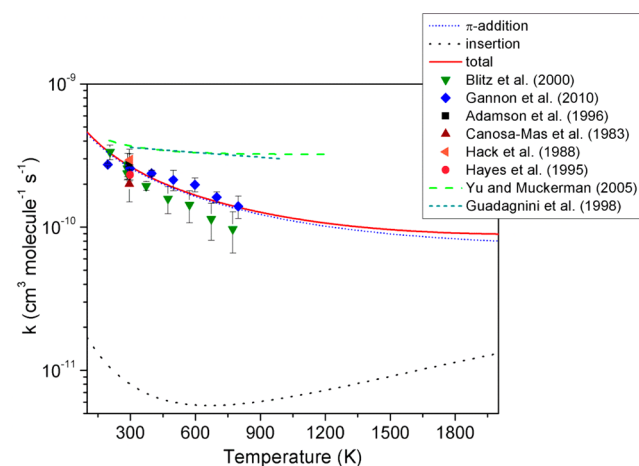
The direct variable reaction coordinate (VRC)-TST approach<sup>85</sup> provides a useful procedure for accurately evaluating the entropic effects for barrierless reactions such as radical-radical and ion-molecule recombinations (and their reverse unimolecular decompositions). In this approach, the modes are separated into the (i) “conserved” vibrational modes of the fragments, which retain the same character throughout the reaction, (ii) transitional modes, which transform from fragment rotations and relative translations to bending or libration and overall rotations, and (iii) overall translations. The critical step of the VRC-TST approach is the evaluation of the fully anharmonic and mode-coupled transitional mode contribution to the transition-state partition function via Monte Carlo integration of its phase space representation. The requisite potential energies are evaluated with direct sampling of electronic structure energies determined at the CASPT2 or MRCI level, respectively. For the conserved modes, the anharmonic effects are assumed to be similar for the reactants and the transition state and to effectively cancel in the evaluation of the rate expression. For torsional modes this may not always be true, as the recombination process often leads to a tightening of some of the torsional modes. One could generalize the VRC-TST approach to include some torsional modes in the transitional mode space, but this has not yet been done. Treatment of bond fissions in cyclic molecules also requires some generalization of this approach.

The minimum energy path for a barrierless reaction often shows interesting non-monotonic coordinate variations related to the different orientation dependences of long-range interactions (e.g., dipole-dipole, dipole-induced dipole, dispersion) and short-range chemical bonding interactions. The transformation from long-range dominated to short-range dominated with decreasing reagent separation generally results in the presence of two distinct transition states for barrierless association and dissociation reactions.<sup>86–90</sup> The outer transition state is largely determined by the centrifugal barriers on the long-range potential, while the inner transition state is largely determined by the reduction in entropy that arises from the

tightening of bends during the formation of chemical bonds. The range of separations between the inner and outer transition states corresponds to what one typically thinks of as van der Waals separations.

Notably, in the inner transition-state region there are often multiple distinct chemical processes that may occur. For instance, in a radical-radical reaction, an incoming radical may bind to the radical site of the other fragment to form a chemical adduct, or it may abstract an atom to form two closed-shell molecules. Alternatively, with a resonantly stabilized radical the other radical may bind to either of the two (or more) delocalized radical sites. These distinct chemical reactions are generally separated by orientational saddle points in the van der Waals region between the inner and outer transition states.<sup>91</sup> These orientational transition states have come to be called roaming saddle points.<sup>73,92,93</sup> More broadly, roaming has been defined as the case where fragments separate to van der Waals distances and undergo large angular reorientations that result in products that differ from those expected for the incipient dissociation.<sup>88,91,92</sup> Notably, the roaming-induced abstraction concept helps to explain a number of detailed observations of vibrational product distributions in photodissociation, and the concept was first introduced to explain such phenomena.<sup>93–95</sup>

A steady-state treatment of the kinetics of the formation and decomposition of the intermediates in the van der Waals region yields a multistate TST approach for predicting the overall kinetics and the product branching.<sup>88</sup> This methodology has been applied to treat the kinetics of a variety of radical reactions with roaming transition states. A modified phase space approach,<sup>96</sup> which partitions the reactive flux according to the kinetic energy at the transition state, provides an alternative statistical theory approach to modeling the kinetics of roaming reactions. A recent application of the multistate TST approach considers the branching between cyclic addition and insertion in the reaction of singlet methylene with unsaturated hydrocarbons.<sup>86</sup> Figure 1 provides an illustration of the success of these fully ab initio TST calculations for the particular case of  $^1\text{CH}_2 + \text{C}_2\text{H}_2$ . An earlier two-transition-state theory,<sup>97</sup> which might be viewed as a simplified version of the multistate TST,



**Figure 1.** High-pressure limit rate coefficients for the  $^1\text{CH}_2 + \text{C}_2\text{H}_2$  reaction. The predicted total (solid red line),  $\pi$ -addition (dotted blue line), and insertion (dashed black line) rate constants are compared with experimental measurements (symbols) and other theoretical predictions (lines). Reprinted with permission from ref 89. Copyright 2013 American Chemical Society.

has proven useful in the treatment of radical–molecule reactions.

There is often a tight transition state that leads to the same products as those arising from the roaming radical process. In this instance, one should properly consider a global TST dividing surface (a dividing surface is the hypersurface in phase space that separates reactants from products, and the TST dividing surface is the surface that TST assumes to be crossed only once) that includes both the variational transition state for the tight process and the local variational transition state for the roaming process. This global dividing surface should pass through (or near) a second-order saddle point or conical intersection that connects the two first-order saddle points.<sup>98</sup> This second-order saddle point or conical intersection yields an energetic criterion for the separability of the tight and roaming process. Consideration of the differential contributions to the reactive flux provides a dynamic criterion for separability.<sup>98</sup>

At low temperatures, the outer transition state is dominant, and this transition state moves to large separations where only the longest-ranged terms in the PES are significant. This simplification allows for the derivation of analytic expressions for the rate constant that depend solely on the nature of the longest-ranged interaction.<sup>99</sup> Such long-range TST results should generally provide an accurate description of the kinetics from about 10 to 100 K. For a number of reactions, recent quantum dynamics studies do not reproduce this expected low temperature behavior, and it is not clear why that is. The long-range TST approach, as well as the closely related adiabatic channel approaches, also allow for the direct treatment of spin–orbit coupling effects.<sup>100,101</sup> Their neglect, which is common, can yield significant errors in the predictions.

As reviewed in a recent PCCP publication,<sup>102</sup> reactions with a valley–ridge inflection point provide cases for which the usual statistical theories do not provide all the answers. A variety of scenarios are possible. In some cases, the reaction path bifurcations are in dynamical bottleneck regions where the PES is very flat, and in some of these cases the kinetics might be treatable by multistate transition-state methods implemented at the  $E_J$  resolved level. Another general class of valley–ridge inflection points consists of those where the reaction path bifurcates after one passes the overall dynamical bottleneck for reaction. If there is a deep intermediate after the overall dynamical bottleneck such that all systems that pass this bottleneck become equilibrated intermediates before reacting further, then this is just a two-step reaction. If, however, the intermediate is not equilibrated, TST predicts the overall reaction rate but not the branching ratio to competing products. [It is better to say that TST does not predict the branching ratio in this case than to say, as some have said, that TST fails. The reason for this is that the TST should be well known to be a theory applicable only at the overall dynamical bottleneck, and TST should not be applied downstream of the overall dynamical bottleneck.] If the reaction occurs in the gas phase, this is a standard case for master equation treatment, and one expects pressure-dependent rate constants. Much recent interest, however, has focused on cases where such a post-bottleneck bifurcation occurs for reactions in liquid-phase solutions. Two related approaches to this class of systems have been proposed. In one approach,<sup>103</sup> systems that pass the overall dynamical bottleneck are divided into two groups. One group, called indirect, is equilibrated (by intramolecular vibrational energy redistribution and solvent interactions), and the ultimate fate of this group is predicted by statistical

