



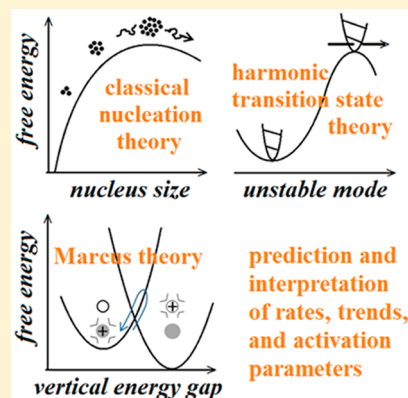
# Common Features of Extraordinary Rate Theories

Baron Peters<sup>\*,†,‡</sup>

<sup>†</sup>Department of Chemical Engineering, University of California, Santa Barbara, California 93106, United States

<sup>‡</sup>Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States

**ABSTRACT:** We examine the capabilities and foundations of three landmark rate theories: harmonic transition state theory, classical nucleation theory, and the Marcus theory of electron transfer. Each of the three classic rate theories is widely used to *predict rates and trends*. They are also used “in reverse” to *interpret* experimental data with no computation at all. Their common foundations include a quasi-equilibrium assumption and dimensionality reduction to a physically meaningful, one-dimensional, and broadly applicable reaction coordinate. Many applications lie beyond the scope of the classic theories, so rare events research has pursued trajectory-based methods that efficiently predict accurate rate constants even when the reaction coordinate and mechanistic details are unknown. Trajectory based rare events methods achieved these ambitious goals, but (by construction) they provide rates rather than mechanistic understanding. We briefly discuss recent efforts to identify reaction coordinates, including methods which provide abstract statistically defined coordinates and those which identify physical collective variables. Finally, we note some natural synergies between existing simulation methods which might help discover simple and powerful quasi-equilibrium theories for the many applications that fall beyond the scope of the classic rate theories.



## INTRODUCTION

The theory of rare events concerns the flux through rarely visited bottlenecks in the phase space of a dynamical system.<sup>1–3</sup> In chemistry and physics, the theory of rare events provides a common framework for understanding many activated processes that are associated with rate constants. Examples include chemical reactions which proceed through rare transition states,<sup>4</sup> nucleation which proceeds through rare critical nuclei,<sup>5</sup> and electron transfer which proceeds via rare solvent preorganized donor–acceptor pairs.<sup>6</sup> For the discussion in this paper, we group theories and computational methods for studying activated processes into three categories: empiricisms, theoretical models, and trajectory-based rare events methods.

As for most branches of science, the earliest advances were empiricisms. Students of chemistry and engineering learn that the Arrhenius law<sup>7</sup> ( $k = A \exp[-E_a/k_B T]$ ) describes the temperature dependence of reaction rate constants. The Arrhenius law was (and still is) widely used to interpret experimental reaction rates. It remains particularly valuable for summarizing the temperature dependence of complex multistep reactions where the mechanisms are unknown. However, the correspondence between Arrhenius parameters (prefactor  $A$  and activation energy  $E_a$ ) and molecular properties<sup>8</sup> is not adequate for first-principles prediction. Thus, the Arrhenius law is primarily useful for interpretation.

Theories with superior predictive power emerged in rapid succession during the decades following Arrhenius' work. Enduring contributions from this era include Smoluchowski's theory of diffusion control,<sup>9</sup> the classical nucleation theory (CNT),<sup>10–12</sup> the theory of mean first passage times (MFPTs) by Pontryagin,<sup>13</sup> transition state theory (TST),<sup>14–18</sup> Kramers

theory,<sup>19,20</sup> RRKM theory,<sup>21–23</sup> and Marcus theory.<sup>6,24</sup> Each of these theories emerged from efforts to eliminate empiricisms in their respective domains. Each was built upon a simple flux-over-population<sup>25</sup> model of the molecular-level physics which enabled quantitative (but not always accurate) predictions. Several of the theories from this area have particularly strong connections to experiment. Additionally, these theories inspired an extensive computational apparatus including transition state search algorithms,<sup>26–30</sup> importance sampling methods for computing free energy barriers,<sup>31–34</sup> and kinetic Monte Carlo algorithms for using predicted reaction rates to simulate reaction networks.<sup>35,36</sup>