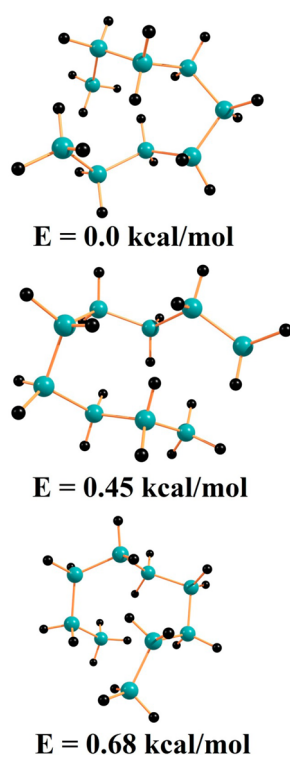
methods for the probabilities of various ways of leaving the equilibrated intermediate. The other group, called direct, is explicitly not equilibrated, and both the partition of the reactive flux into the two groups and the ultimate fate of the second group must be predicted by nonstatistical dynamics; a model based in part on nonstatistical phase space theory<sup>104</sup> was proposed for this part. The second approach<sup>105</sup> is very similar in spirit but is cast into master equation language, even though the reaction is in solution and one does not usually discuss energy transfer in master equation language in solution. Both approaches avoid the naïve assumption that the solvent instantaneously removes energy from the reaction coordinate as the system progresses downhill from the overall dynamical bottleneck, which would prevent direct reaction.

**Entropy in Complex Systems.** For reactions with tight transition states, the evaluation of the torsional entropies often presents the greatest uncertainty in the kinetic predictions. For cases with just two torsions, fully quantum mechanical treatments are effective.<sup>106</sup> Uncertainties arise when there are more than two torsional degrees of freedom, and even for two torsions the fully quantal treatment neglects rotation–vibration coupling. Waroquier and co-workers provided some interesting studies of the effect of mode coupling on the torsional partition functions for multiple hindered rotor cases<sup>107–109</sup> and have presented a code for performing such calculations.<sup>110</sup> For many reactions (a simple example being OH + ethanol<sup>70</sup>), the transition state involves some degree of hydrogen bonding and the extent of this hydrogen bonding varies with torsional configuration. Such cases, which are common, for example, in the abstraction kinetics of importance to the combustion of oxygenated fuels, result in strong failures of the standard one-dimensional hindered rotor approaches.

Torsions can be considered as anharmonic, multiple-minima vibrational modes of a single structure, but one can also think of the minima as multiple structures. This is an especially powerful viewpoint when the barriers separating the minima are much higher than  $\tilde{k}T$  or when torsions are strongly coupled. Textbooks often present an approximate factorization of molecular partition functions into electronic, vibrational, rotational, and translational factors. When we think of multiple minima of the PES as multiple structures, there is another factor, namely the conformational one, which can differ from unity by one or more orders of magnitude. Just as a correct treatment of the electronic degrees of freedom of a single-structure system requires a vibrational–rotational partition function for every electronic state, a correct treatment of the conformational structures requires a vibrational–rotational partition function for every conformation (i.e., every structure) of every electronic state.

A multistructural torsional approach, called MS-T, was recently developed<sup>111,112</sup> to treat this situation, and a freeware implementation of the code has been made available.<sup>113,114</sup> A key issue is that the structures effectively blend together as the temperature is raised so that  $\tilde{k}T$  successively becomes higher than each of the barriers separating the minima. The MS-T approach interpolates between a harmonic oscillator or harmonic-oscillator-like regime at low temperature and the free rotor limit at very high temperature. The MS-T treatment of torsional anharmonicity has been combined with TST treatments of reaction path variational and tunneling effects.<sup>115–118</sup> One important aspect of this combination is that multiple structures of the transition state engender multiple reaction paths, and many reaction paths may

contribute to a single rate constant. This approach has proven to be very effective even for treating systems with hundreds of equilibrium structures, a number reached for even moderately sized molecules—for example, *N*-acetyltryptophan methyl amide has 64 conformers,<sup>119</sup> the transition state of the reaction of OOH with C-3 of 1-butanol has 262 structures,<sup>120</sup> and *n*-nonasilane has 543 structures<sup>121</sup> (see Figure 2). The conforma-



**Figure 2.** Three lowest-energy structures of nonasilane calculated by BMC-CCSD//M06-L/MG3S.

tional–vibrational–rotational partition function of *n*-nonasilane is  $3 \times 10^5$  times larger than the harmonic oscillator one at 1000 K.<sup>121</sup> The MS-T method includes not only the coupling of torsional modes but also torsion-rotation coupling. For molecules with several torsions, a number of low-frequency nontorsional modes often mix with the torsional ones. Green and co-workers have presented a method for projecting out these modes.<sup>122</sup> (This treatment is not needed in MS-T because the torsions are separated from other degrees of freedom by using intanl coordinates.) Progress has also been made on the torsions of hydrated biomolecules.<sup>123</sup>

As an example of the effect of multiple minima and torsional potential anharmonicity on rate constants, consider the reaction in which HO<sub>2</sub> abstracts a hydrogen atom from the C-3 position of 1-butanol.<sup>120</sup> At 200 K, the combination of these effects lowers the forward rate constant by a factor of 3 and lowers the reverse rate constant by a factor of 8. At 500 K, these effects raise the forward rate constant by a factor of 4 and the reverse rate constant by a factor of 1.3. The effect on the forward rate constant increases to factors of 45 at 1000 K and 146 at 2000 K. For a second example, consider the reactions of HO<sub>2</sub> abstracting a hydrogen atom from the various positions in butanal.<sup>124</sup> The multiple-structure and torsional-potential anharmonicity effects change the relative yields by as much as a factor of 7 at 200 K, a factor of 5 at 298 K, and a factor of 4 in the other direction at 2400 K.

Anharmonicities in other modes, such as bond stretches and bends, may also have significant contributions to the entropy at high temperatures. Such effects may largely cancel in the high-pressure limit of a unimolecular reaction, when one takes the ratio of the transition state and reactant partition functions (although this will not always be the case). In contrast, the rate coefficient for the low-pressure limit of a unimolecular reaction effectively reduces to the ratio of the density of states for the complex at the dissociation energy, divided by the partition function for the reactants. For this ratio, the anharmonic effects are less likely to cancel. Vibrational perturbation theory based on a second-order treatment of the cubic terms in the potential energy and a first-order treatment of the quartic terms, provides one possible approach to estimating such anharmonic effects.<sup>125–137</sup> This approach can be effective at low temperatures, but becomes problematic at high temperature due to failure of the perturbation theory, although a quasiharmonic approach has been suggested for avoiding this failure.<sup>129</sup> An alternative approach employs direct evaluation of the configuration integrals arising from classical phase space representations.<sup>138,139</sup>

**Tunneling.** For reactions with low barriers, uncertainties in the tunneling correction are often the dominant uncertainty, especially at lower temperatures. Procedures for incorporating tunneling corrections within variational TST have been described in prior reviews.<sup>54,140,141</sup> These procedures are well validated,<sup>142,143</sup> are applicable to both large and small molecules in both gaseous and condensed phases, and are implemented in the POLYRATE software;<sup>144</sup> they have found considerable utility over the years. The ring polymer MD approach, although less well validated, is an alternative TST approach that is also being used for some recent gas phase kinetics studies;<sup>145</sup> a general code for such calculations has recently been published.<sup>146</sup> One of the challenges of including tunneling is that it involves a larger portion of the PES than just the region near the conventional or variational transition state. This requirement sometimes results in the use of electronic structure or dynamical methods of limited accuracy. We especially caution that methods that only utilize information about the region near the saddle point do not deal effectively with the deep tunneling regime, while inadequate electronic structure methods often yield poor predictions of the barrier widths to which the tunneling rate is exquisitely sensitive. There is more discussion of tunneling at the end of section 3.

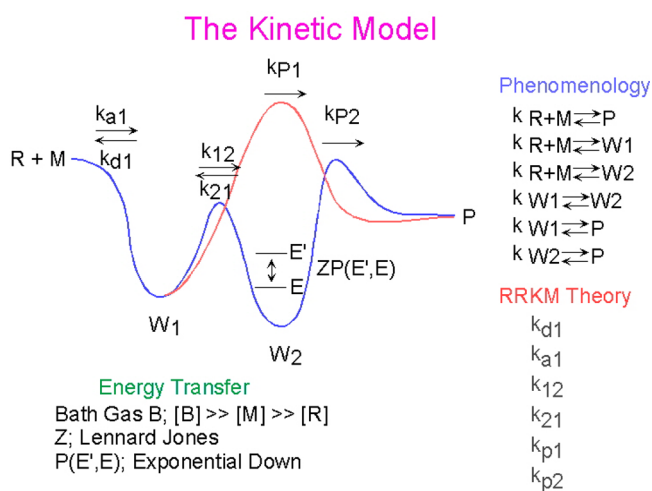
**Pressure Dependence.** Reactions that involve passage over potential energy wells present additional complexities for rate constant predictions. For such reactions, the rate coefficients written in terms of chemical concentrations are pressure dependent because the energy distribution of the reacting complexes is affected by collisions with bath gas molecules. A master equation expresses the time dependence of the energy-resolved reactive complex populations in terms of rates and distributions for collision-induced energy transfer, coupled with microcanonical rates for chemical isomerization, unimolecular decomposition, and complex formation from bimolecular species.<sup>24,43,147–150</sup>

Figure 1 provides a schematic picture of a typical kinetic model that is treated with the master equation approach. The chemical processes occurring at fixed energy include isomerization between the two wells  $W_1$  and  $W_2$  with rate constants  $k_{12}$  and  $k_{21}$ , dissociation from each of the wells to the products with rate constants  $k_{p1}$  and  $k_{p2}$ , dissociation back to bimolecular reactants with rate constant  $k_{d1}$ , and bimolecular association



with rate constant  $k_{a1}$ . These microcanonical rate constants are generally obtained by TST for a unimolecular process, as in Rice–Ramsperger–Kassel–Marcus theory. Inelastic collisions with bath gas B lead to transitions in energy within each well. These transition rates are typically modeled as a product of a Lennard-Jones collision rate  $Z$  and an energy transfer probability  $P(E',E)$  that decays exponentially with the energy of the transition. The solution of the master equation directly yields time dependent populations and energy distributions within each of the wells. However, global kinetic models instead require representations of the temperature and pressure dependence of the phenomenological rate coefficients describing the overall processes ( $k_{R+M \rightarrow P}$ , etc.) that can occur on the PES.

For reactions that sample only a single well, the rate coefficients are readily related to the solutions of the master equation.<sup>148</sup> However, for reactions that sample multiple potential wells (as illustrated in Figure 3), the situation is



**Figure 3.** Schematic diagram of a generic kinetic scheme for a multiple-well reaction. The rate constants are denoted by  $k$ .

considerably more complex. Approaches that attempt to relate phenomenological rate coefficients to numerical time dependent populations encounter ambiguities due to the blurring of time scales for different processes. Such difficulties become particularly severe at high temperatures and for reactions with multiple chemical processes. Direct correlation of the time dependence represented by an expansion in the eigensolution for the transition matrix with that implied by the phenomenological rate equation bypasses these difficulties. This correlation hinges on a separation of time scales/eigenvalues into those for the slow chemical processes (CSEs) and those for the fast energy relaxation (IEREs). Although this is not always obeyed,<sup>151</sup> when it is obeyed, it yields an analytic connection between the CSEs and the phenomenological rate coefficients,<sup>43,152</sup> which removes all ambiguities in the definition of the rate coefficients.

One significant outcome of the CSE approach is a clarification of precisely when a phenomenological rate description is appropriate.<sup>43,153</sup> The separation of time scales may disappear for some of the CSEs as the temperature is increased and/or the pressure is decreased, which implies that some chemical process(es) are equilibrating on the same time scale as the energy relaxation process. In this instance, one can no longer define proper phenomenological rate constants for

the corresponding chemical process(es). The original chemical species can no longer be isolated under the given conditions of temperature and pressure and the two rapidly equilibrating species should be merged together and thought of as a single species. With this definition of merged chemical species the CSE-based formalism is applicable to the derivation of rate coefficients for the remaining chemical processes.<sup>154</sup>

An automated procedure for performing this reduction in species, which is based on maximizing the correlation between chemical subspaces and chemical eigenvectors, has recently been derived.<sup>155</sup> This approach builds off a recent reformulation of the master equation,<sup>156</sup> which also led to the development of a low-eigenvalue perturbative expansion approach. This low-eigenvalue approach is particularly valuable at low temperatures, where the standard eigenvalue expansions fail due to the numerical dispersion in the eigenvalues. Other approaches such as the reservoir state method,<sup>157</sup> direct numerical integration, matrix eigenanalysis,<sup>158</sup> and stochastic simulations<sup>159</sup> also provide effective solutions for the low temperature problem.

Many of the rate constants that go into a full master equation simulation of combustion are reaction rates of species whose rate constants have never been measured, and in some cases the intermediates have been impossible to even observe. This is one aspect of complex mechanisms where theory is invaluable, since theory can calculate the rates even for such unobserved species.

Historically, the energy transfer portion of the master equation has been treated empirically, via fits to experiment of limited parameters in simplified presumed forms for the energy dependence of the energy transfer kernel. Jasper and co-workers have recently begun coupling explicit calculations of the energy transfer distributions with the master equation analysis.<sup>160</sup> An initial implementation of this approach led to rate coefficients that appeared to overestimate the observed rate coefficients by about a factor of 2, at least when anharmonic effects are accounted for. This overestimate apparently arises from the common assumption of rapid rotational energy transfer resulting in statistical rotational distributions, which is required in order to reduce the two-dimensional master equation in energy  $E$  and total angular momentum  $J$  to one in  $E$  alone. A recent calculation demonstrates that a similar classical trajectory-based treatment of the full two-dimensional energy transfer kernel in  $E$  and  $J$  coupled with a two-dimensional master equation leads to quantitative agreement with experiment for the  $C_2H_3$  reaction system.<sup>161</sup>

The chemical activation process (production of the energized unimolecular reactant by a chemical reaction rather than by thermal equilibration) often yields further complications for modeling.<sup>162</sup> For example, when the exothermicities arising from the addition (and perhaps subsequent isomerization steps) are very large, the further chemical steps (dissociation and/or isomerization) may occur so rapidly that statistical theories are not applicable.<sup>163</sup> Furthermore, any resulting bimolecular products may be formed with so much energy that they also dissociate without any further collisions.<sup>164</sup> The analysis of this dissociation probability requires some knowledge of the proportioning of energy within the products, which is generally not well described by statistical theories. Classical trajectory methods are readily applicable to these phenomena since they are short-time-scale phenomena that should not be dominated by threshold effects due to their large exothermicities.