A third branch of rare events research began in the late 1970s with the reactive flux formalism<sup>37,38</sup> and Grote–Hynes theory.<sup>39–41</sup> These frameworks advanced our understanding of transmission coefficients by making direct use of dynamical trajectories and time correlation functions. Apart from force-field limitations, these theories showed how short dynamical trajectories could provide essentially exact rates *even when used with inaccurate dividing surfaces*.<sup>41,42</sup> The reactive flux approach inspired methods like transition path sampling (TPS),<sup>43–45</sup> transition interface sampling (TIS),<sup>46–49</sup> and forward flux sampling (FFS)<sup>50–52</sup> that yield rate constants directly from path-space umbrella sampling procedures with no dependence on any assumed reaction coordinate.

Additionally, there has been heightened interest in Markov state models (MSMs)<sup>53</sup> which essentially summarize all aspects

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of the natural dynamics in a discrete Markovian model.<sup>53</sup> The continuous counterpart to a discrete MSM is diffusion map<sup>54,55</sup> which also summarizes the complete dynamics in a Markovian model.<sup>54</sup> MSMs and related methods directly use dynamical trajectories, but they do not focus specifically on dynamical bottlenecks. Most MSMs and diffusion maps have been constructed from long unbiased trajectories. These approaches are best suited for conformational transitions in biomolecules where barriers are often small. However, there are ongoing efforts to incorporate importance sampling ideas for the construction of MSMs and diffusion maps.<sup>56,57</sup> These new methods will extend the scope of MSMs and diffusion maps to processes with free energy barriers much larger than  $k_B T$ .

The early empiricisms, the classic rate theories, and trajectory-based computational methods are all important in modern theoretical research on rare events and kinetics. Each group of theories and methods has its advantages and disadvantages. Empiricisms like the Arrhenius law are useful models for many complex phenomena but limited in their ability to provide molecular level insights. Modern trajectory based rare events methods provide accurate rates and exquisitely detailed paths, but the insights gained from simulations at one condition are not easily generalized to other conditions. The classic theories are easily and frequently connected to experiments, but they require a precise understanding of the mechanism. This article examines some shared characteristics of those most enduring and versatile of the classic rate theories. Our observations suggest natural synergies between theoretical analyses and trajectory based methods that might help discover more of these simple, powerful, and generalizable rate theories.

## ■ COMMON FEATURES OF THE CLASSIC THEORIES

The term “rare event” refers to a time scale separation:<sup>37</sup> the long time scale is that between reaction events, and the fast time scale is that for molecular relaxation following activation. Time scale separation poses an insurmountable problem for standard brute force simulation, but rare events simulations exploit the time scale separation and turn it into a computational advantage. Time scale separation allows the system to visit a representative sample of equilibrium reactant states before escape to the product state. Accordingly, CNT, TST, MFPT, Kramers theory, and Marcus theory all assume a nearly equilibrated distribution of reactants. For this reason, we refer to all of them as quasi-equilibrium (QE) theories. When barriers are much larger than  $k_B T$ , these theories can predict nonequilibrium rates and fluxes entirely from equilibrium properties.

This article focuses on three classic QE theories which stand out for their tremendous impact on later experimental and theoretical work: harmonic TST,<sup>14–16</sup> CNT,<sup>10–12,58,59</sup> and Marcus theory.<sup>6,24,60</sup> These classic theories differ in many details. For example, transition state theory (TST) takes the equilibrium assumption farther than the others, assuming equilibrium extends from reactants to the transition states.<sup>14,15</sup> Each of the three classic theories makes different assumptions about the dynamics of passage through the transition state. CNT invokes a generalized diffusion along a nucleus size coordinate,<sup>5</sup> TST invokes ballistic crossing of the transition state,<sup>14</sup> and Marcus theory invokes a nonadiabatic transition between diabatic free energy surfaces.<sup>6</sup> Despite their differences, there are some profound similarities between harmonic TST, CNT, and Marcus theory.