A particularly important complication is related to the fact that chemically activated molecules may react with additional reactants while the initial complex is still hot. A recent study of the  $C_2H_2 + OH + O_2$  reaction demonstrated the effect on product branching of such hot molecule reactions,<sup>165</sup> while a study of the methacrolein +  $OH + O_2$  reaction demonstrated the effect on product energy distributions.<sup>166</sup> Unfortunately, such effects generally have a nonlinear dependence on the concentration of the third reactant and so are not readily modeled with the standard kinetics phenomenology. Such hot-molecule reactions are also expected to be important in combustion chemistry.<sup>167</sup>

**Non-Born–Oppenheimer Processes.** Sometimes chemical reactions are coupled with non-adiabatic transitions of the electronic state, often involving spin transitions.<sup>168</sup> One recent study has explored the coupling of statistical theories for this process with the master equation.<sup>169</sup> However, the accurate prediction of such transition probabilities often requires more dynamical treatments such as that employed in a recent study of the  $O(^3P) + CO \rightarrow ^1CO_2$  reaction.<sup>170</sup> Coverage of non-Born–Oppenheimer processes and photochemical reactions is outside the scope of this Perspective.

**Analytic Potentials.** Although the present Perspective is mainly focused on thermal rates, much of our understanding is fueled by more detailed dynamics studies, and we cannot end this section without mentioning a revolution in theoretical understanding of detailed dynamics that has been occasioned by the dramatic increase in the number of analytic global PESs for polyatomic reactive systems, arising from rapid progress in surface fitting methods.<sup>17–20</sup>

### 3. KINETICS AND DYNAMICS OF CHEMICAL REACTIONS AT GAS–SURFACE INTERFACES, IN LIQUID SOLUTIONS, AND IN ENZYMES

A main reason why the treatment of reactions involving well-ordered condensed phases must differ from the treatment of gas-phase reactions is that the systems are large. Furthermore, real condensed phases are seldom well ordered; for example, even reactions at crystal–air interfaces are usually complicated by surface relaxation, reconstruction, and defects, all of which are coverage dependent; this adds considerable further complications.

**Solid–Gas Interfaces.** A good example of the complexities of including mechanisms into rate calculations for real-world time and length scales is provided by oxidation of NO catalyzed by precious metals (Pt and Pd), which is an important process in three-way catalytic converters employed to control emissions in automobile exhausts. A simple model would be based on specific rate constants such as adsorption of  $O_2$ , dissociation of  $O_2$ , and Langmuir–Hinshelwood reaction of NO with adsorbed O. However such a model would be totally inadequate.<sup>172,173</sup> The atomic scale binding sites, binding energies, and reaction rates all depend on coverage, and coverage depends on thermodynamic conditions, especially the chemical potential of oxygen. A key parameter is the O binding energy, calculated to be 4.39 eV at low coverage on Pt(111), but 4.49 eV per oxygen atom with O atoms at nearest neighbor sites. The increase is even larger for N adsorption, from 4.72 to 4.90 eV. It turns out that the reaction  $NO + \frac{1}{2}O_2 \rightarrow NO_2$  is nearly thermoneutral at low coverage but, due to lateral interactions, becomes 0.28 eV exothermic if O coverage is increased to 31% before adding NO.

As already mentioned, taking account of this coverage dependence creates complications. On the PES side one must use large supercells to study lateral interactions, and questions still remain about the adequacy of popular exchange-correlation potentials for treating such interactions. On the thermodynamics side there are questions of fully accounting for configurational entropy and the entropy of low-frequency modes. On the kinetics side, the simplest way to include coverage effects is a mean-field kinetic Monte Carlo treatment.<sup>172,173</sup> In kinetic Monte Carlo<sup>174</sup> we first make a catalog of elementary processes. In the mean-field approximation, we do not assign rate constants to individual arrangements of adsorbates on the surface but rather we assign an average rate constant to a given percentage coverage. A more realistic model would involve dealing with individual arrangements of molecules on a lattice and with individual reaction pathways associated with various site occupancies.<sup>175,176</sup> For dealing with real solid catalysts one needs to consider not just sites on a face with given Miller indices<sup>177</sup> but also a distribution of surfaces with a variety of indices and extents of reconstruction. For nanostructured catalysts one must also consider nanoparticle size. Very quickly it becomes impractical to construct a catalog of possible processes for kinetic Monte Carlo studies. For disordered materials one might even say it is impossible because the number of elementary rate constants becomes very large.<sup>178</sup> Similar difficulties arise in, for example, gas-phase combustion mechanisms, due to a large number of species and reactions,<sup>179</sup> but in surface science they arise even with a small number of species, due to the variety of surface sites and coverages. It is useful to try to determine which rate constants most “control” the rate, i.e., are “rate-limiting steps”. Due to network effects, which are also well known in the gas phase,<sup>25,26</sup> there can be multiple bottleneck steps.<sup>180</sup> (Network effects are considered further in section 4.<sup>32,181</sup>) Kinetic Monte Carlo is a form of rare-event sampling in that one does not follow the time evolution of the system on the atomic-motion time scale, as in MD, but rather with a course-grained time step. Advanced rare-event sampling strategies have been developed to allow simulations up to times  $\sim 15$  orders of magnitude longer than MD time steps.<sup>182,183</sup>

Another complication in models of both gas-phase combustion and real heterogeneous catalysis is that the molecular processes must be coupled to a fluid dynamical treatment of the flow of reagents.<sup>176,184–187</sup> A coupled treatment of molecular reaction steps and macroscopic flow is an example of “mesoscale modeling”, and there is increasing realization that the development of coarse graining algorithms and the identification of collective field variables for mesoscale modeling is the next big challenge for extending computational modeling to the important complex problems associated with energy and the environment.

An important practical question that arises in treating heterogeneous reactions is whether to use periodic models or cluster models. Periodic models allow one to model unperturbed crystal lattices in a natural way, but they become problematic for treating nonperiodic reaction sites where large unit cells may be required. Cluster models may also require large model systems to adequately include electronic and vibrational effects. In one example where the two approaches were compared, it was found in a study of  $N + H \rightarrow NH$  (a step in the Haber–Bosch synthesis of ammonia<sup>188</sup>) on Ru(0001) that similar results could be obtained with a cluster of 8 Ru atoms or a slab with 12 atoms in the unit cell.<sup>189</sup> Reaction rate



constants were calculated with the slab model including tunneling effects.<sup>190</sup> Another example of a comparison of cluster models to periodic models is a recent study of the ability of the metal organic framework V-MOF-74 to separate N<sub>2</sub> from CH<sub>4</sub> in a gas stream; very similar results were obtained with an 88-atom cluster and a periodic model.<sup>191</sup>

Although absolute reaction rates calculated for reactions at interfaces still have considerable uncertainty, work is progressing trying to make more definitive calculations for the simplest reactions, for example, the dissociative chemisorption of H<sub>2</sub> on metal surfaces<sup>188,192–197</sup> (another elementary step in the Haber–Bosch process), where attention has been focused on the use of quantum mechanical scattering calculations of the probability of reaction as a function of energy and the sticking probability. The attention is focused on reaction probabilities on low index metal surfaces because their determination by experiments is less ambiguous. In molecular beam experiments on reaction at specific translational energies, it can be ascertained that the reaction is dominated by the terraces of the low-index face selected in the experiment. For most activated reactions, reaction rates measured under thermal conditions are dominated by steps (or more generally defects)—no matter how hard the experimentalists work to avoid miscutting of their single crystal. To predict the rate when reaction occurs at a particular type of defect or step, one must be able to estimate the concentration of such sites; in favorable cases this can be done by a combination of transmission electron spectroscopy and surface free energy considerations.<sup>198</sup>

Although the introduction to this Perspective indicated that the focus is on thermal and Born–Oppenheimer reactions rather than coupled electronic states, photochemistry, and non-Born–Oppenheimer reactions, when one considers reactions at metal surfaces, an overriding question is often to first determine whether or not the process is indeed occurring electronically adiabatically. When metals are involved the physics changes to some extent; for example, electronic excitations become electron–hole pairs. There has been tremendous progress both experimentally and theoretically in sorting out the issues of when surface reactions at metal surfaces are electronically adiabatic.<sup>199–201</sup> The H<sub>2</sub>–metal surface systems mentioned in the previous paragraph are ideal for testing electronic structure methods for molecule–metal surface interactions because they allow one to avoid the electron–hole pair excitation problem.<sup>202</sup>

Despite the difficulties, theoretical kinetic modeling of heterogeneous catalysis is reaching a point where it can be useful in industrial settings.<sup>203</sup>

**Reactions in Solution.** As one moves from gas–solid interfaces to liquids, one might at first think that liquids have all the problems of disordered solids. But actually, in some senses they are easier because the assumption that a liquid is homogeneous is often reasonable.

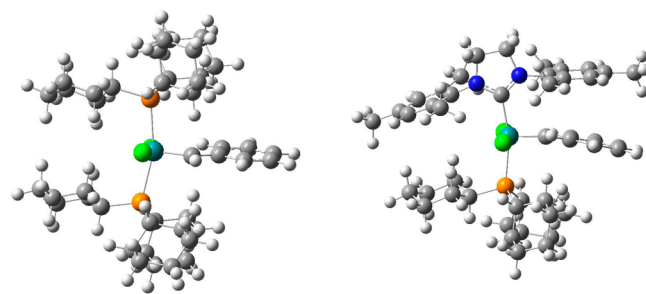
When one calculates rates for reactions in liquids or amorphous solids, one must consider statistical mechanical averaging over ensembles. If one treats the whole system at a given level of electronic structure, one must usually either use a lower than desirable level or skimp on the ensemble averaging. For this reason there has been considerable interest in multiscale methods such as fragment methods where a small-scale subsystem involving a chemical reaction is embedded in a larger subsystem. If the larger subsystem is still treated in molecular detail, this may be called a fragment method, which is often a combined quantum mechanical and molecular

mechanical (QM/MM) method.<sup>204–206</sup> Some fragment methods use the same level of quantum mechanics in all the fragments.<sup>207–212</sup> If the larger subsystem is treated by a coarse-graining<sup>213,214</sup> or continuum approximation,<sup>215–219</sup> this provides another example of mesoscale modeling.

Continuum solvation models are also called implicit solvation models; the solvent molecules are not represented explicitly but their effect is nevertheless included. For example, the electrostatic polarization of the solvent and its back reaction<sup>220</sup> on the solute are typically modeled by treating the solvent as dielectric medium, and the first-solvation-shell effects (such as dispersion-like attraction and hydrogen bonding) are neglected or—in better models—treated in terms of solvent-accessible surface areas, which are the portions of the surface areas of the solvent atoms that are exposed to solvent. For a solvent modeled as a structureless medium without molecular structure (i.e., modeled as a continuum), these surface areas would be a measure of (or even in some sense proportional to) the average number of solvent molecules in close contact with the solute.<sup>221</sup>

Most solution-phase reactions are treated by TST<sup>5,222,54</sup> or Marcus theory.<sup>7,223</sup> An example of what can be learned from modern solution-phase rate constant calculations is provided by a recent study of Diels–Alder reactions,<sup>224</sup> which delineated preorganization, diene strain, and tethered-alkene stabilization factors underlying experimentally observed reactivity. Another example would be the elucidation of the mechanism, kinetics, and environmental effects on the free radical scavenging activity of 6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid.<sup>225</sup> A third example is the elucidation of solvent effects<sup>226</sup> on the hydrogen abstraction from alkanes by CN radical.<sup>227</sup>

For another example of a complex reaction mechanism elucidated by theory we mention the metathesis of olefins by Grubbs catalysts; the precatalysts are shown in Figure 4.



**Figure 4.** First- and second-generation Grubbs precatalysts (left and right, respectively). The difference between the Grubbs I and II catalysts is the substitution of one of the phosphine ligands, usually tricyclohexylphosphine, PCy<sub>3</sub>, (shown as the top ligand on the left) of the bisphosphine first-generation precatalyst, (PCy<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>Ru=CHPh, by an *N*-heterocyclic carbene (NHC), usually 1,3-dimesityl-4,5-dihydro-2-ylidene (H<sub>2</sub>IMes).

Theory explained why the second-generation catalyst is formed more slowly from the precatalyst.<sup>228,229</sup> Theory also uncovered the role of multiple conformational structures in two steps of the catalytic mechanism;<sup>229</sup> such detailed understanding could not be achieved from experiment, even for this well-studied catalytic system, where intermediates (just like combustion intermediates in the previous section) are very difficult to observe.

Often the first step in understanding a complex mechanism is to sort out the energetic, enthalpic, and free energy changes

between the reactants and products, and progress is being made in doing that for more and more complex reactions.<sup>230,231</sup> A question that often arises is whether it is necessary to optimize the geometries of reagents and transition states in solution, or if using gas-phase geometries and vibrational frequencies is sufficient.<sup>232</sup> The answer depends on the system, but for polar or ionic species, the difference can be significant<sup>233–235</sup> or even essential.<sup>236,237</sup> One advantage of continuum solvation models is that it is straightforward to optimize geometries and calculate vibrational frequencies in solution because the reaction field corresponds to an ensemble average. However, for hydrogen bonding between the solute and solvent, it is sometimes necessary to include explicit solvent molecules and perform an explicit ensemble average over their positions. One practical method is to use molecular mechanics or combined quantum mechanics/molecular mechanics to simulate the liquid solution to produce an ensemble average of solvent positions, and then to perform quantum dynamics calculations with a small number of explicit solvent molecules, whose locations are taken as the locations of the closest solvent molecules in this simulation, and to model the rest of the solvent as implicit.<sup>238</sup> Fortunately, the number of solvent molecules that needs to be included explicitly in the second step is small, typically one solvent molecule next to each solute atom whose partial atomic charge has a magnitude greater than or equal to the magnitude ( $\sim 0.64$ ) of the partial atomic charge on O in water.<sup>239</sup> If one puts these explicit solvent molecules at positions optimized for the supermolecule (i.e., the micro-solvated solute), one runs a serious risk of overestimating the solute–solvent interaction, because in a real solution the first-solvation-sphere solvent molecules populate compromise positions not only based on optimizing their interaction with the solute but also based on not disrupting the solvent–solvent network too much.

**Enzymes.** Reactions in enzymes share some features of reactions in liquid solutions, but they also have many important differences.<sup>140</sup> In particular, enzymes do not provide a homogeneous environment, and in this respect they are sometimes more like reactions at rigid interfaces. For enzyme reactions, good results have been obtained by using ensemble-averaged variational TST with multidimensional tunneling.<sup>240</sup> To use this method, one first defines a reaction coordinate leading from reactants to products. Then one finds a variationally best transition state along this coordinate, where the variational transition state minimizes the reactive flux averaged over a whole ensemble at a given temperature; this transition state is a compromise to yield the best result that can be obtained by using a single transition state for the whole ensemble. Next one selects several reaction paths that go through various members of the ensemble of transition structures, and for each of these one calculates a transmission coefficient. Each of the path-specific transmission coefficients accounts, for that path, for tunneling and for recrossing of the compromise transition state.<sup>241</sup> One finds quite a large variation in these path-specific transmission coefficients<sup>242</sup> (a feature that should be amenable to study by single-molecule kinetics<sup>243</sup>). Averaging these variations gives the final transmission coefficient for the calculation.