- **Theoretical predictions:** The classic theories can (approximately) predict rates. As for other methods, inaccuracies in the predicted rates are primarily caused by inaccuracies in the molecular potential energy surfaces.

There is nothing especially remarkable about predicting absolute rates. Any *bona fide* rate theory, often even  $\mathbf{f} = \mathbf{M}\mathbf{a}$  given a sufficiently long trajectory, can predict rates.

- **Physical activation parameters and kinetic trends:** The classic theories identify activation parameters that allow direct prediction of kinetic trends from a single calculation. For example, the activation enthalpy  $\Delta H^\ddagger$  and entropy  $\Delta S^\ddagger$  in harmonic TST allow a single calculation to predict rates at many temperatures ( $T$ ) via  $k_{\text{TST}} = (k_B T/h) \exp[\Delta S^\ddagger/k_B] \exp[-\Delta H^\ddagger/k_B T]$ . Similarly, the reorganization energy  $\lambda$  and the coupling strength  $|V_{12}|$  predict the electron transfer rate at many electron transfer driving forces ( $\Delta G$ ) via  $k_{\text{ET}} = k_0 \exp[-(\lambda - \Delta G)^2/4\lambda k_B T]$ , where  $k_0$  depends on  $|V_{12}|^2$ . Finally, the barrier parameter  $4(\beta a \gamma/3)^3$  and the attachment frequency  $\nu_{\text{attach}}$  predict nucleation rates at many supersaturations ( $S$ ) via  $J = J_0 \exp[-4(a \gamma/3 k_B T)^3/\ln^2 S]$ , where  $J_0$  depends on  $\nu_{\text{attach}}$ .

In comparison to trajectory based methods, the classic rate theories more naturally and directly predict kinetic trends. Of course, one can exhaustively identify trends from a series of trajectory-based calculations at different conditions, but the emerging trend would provide no more insight than an empirical correlation. Additional analyses, and particularly a simple model, would be needed to *understand* the observed trend. Such thorough analyses have occasionally been done,<sup>61</sup> but all too often there is no subsequent effort to identify or explain trends. What significance can be ascribed to a single rate prediction at one condition? When the rate agrees with experiment, one hopes that the right answer was obtained for the right reasons and not from a fortuitous cancellation of errors. When a computed rate disagrees with experiment, one hopes the reason is a minor flaw in the force field and not a more serious problem. Even with robust force fields and the most powerful trajectory based methods, one can still make errors, e.g., by computing rates for the wrong nucleation process, by omitting the most important active sites, by treating a solvent that participates in the reaction as an inert medium, by neglecting strong finite size effects in nucleation, etc. These serious errors can corrupt predictions of both trends and absolute rates. The danger in predicting only the absolute rates is that one *expects* rates to be inaccurate, so serious errors might go unnoticed. Such errors are more likely to be noticed if one also predicts trends.