Kinetic isotope effects are widely used as a mechanistic probe in enzyme kinetics, for example, for identifying the slow step in a mechanism, and good agreement with experiment has been obtained for quite a few kinetic isotope effects,<sup>240,242,244</sup> including some that were essentially impossible to obtain by

one-dimensional tunneling models<sup>245</sup> and including the temperature dependence of kinetic isotope effects.<sup>246–248</sup>

**Free Energy Surfaces.** One important quantity for studying complex reactions is the potential of mean force (PMF), also called a free energy surface (FES), a free energy landscape, or a mean-field potential. This important concept, although it will surely be more widely appreciated in the future, will not be known to all readers, so we provide a simple explanation. First one singles out the degrees of freedom of explicit interest, these can be called the primary degrees of freedom; they might, for example, be any pair of two coordinates or all the coordinates of the reactant. The remaining degrees of freedom constitute the secondary subsystem; this could include most of an enzyme and the solvent. The PMF involves an ensemble average over the secondary subsystem such that it represents a free energy with respect to that subsystem but an ensemble-averaged potential energy for the primary system. The gradient of the PMF represents the mean force on the primary subsystem, averaged over the environment. This is not quite what one wants; one wants to carry out dynamics on the true PES and average the dynamics. But the minima of the PMF do give information about the ensemble-averaged geometries of the primary system under the influence of the secondary one, and the saddle points of the PMF give one all the information one needs to carry out TST,<sup>249</sup> and that can be very accurate. In fact, in complex condensed-phase systems (such as enzyme-catalyzed reactions), it is very common to report a phenomenological free energy of activation rather than the actual rate constant since, at least when TST without a transmission coefficient is valid, they provide equivalent information. When a dynamical calculation such as tunneling is included in a transmission coefficient, it is an additional, but well-defined, approximation to calculate the tunneling from the FES rather than to calculate an ensemble of dynamical events, each governed by the PES along its specific path, and then average the dynamics. [This is called the zero-order canonical mean shape (CMS-0) approximation.<sup>250</sup>]

A recent discussion<sup>219</sup> of FESs attempted to elucidate their fundamental role in condensed-phase chemistry as the analogue of PESs in gas-phase chemistry—with special emphasis on their relationship to the quantities calculated by continuum solvation models. With continuum solvent calculations, the FES is calculated directly; the concept is equally applicable to a calculation where the whole system (e.g., solvent) is treated explicitly, but in such a case it must be obtained by explicit ensemble averaging.<sup>251–260</sup>

An important question when considering free energy landscapes is the selection of the coordinates used as primary coordinates for the FES. In some cases multiple reaction paths can be projected into a single one using collective coordinates (such as, for example, coordination numbers), and this approach, which has a history dating back to the Marcus theory of weak-overlap electron transfer,<sup>7</sup> is becoming popular in wider context.<sup>261–269</sup> When the number of degrees of freedom on which the PMF depends is taken as just one, the FES reduces to a free energy profile (or generalized free energy of activation profile) and the single coordinate is usually called the reaction coordinate. The choice of reaction coordinate for complex reactions has been widely discussed.<sup>270–272</sup> In enzyme reactions in particular, there has been considerable discussion of the extent to which the enzyme and solvent degrees of freedom participate in the reaction coordinate.<sup>140,272–276</sup> An important finding is that one can obtain similar results with

atom transfer coordinates and with collective coordinates based on an energy gap.<sup>273</sup>

Since free energy is a thermodynamic concept it is clearly incompatible with nonequilibrium distributions. Transition state theory rests on a quasiequilibrium assumption by which the transition-state region is in quasiequilibrium with reactants, even if products are not in equilibrium with reactants. [The “quasi” qualifier in “quasiequilibrium” is necessary both because a transition state, having one degree of freedom missing, is not a thermodynamic species and also because the product is not necessarily at equilibrium.] The question of the choice of primary coordinates (or, when there is only one, of the choice of reaction coordinate) is perhaps best illustrated by discussing the meaning of what is often called “nonequilibrium solvation.”<sup>140</sup> Suppose that we have a system with a quasiequilibrium distribution in the transition-state region, and we define a transition-state dividing surface that is imperfect, i.e., the flux through this surface toward the products is not the same as the net reactive flux. The definition of the transition-state dividing surface is equivalent to locally defining a reaction coordinate, since the reaction coordinate is the degree of freedom missing in the surface (i.e., the degree of freedom normal to the surface); the fact that the transition-state surface is imperfect means that the reaction coordinate is imperfect, and we need to use additional coordinates to define a more perfect dividing surface. If we cannot achieve a sufficiently perfect dividing surface without using solvent coordinates (for example, a coordinate involved in a hydrogen bond to the solvent), the situation is called nonequilibrium solvation. Why? The phase space distribution is still at equilibrium in the transition-state region (by hypothesis in this example), but the distribution of trajectories that contributes to the net reaction rate is less than the full distribution; i.e., it does not correspond to an equilibrium distribution because of coupling of the reactive solute to the solvent. Sometimes the dividing surface can be made much closer to perfect by adding one collective solvent coordinate to one solute coordinate.<sup>277,278</sup>

An example of a system where the free energy landscape was used to elucidate the dynamics is the enzymatic hydrolysis of glycosidic bonds by glycosidases.<sup>279</sup> This problem provides a good example of how mechanistic explanations must start with mapping out reactant conformers (different in the enzyme–substrate complex than in the free molecule) and determining reaction paths (again in the presence of environmental influences, in this case enzyme and solvent) before rate calculations can even be contemplated. The PMF in this case has been mapped by the method of metadynamics,<sup>280</sup> another example of rare-event sampling. Another recent example of the power of the metadynamics approach is the study of the aggregation process of a segment of an intrinsically disordered protein involved in Alzheimer’s disease.<sup>281</sup>

Although coarse-grained methods are very important and are sure to get more important, what is happening in parallel is that some processes once amenable only to coarse-grained simulation are now being attacked by all-atom simulation. An example is provided by the recent work of Choubey et al.,<sup>282</sup> who calculated the rate constant for cholesterol flip-flop in a dipalmitoylphosphatidylcholine bilayer and the time for transport across the bilayer by all-atom simulation.

**More on Tunneling.** There is considerable recent interest in tunneling in organic chemistry—both in solution and in low-temperature matrices—and in enzymes,<sup>48,240–242,244–248,274,283–286</sup> e.g., highlighting the impor-

tance of tunneling in the control of reaction pathways<sup>283</sup> and in the enhancement of low-temperature reaction rates.<sup>285</sup> Several aspects of tunneling that are well known from extensive physical chemical studies are sometimes re-emerging under this broader attention. For example, we have enough experience to know that any hydrogen atom transfer reaction, proton transfer reaction, or hydride transfer reaction with a barrier of several kcal/mol or more is probably dominated by tunneling at room temperature. We know that tunneling may increase such rate constants by factors as small as  $\sim 2$  or as large as a couple of orders of magnitude at room temperature and by much larger factors as temperature is lowered. We know that tunneling leads to a lowering of the Arrhenius energy of activation (defined as the local slope of an Arrhenius plot), and the Arrhenius energy of activation may vary greatly with temperature,<sup>115,116,287–290</sup> but it only becomes zero (temperature-independent rate) at very low temperature<sup>291,292</sup> ( $\lesssim 10$ – $50$  K). We know that a tunneling reaction proceeds by a combination of classical motion up to some pretunneling geometry, followed by the actual tunneling event, and an ensemble of isotope-dependent pretunneling geometries may be involved,<sup>242,293,294</sup> there are quasiclassical kinetic isotope effects involved in reaching the pretunneling geometry and isotope-dependent tunneling probabilities involved in motion along the tunneling path. There is no reason to assume that tunneling is qualitatively different in the gas phase and in condensed phases.<sup>274,295</sup>