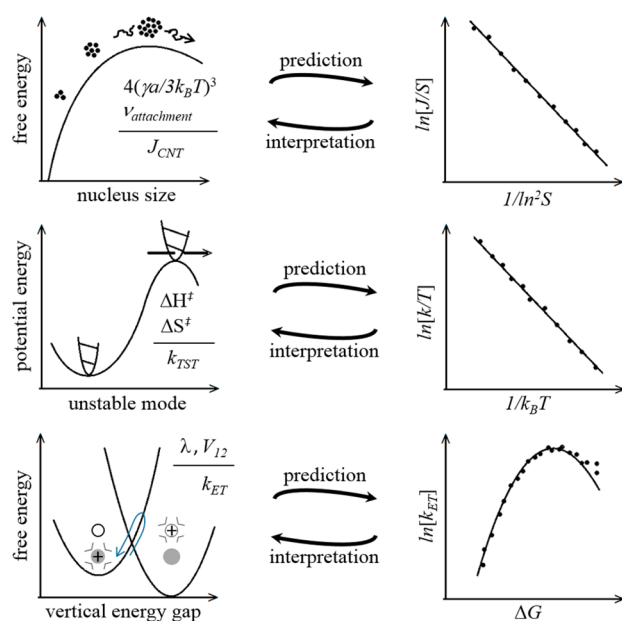
- **Corollary theories:** Because the activation parameters in harmonic TST, CNT, and Marcus theory are thermodynamic quantities associated with specific physical processes, one can construct auxiliary theories to predict and/or interpret the effects of variables that do not explicitly appear in the rate expressions.

There are many examples of these corollary theories, particularly in efforts to engineer catalysts, nucleants, and electrochemical systems to control the kinetics of complex processes. Frequently, these corollary theories are used in “ $\Delta\Delta G^\ddagger$ ” calculations, where  $\Delta\Delta G^\ddagger$  is the change in an activation parameter due to changes in quantities that do not explicitly appear in the rate expression. For example, ionic

strength and pH may influence reaction rates depending on the charge and protonation state of the transition state.<sup>62,63</sup> Additives may enhance nucleation rates depending on their affinity for the nucleus–solution interface.<sup>64,65</sup> A few self-exchange electron transfer rates can be used to predict the rates of electron transfer between many heteroion pairs.<sup>66,67</sup> The corollary predictions, when coupled with experimental data, often provide important hints about the mechanisms of new reactions.

- **Theoretical reversibility:** The classic theories can be used “in reverse” to extract insights about the nature of the transition states directly from experimental data with no computation. Their simultaneous capacity for both prediction and interpretation sets the classic theories apart from both empiricisms and trajectory based rare events methods.

This powerful capability gives the classic theories an unrivaled connection to experiment. Indeed, the classic theories are widely used in primarily experimental studies. Figure 1 shows a few of many ways the classic theories can help interpret experiments. More examples of their capacity for interpretation could be constructed from the corollary theories.



**Figure 1.** (Schematic) Classical nucleation theory (top), harmonic transition state theory (middle), and Marcus theory (bottom) are “theoretically reversible” because they can be used for predictions and for interpretation of experimental data. These theories have a unique ability to extract microscopic insights directly from the experimental kinetics. In each case, these capabilities stem from their use of a single physically meaningful reaction coordinate.

The ability to *predict and interpret kinetic trends* makes harmonic TST, CNT, and Marcus theory extraordinary. By comparison, the most powerful trajectory-based methods for computing rates can only predict trends by performing separate simulations at a series of temperatures, concentrations, ionic strengths, etc. Interestingly, a common feature at the foundation of these three classic theories leads to their extraordinary capabilities.

- **One-dimensional and physically meaningful reaction coordinates:** The classic theories are each built around a

single physically meaningful reaction coordinate: an unstable vibrational mode, a cluster size coordinate, and a vertical energy gap, as shown in Figure 1. The reaction coordinates are specific and physically meaningful characteristics of the molecular configurations. At the same time, these reaction coordinates are broadly applicable to many reactions, nucleation processes, and electron transfer processes.

In each of the classic theories, the accurate reaction coordinate leads to a simple one-dimensional free energy profile, to a physical interpretation for the activation parameters, and to prefactors that depend only on dynamics in the immediate vicinity of the barrier top. In effect, these classic theories employ a reaction coordinate to achieve an incredible feat of coarse graining: a reduction from  $3N$  degrees of freedom to *one*, while preserving the thermodynamics, and *all consequential aspects of the dynamics*. The power of these classic theories shows that accurate reaction coordinates can do far more than maximize the efficiency of the free energy, transmission coefficient, and rate calculations.

Is it possible to translate these achievements to phenomena beyond the scope of harmonic TST, CNT, or Marcus theory? If simple and generalizable theories for new types of rate processes exist, they are likely to also be QE theories. The above considerations suggest that existing QE theories may be sufficient, and that we only need the mechanistic models and associated reaction coordinates to make progress. Let us examine this possibility by first discussing the scope of the QE theories.

## ■ SCOPE OF QE THEORIES

The central justification for using any of the QE theories (not just the three classics) is an adequate time scale separation. Time scale separation breaks down for processes with very small free energy barriers. In such cases, lifetimes of the reactants become dependent on detailed initial conditions and therefore no one rate constant can characterize their typical lifetimes. In certain cases, time scale separation can also break down for large barriers. For example, in the Berezhkovskii–Zitserman regime,<sup>68</sup> there are two important coordinates associated with extremely different mobilities. The mobility anisotropy becomes important when the fast variable is associated with motion over the barrier, i.e., along the minimum free energy path,<sup>69</sup> and the slow variable is associated with motion in an orthogonal direction. In this case, the slow variable appears frozen while the fast variable escapes over the barrier along a path that deviates widely from the minimum free energy path.<sup>68,70</sup>

Some processes do not have a true equilibrium distribution; e.g., some biochemical network models involve intrinsically nonequilibrium “creation” and “destruction” of species according to phenomenological rate equations.<sup>50</sup> Some of these processes may still be described by QE theories if one uses the stationary distribution in a flux-over-population approach.

Beyond the above fundamental limitations of the QE theories, there is a practical limitation. The QE theories require an accurate reaction coordinate. Reaction coordinates for harmonic TST,<sup>16</sup> CNT,<sup>10</sup> and Marcus theory<sup>24</sup> were prescribed by their discoverers, but reaction coordinates for many phenomena of current interest remain unknown. Frontier challenges include reactions in solution, reactions in enzymes,



catalysis with dynamically disordered metal clusters, etc. The unstable mode reaction coordinate that emerges from harmonic TST is often not applicable to these processes. However, there may be reaction coordinates and activation parameters for which generalized TST can describe chemical reactions in such complex environments.

Perhaps the most challenging situations arise in biomolecular processes. Consider the dock and lock steps in attachment of a monomer to a growing amyloid fibril. One expects MFPT<sup>13</sup> formalisms are applicable, but what coordinate should be used? Pontryagin's abstract formalism did not specify the coordinate. Several works have proposed using reaction coordinates in studies of protein folding.<sup>71–73</sup> Krivov and Karplus wrote:<sup>74</sup> "...to determine both the pre-exponential factor and the free energy barrier from simulations, it is necessary to have a method of constructing the one dimensional projected FES in terms of an appropriate reaction coordinate..." Folding usually involves two highly metastable states (folded and unfolded) that interconvert via many short-lived intermediates and pathways. MSMs overcome this complexity with a discretized state-to-state transition matrix,<sup>53,75</sup> and all pathways can be reconstructed from its spectrum of eigenvalues (time scales) and eigenvectors. There are now several procedures that project the intermediates onto *abstract* reaction coordinates with statistical definitions like the committor,<sup>76,77</sup> mincut coordinates,<sup>74,78</sup> diffusion maps,<sup>54,79</sup> or the slowest mode of the MSM.<sup>75,80</sup> Intriguing diffusion equations have been derived for the dynamics along these abstract coordinates.<sup>78,81</sup> However, *abstract* coordinates provide limited mechanistic insight for proteins that fold via a large ensemble of pathways and intermediates. Along separate folding pathways, structures with the same committor may have no common features other than the committor itself. *Physical* reaction coordinates that simultaneously describe each of the separate pathways have only been found for small proteins and simple models.<sup>72,82,83</sup> This has led both opponents and advocates of reaction coordinate approaches to express pessimism about the existence of a physical and "global" protein folding coordinate.<sup>84–86</sup>

For all of these frontier applications, the classic QE approaches are seemingly at an impasse. Fortunately for the QE theories, elusive reaction coordinates are becoming less and less elusive. The following section briefly outlines the modern suite of computational methods for applying QE theories to new problems.