A seemingly controversial issue is whether tunneling contributes to catalysis. Catalytic reactions are often so slow in the absence of catalysis (“enzymes differ enormously in the rate enhancements ( $k_{\text{cat}}/k_{\text{non}}$ ) that they produce, ranging from  $10^7$ -fold to  $10^{19}$ -fold”<sup>296</sup>) that the uncatalyzed reaction is unobserved or proceeds by a different mechanism, so the actual “speedup” of a catalytic reaction is often based on theory. But if room temperature tunneling enhances reaction rates by at most a few orders of magnitude, it cannot be responsible for speedups greater than that, and in fact, since tunneling would also contribute to the uncatalyzed reaction, the catalytic speedup effect of tunneling could be smaller than the speedup of the uncatalyzed reaction. Would we expect the catalyzed reaction to have more or less tunneling than the uncatalyzed one? Since higher barriers tend to be thinner, tunneling might usually enhance the uncatalyzed reaction to a greater extent if the mechanism and number of intermediates do not change, but certainly if one considers the wide diversity of catalytic reaction mechanisms, one expects that both situations will be found. In any event, the more important goal is probably to understand the catalyzed reaction than to compare it to a hypothetical uncatalyzed one, and since many catalyzed reactions involve proton, hydride, or hydrogen transfer, one must include tunneling in a realistic treatment.

#### 4. COMPLEX DYNAMICS OF BIOMOLECULES

Proteins play a central role in biology, acting as catalysts, sources of molecular recognition, and structural elements, among many other roles. However, before they can carry out these functions, proteins must first assemble themselves, by folding into their biologically functional or “native” state.<sup>297</sup> We have already discussed in section 3 some of the complications one encounters in studying proteins, in particular in enzyme kinetics. In enzyme kinetics the protein serves as a scaffold and active environment for chemical reaction, and an important aspect of current research is understanding and even quantifying how enzyme motion affects the kinetics. When



we consider protein folding, a motion involving all the atoms of the protein becomes a relevant degree of freedom. The natural question is, what is the mechanism of protein folding? Answering this question would be a resolution to a “grand challenge” problem in molecular biophysics, and protein folding has received considerable theoretical and computational attention, with many reviews available.<sup>298–301</sup>

Since proteins are polymers consisting of dozens to thousands of amino acids, folding must overcome an enormous amount of conformational entropy, and the fact that proteins self-assemble to an essentially unique fold is a triumph of natural selection. Furthermore, understanding how proteins fold has emerged as a central part of understanding the molecular mechanism of many diseases, such as Alzheimer’s disease or Huntington’s disease, where it is believed that incorrect folding of proteins (misfolding) is a critical part of the disease pathology.

The biophysical and biomedical aspects of protein dynamics have created many challenges. First, even small changes, such as a mutation of a single amino acid, can lead to changes in protein dynamics. Moreover, studying protein dynamics experimentally is fraught with many difficulties, given the stochastic and heterogeneous nature of an ensemble of folding proteins. Beyond studying protein folding, protein dynamics within the native state is often critical for function, yet it too shares the challenges of sensitivity to details, long time scales, and complex dynamics, making protein folding a useful model system for protein dynamics more generally. As self-assembly is at the heart of many biological processes as well as the inspiration for much of modern nanotechnology, understanding how proteins fold can also have an impact on many other fields, and the methods used can serve as a paradigm for tackling complex problems in kinetics.

These challenges suggest an opportunity: *simulating* protein dynamics as a means to gain new insight into this challenging problem.<sup>302</sup> We wish to use theory and simulations to understand folding at the atomic scale. Ideally, simulations can shed new insight into how proteins fold and suggest new hypotheses, as well as suggest new interpretations of experiments. When tightly combined with experiments, simulations and the theory they engender have the hope of addressing these questions in chemical detail. Our goal in the present section is to present a focused review of some recent efforts in atomistic simulation, especially as they connect to simulation-parametrized master equations.

There are three primary challenges in any simulation; two of them have been seen already in the previous sections of this Perspective, and the progress on the third is the main focus of the present section. First, is our model for the PES (whose gradient field is the “force field” that governs the dynamics) sufficiently accurate to predict the behavior of interest? This has been a challenge since the beginning, but recent work has suggested that current force fields are sufficiently accurate for the quantitative prediction of a wide-range of bimolecular properties, but with certain known limitations.<sup>303</sup> Second, can one simulate the time scales relevant for the phenomena of interest? This too has been a central challenge, since until recently, experimentally relevant time scales (microseconds to milliseconds) could not be reached with modern computer power using sufficiently accurate, atomically detailed models. Finally, a third challenge arises now that one can simulate long time scales with sufficiently accurate models: how can one use the resulting sea of data to gain some new insight? With the

first two challenges now within reach for protein dynamics on the millisecond time scale, the third challenge of gaining new insight has come into the forefront, and we will discuss it here in terms of a case study involving protein dynamics.

The end goal of a simulation of protein folding is the elucidation of the mechanism by which a protein folds, i.e., what are the steps a protein takes in assembling itself, and what are the rates of these steps? There are several questions associated with this, including the following:

**Does Protein Dynamics Occur along a Single Pathway or along Many Parallel Paths?**

This kind of question has already been discussed in earlier sections; it is relevant here both for the basic biophysics of protein folding and for protein dynamics.<sup>304–307</sup> This question also has important biological significance. For example, consider the biochemistry of chaperonins, which are proteins that catalyze the folding of some protein substrates.<sup>308</sup> If folding occurs via a single, well-defined path, then catalysis could naturally take the form of the recognition of some well-defined transition state in the folding process. If folding occurs via multiple paths, then the resolution of the mechanism of catalysis is considerably more complex.

**What Is the Role of Non-native Interactions?** Current wisdom<sup>306,309,310</sup> suggests that protein folding is dominated by native interactions, which suggests that simpler models (known in the literature as “structure-based models”, “native-centric models”, or Go models<sup>311</sup>) can be predictive of folding behavior;<sup>312</sup> these models work by creating a new Hamiltonian that is dictated not by the physical interactions of atoms but by whether the specific amino acids in contact are present in the native state. The presence of significant non-native interactions would suggest new insight and new challenges for understanding folding.<sup>313–315</sup>

**Are There Intermediates Involved with Native Conformational Dynamics and Protein Folding?**

A common paradigm in the protein folding field is that simple proteins fold in a “two-state” manner, i.e., with just the unfolded and folded states and no intermediates between them.<sup>307,316–320</sup> Another way to state this question is, is there a separation of time scales between the slowest time scale (corresponding to folding) and the next slowest time scale, and is this gap large compared to the folding time itself (for a “two-state” system) or not? Simulations can help probe this hypothesis in a way that experiments cannot, due to their limitations in what they can measure.

**Is the Mechanism Robust?** The entire discussion of a “mechanism” of a given type of protein dynamics is hinged on the concept that the mechanism is robust to subtle changes in the environment (pH, temperature, cosolvents, etc.) as well as to variations in the force fields used to simulate protein dynamics. Mechanistic properties that are robust have the possibility of being compared to experiment in the least ambiguous way, whereas mechanistic properties that are not robust raise the possibly illuminating question of why not.