## ■ MODERN COMPUTATIONAL APPARATUS FOR THE QE THEORIES

The sections above advocate a larger role for simple theoretical models in rare events research. Of course, simple theories would not diminish the present importance of computation. Indeed, computational applications of the classic theories drove tremendous efforts in computational method development. There are obvious computational needs for more accurate energy landscapes, but we leave this topic for the broader areas of molecular simulation and quantum chemistry. Here, we primarily focus on emerging rare events capabilities and long-term needs in rare events methodology. First, let us recount some of the established rare events methods that are often used in applications of the QE theories.

1. Transition state search algorithms<sup>26–30</sup> can efficiently identify saddle points on *ab initio* molecular potential

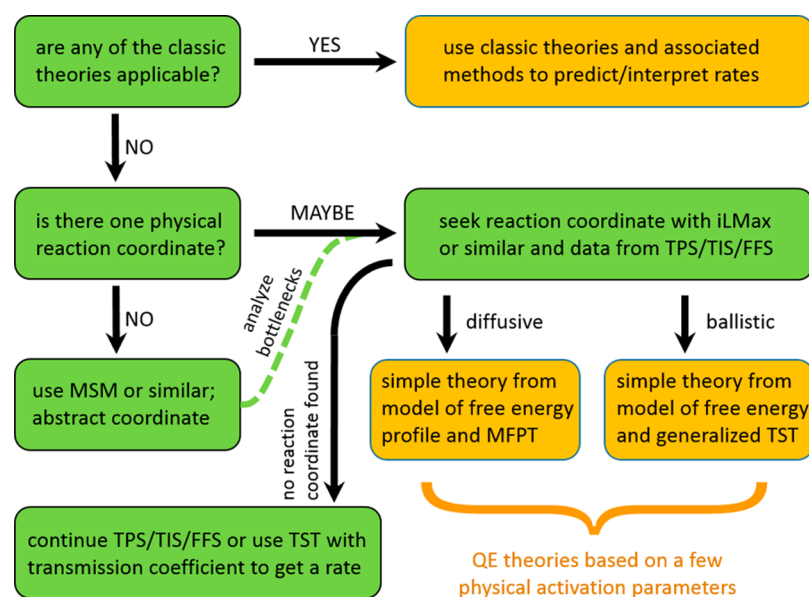
energy surfaces for applications of RRKM theory and TST. These algorithms have tremendously advanced our understanding of gas phase chemistry, heterogeneous catalysis, and processes like diffusion in solid-state materials.

2. Umbrella sampling and other importance sampling methods<sup>31–34</sup> were developed to compute free energy profiles for mean first passage times in applications like nucleation and biomolecular conformational transitions. Energy gap coordinates and empirical valence bond models<sup>87–90</sup> extended the scope of importance sampling methods to electron, proton, and hydride transfer processes.
3. Kinetic Monte Carlo and other stochastic simulation algorithms<sup>35,36</sup> can efficiently simulate the stochastic sequence of reaction events in complex reaction networks. These algorithms allow computed rates for elementary steps to be incorporated into dynamical models of larger scale reaction networks.
4. Alchemical transformations and/or thermodynamic perturbation theory<sup>91</sup> can be combined with CNT, TST, or Marcus theory to predict the corollary effects of nucleant additives, solvent effects, and substituent effects.

The computational procedures for applying the classic theories were profoundly influenced by the central importance of the reaction coordinate. For example, applications of harmonic TST rely upon algorithms that identify transition states and unstable mode coordinates *BEFORE* free energies and rates are computed. Similarly, computational studies of nucleation rely on accurate nucleus size metrics.<sup>92–96</sup>

How can these innovations be extended to new applications where the reaction coordinates are unknown? Du et al.<sup>83</sup> and Geissler et al.<sup>97</sup> introduced a simple (but expensive) committor test to gauge the accuracy of trial reaction coordinates. Coordinate validation procedures were a major advance, but to move beyond trial-and-error procedures,<sup>98</sup> one also needs an efficient method for *discovering* the reaction coordinate in a system with many degrees of freedom. In principle, variational TST can identify reaction coordinates for inertial barrier crossings,<sup>99,100</sup> but full variational optimizations remain elusive despite many efforts.<sup>41,42</sup> Similarly, variational theories can optimize reaction coordinates for diffusive barrier crossings,<sup>101</sup> but in practice, these again require *a priori* identification of the few most important degrees of freedom. How does one discover the few most important coordinates when there are hundreds or thousands of potentially important degrees of freedom?

Methods for discovering reaction coordinates<sup>72,85,102–106</sup> arose, somewhat ironically, from the path sampling methods which had been designed to circumvent the need for reaction coordinates. There are only a few performance comparisons for reaction coordinate identification procedures, but thus far, approaches that combine path sampling and likelihood maximization techniques appear to be the most efficient, reliable, and versatile.<sup>86,104,106,107</sup> These begin with data from TPS or TIS and then use likelihood maximization to construct a reaction coordinate from a database of candidate collective variables. Related procedures can be devised using FFS data.<sup>108</sup> The original TPS and TIS algorithms, the original likelihood maximization procedure, and the original coordinate validation tests have each been extensively documented elsewhere. Here we note some recent advances:



**Figure 2.** Roadmap for analysis of rates and mechanisms in rare events which starts in the upper left and, where possible, ends at a simple but accurate quasi-equilibrium theory. When a reaction coordinate cannot be identified, the roadmap still leads to accurate rates.

1. New TPS and TIS algorithms are more efficient and more broadly applicable than the original versions. New algorithms have been developed for diffusive dynamics,<sup>107,109,110</sup> for discrete dynamics of kinetic Monte Carlo,<sup>111,112</sup> and for microcanonical simulations of inertial barrier crossings.<sup>113</sup> Replica-exchange ideas have even allowed simultaneous sampling of landscapes with multiple intermediates and reaction channels.<sup>114</sup>
2. The new inertial likelihood maximization (iLMax) procedure<sup>106</sup> optimizes an inertial reaction probability<sup>39</sup> rather than the committor. iLMax outperforms the original likelihood maximization (oLMax) across the entire spectrum of dynamical barrier crossing regimes. Particularly for reactions in solution where there are many possible solvent coordinates and yet barrier crossings remain inertial,<sup>115</sup> iLMax appears to be a powerful and practical alternative to variational TST.<sup>41,42</sup>
3. A binomial deconvolution procedure dramatically reduced the cost of the committor test for coordinate validation.<sup>116</sup>

These powerful new methods can systematically optimize trial coordinates using a modest collection of transition path sampling data,  $\mathcal{O}(1000)$  transition paths. From each new system which is “solved”, we learn tricks which help tackle related problems. One hopes that we will eventually learn to anticipate which reaction coordinates are important for which types of processes. Already, coordinate identification and validation often requires less computation than some widely used rare events methods. Thus, for many problems, reaction coordinate identification is now a rather inexpensive preliminary step that pays dividends in mechanistic insight and in the computational efficiency of later tasks.

We stress that the new reaction coordinate optimization procedures are not always necessary. For some applications, one can immediately adopt an unstable mode, a vertical energy gap, or a nucleus size coordinate. Figure 2 shows a logical roadmap for analysis of rare events that uses the classic theories where they are applicable, and which may help discover powerful new theories where they are not. Figure 2 specifically

suggests iLMax for reaction coordinate identification because it additionally determines whether dynamics along the optimal coordinate are ballistic or diffusive. There are several alternative coordinate identification procedures, but the dynamical regime is important in formulating a quasi-equilibrium rate theory. For example, if barrier crossing is ballistic, one might construct a transition state theory, while if the barrier crossing dynamics resemble diffusion one might construct a theory for the mean first passage time.