**Can We Use Markov State Model (MSM) Approaches To Simulate Long Time Scale Dynamics?**

Recently, discrete-state master equation or Markov state models have had success at modeling long-time statistical dynamics.<sup>321–323</sup> In these models, metastable conformational states are identified such that the intrastate dynamics are much faster than interstate dynamics (so the time evolution is Markovian). Transition rates between the states are estimated from MD simulations. If the model is shown to self-consistently statistically recapitulate the dynamics of the trajectories from which it was constructed, it

can be used to simulate the statistical evolution of a non-interacting ensemble of molecules over much longer times than the lengths of the individual trajectories from which it is constructed. Experimental observables can be computed directly from MSM probability-weighted linear combinations of the observables of each state, and direct comparison with experimental data can be carried out.<sup>324–326</sup>

With all of its promise, the key challenge in MSM construction is its computational demands. Practically, constructing an MSM requires two steps. First, one must generate a state decomposition; i.e., one must cluster structures into states that are kinetically connected (not just geometrically similar). Second, one must sample the transition probabilities  $p_{ij}(\Delta t)$ , i.e., the probability of starting at state  $i$  and ending at state  $j$  in a time  $\Delta t$ . As detailed below, adaptive approaches can dramatically aid in both of these steps: one runs simulations only where needed (e.g., as dictated by link between the uncertainty in observables of interest and sampling from specific states). The application of adaptive sampling,<sup>327</sup> combined with graphics processing units (GPUs),<sup>328,329</sup> and distributed computing<sup>330</sup> is particularly powerful, enabling simulations on millisecond to second time scales.

**What Insights Are Gained by Direct Simulation of Protein Folding?** Given that the sampling at millisecond time scales has only been possible since 2010, our investigations into protein dynamics using all-atom MD are still at very early stages. Despite this relative immaturity, atomistic simulation has already begun to influence our view of protein folding. Detailed comparisons to experiment have been performed for many specific proteins. With the ability to simulate proteins which fold on long time scales (milliseconds) and for nontrivial sizes (approaching 100 amino acids), MSM simulations have the hope to shed new insight into how proteins fold. Below, we summarize three key results that have been seen so far.

**Proteins Fold via Parallel Pathways Comprised of Metastable States.** One of the principal results we have seen is that the mechanism of protein folding appears to involve the interconversion of many metastable states. While an overall reaction may be dominated by a single slow time scale, leading to apparent “two-state” folding, more microscopically, folding looks much more detailed and complex. Where does this complexity go when examined experimentally? This complexity easily can be hidden when projected onto a given reaction coordinate.

For example, consider Acyl-CoA binding protein (ACBP), which folds on the 10-ms time scale.<sup>315</sup> While the MSM is complex, comprised of numerous states, ACBP appears to be only a three-state folder experimentally. However, when the MSM is projected onto the committor (an idealized reaction coordinate<sup>331</sup>), we see that the MSM simplifies to look very much like a three-state folder. This also opens the door to folding simulations helping to identify new experiments that can more readily reveal this complexity.

**These States Have Non-native Structural Elements: Register Shifts and Intramolecular Amyloids.** With the illumination of these metastable states, one can interrogate the structural nature of these states to gain new insight into how proteins fold. One general property observed is that these states have an abundant degree of non-native structure. In particular, there are three forms of non-native structure that seem particularly common:

First, in  $\beta$  sheet proteins, we often see states register shifts. In these cases, the natural turn of a  $\beta$  sheet is misplaced, leading to

a different  $\beta$  sheet structure. As turns can be formed in many places, sequences permit this reasonably easily in many cases.<sup>332</sup> Second, we often see elongated helices. In this case, a helix in a given intermediate state may be longer than in the native state. This is also natural given the commonality of helical propensity in amino acids, even in cases where the structure is not a helix natively. Finally, and perhaps most strikingly, we have seen intramolecular amyloids—cases where  $\beta$  sheets form in  $\alpha$ -helical proteins. This formation is not unlike the formation of intermolecular amyloids, where proteins spontaneously form  $\beta$  sheet structures. Once a protein gets to be sufficiently long, it can be argued that it can act in the same fashion intramolecularly.

**The Connectivity of These States Suggests That the Native State Is a Kinetic Hub.** Finally, how are these states “connected”; i.e., what are the nonzero conditional probabilities to go from one state to another? Addressing this question yields another aspect of the mechanism of protein folding. In MSM studies of protein folding, the native state has appeared to be a kinetic hub,<sup>333,334</sup> defined as a state into which there are relatively many paths, compared with other states. This particular pattern is common in other types of networks,<sup>335</sup> and this suggests that the intrinsic kinetics of protein folding may have been evolutionarily optimized for kinetic properties including the kinetic network.

**Can We Formulate an Analytic Theory of Protein Folding?** Given that MSMs are equivalent to numerical master equations, it is natural to use the insight gained from MSMs to construct master equations as models of protein folding, and indeed there is a distinguished history of master equation studies of protein folding.<sup>336–343</sup> Recent simulations have been able to give new insight into the key challenges of master equations for this problem: how to define states and determine the rates between them. One ultimate goal of computational master equation approaches is the hope for these models to give insight into analytic master equations. This has recently been done, yielding analytic theories that are able to capture the richness described above as seen in computational models.<sup>344,345</sup> In this way, MSM approaches have been very useful in making the connection between large-scale simulations and analytic theory.

## 5. CONCLUDING REMARKS

We have seen a progression in emphasis as one proceeds from gas-phase reactions, to molecular reactions at interfaces or in solution or enzymes, and finally to reactions such as protein folding that involve a large number of atoms in the reaction coordinate itself.

For the gas-phase reactions, the master equation with pressure-dependent equilibration steps as well as elementary reaction steps provides a widely applicable framework, and the emphasis is on improving the individual reaction rate predictions. Dynamical theory has advanced to the point where the ability to obtain realistic potential energy surfaces and to interface them efficiently to dynamics calculations (by general parametrization, by specific-reaction fitting, or by a dedicated strategy) often forms the chief hurdle to progress. Thus detailed discussion of PESs and the electronic structure calculations or empirical parametrization procedure that generates them becomes an inescapable part of any modern discussion of dynamics and rate theories, and we have seen that in the work discussed.

Great advances in theoretical electronic structure methods and dynamical studies, along with advances in experimental dynamics, have opened the door to new capability for theoretical kinetics methods to treat far more complex problems than hitherto possible, at the same time revealing interesting and sometimes unanticipated aspects of chemistry, such as the importance of roaming transition states.

As we move to the condensed phase or realistic interfaces, a catalog of elementary reaction steps usually becomes impossible to achieve, and the emphasis switches to some extent from the mechanics of reaction steps to the statistical mechanics of ensemble averaging, but the accuracy of the same quantities that occur in the gas phase, such as barrier heights and reaction energies, can still be the dominant factor in controlling the accuracy of the ultimate predictions. One key theoretical construct that encapsulates both the reaction mechanics and the ensemble averaging is the PMF, which essentially replaces the PES of the gas-phase cases. The PMF assumes that the environment is equilibrated to the reaction center, and the errors incurred in this assumption can be minimized by considering a larger subsystem as the active reaction zone; in some sense this is an analogue of including nonequilibrium distributions (low-pressure effects) in gas-phase reactions.

A noteworthy aspect of the above discussion is how concepts arising in one branch of kinetics reappear in another. For example, master equation models have been used to explain state-specific energy flow, reaction mechanisms with multiple wells that correspond to different bonding patterns or different conformations, or protein dynamics involving more complicated collective states, and there is also a strong analogy to kinetic Monte Carlo methods. Methods called lumping in some contexts<sup>26</sup> reappear in others<sup>346</sup> as clustering of protein structures. Potential energy surfaces, multiple structures, multiple transition states, multiple pathways, multiple time scales, and tunneling are practical issues that also occur repeatedly.

At the present time, theory and simulation have passed from simply explaining experimental observations to suggesting new experiments and in some cases even replacing experiment as our primary source of knowledge about certain rates and mechanisms. The overriding challenge is extending theory and simulation to more and more complex processes and in ways that are more and more accurate. We hope that this Perspective has conveyed some of our excitement at the progress being made.

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