Figure 2 also emphasizes some potential synergies between reaction coordinate approaches and trajectory based rare events methods. Consider, for example, the special cases where all protein folding trajectories proceed through a clear bottleneck step. For these special cases, Bolhuis and co-workers<sup>117–119</sup> have identified simple physical reaction coordinates. Mechanistic insight on the bottlenecks in an MSM might become useful for engineering conditions or mutations to change the folding kinetics, or in making generalizable predictions beyond the single condition at which the MSM was parametrized.

## ■ OUTLOOK AND NEEDS FOR THE FUTURE

Many modern rare events methods bypass the need for precise mechanistic understanding by using dynamical trajectories to directly generate rates. But are rates more or less important than mechanistic insights and simple theories? Marcus wrote “...as a percentage of total theoretical research effort, [analytical theory] is now small compared with computation. I believe the future can be expected to settle on some insightful combination of both, since both are necessary.”<sup>120</sup> In that spirit, this paper promotes a closer integration of simple theories and computational methods. This paper notes some common foundations and capabilities of three classic theories with tremendous achievements and longevity: harmonic transition state theory (TST),<sup>16</sup> classical nucleation theory (CNT),<sup>11,59</sup> and Marcus theory.<sup>24</sup> First, each of these three classic theories makes a *quasi-equilibrium* assumption for the reactants and identifies a few physical parameters that *predict* rates via free energy barriers and prefactors. Second, these classic theories can be used “in reverse” to *interpret* experimental data in terms of

microscopic activation parameters with no computation. The three classic theories predict kinetic trends from a single calculation, i.e., without running a series of simulations at different temperatures, supersaturations, etc. Finally, the three classic theories were each constructed around a *physically meaningful and one-dimensional reaction coordinate*.

The classic theories work poorly or not at all when applied beyond the validity of their assumptions. Trajectory based rare events methods can estimate rate constants for applications which lie beyond the scope of harmonic TST, CNT, and Marcus theory, but the conclusions of trajectory based methods are not easily generalized to conditions beyond those of the simulated trajectories. Thus, trajectory based methods do not readily predict kinetic trends, and they cannot be used “in reverse” to interpret experimental data. We have outlined how combinations of trajectory-based methods and reaction coordinate identification methods could help discover powerful new quasi-equilibrium theories for new applications.

We close by noting the need for certain innovations that would help discover simple and generalizable theories for complex processes. For reactions in solution, there is a need for generalizable solvent coordinates. For fibril growth, there is a need for coordinates that accurately describe dock and lock steps. For protein folding, there is a need for methods that can extract *physical* reaction coordinates from *abstract* coordinates like diffusion maps, MSM eigenvectors, and committors. Finally, there is a need for new ways of visualizing the atom-by-atom contributions to the reaction coordinate. Visualizing the atom-by-atom contributions to progress along accurate and inaccurate reaction coordinates will help to train our intuition, and thereby foster discovery of new and perhaps simpler ways to understand mechanisms of complex processes.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: baronp@engineering.ucsb.edu.

### Notes

The authors declare no competing financial interest.

### Biography

Professor Baron Peters completed B.S. degrees in Chemical Engineering and in Mathematics at the University of Missouri—Columbia and a Ph.D. in Chemical Engineering at Berkeley. He did postdoctoral research with Professors Bernhardt Trout and Berend Smit at MIT and at the CECAM, respectively. He studies chemical reaction kinetics, nucleation kinetics, and catalysis using electronic structure theory, molecular simulation, microkinetic models, and stochastic models. He also develops rare events simulation tools with a particular focus on mechanistic hypothesis testing.

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