# Introduction

*"In the years since 1940, only little cross-fertilization between physics and chemistry has taken place. ...books on physical chemistry and kinetics do not discuss Kramers results. Likewise, rarely does one find a book on kinetics or nonequilibrium statistical mechanics written by a physicist in which is discussed the important transition state theory..."*

**Hanggi et al. Rev. Mod. Phys. (1990)**

## 1.1  Motivation for this book

This book provides a broad introduction to the most powerful theories and computational methods for understanding the kinetics and mechanisms of activated processes in chemistry and physics: chemical reactions, nucleation processes, non-adiabatic rate processes, protein folding, solid-state diffusion, etc. These topics are usually discussed in separate courses, in separate departments, to separate groups of students. Nearly three decades have passed since Hanggi et al. [1] noted the gulf between chemical kinetics and non-equilibrium statistical physics research in reaction rates and rare events, and still the gaps remain. However, a small but growing group of chemists, physicists, engineers, and applied mathematicians has been working to bridge these sub-branches of reaction rate theory and rare events. Their efforts have led to the discovery of several powerful new theories and to the development of entirely new types of rare events methods.

Figure 1.1.1 shows how this book bridges the gaps between chemistry [2], engineering [3], and chemical physics [4] oriented books on kinetics. The featured topics were selected to provide a *practical* foundation for theoretical and computational analyses. Chapters on chemical reaction equilibria, rate laws, and catalysis illustrate how rate constants and equilibrium constants enter phenomenological kinetic models. Several chapters focus on practical theoretical frameworks for predicting rate constants and kinetic trends, e.g. harmonic transition state theory [5], diffusion control theories [6], nonadiabatic reaction rate theories [7], and theories for overdamped barrier crossings [8]. Chapters on transmission coefficients address the effects of tunneling [9], and dynamical recrossing including the Kramers [10] and Grote-Hynes [11] theories and the reactive flux methods [12]. Several chapters focus on computational machinery

including methods for finding saddle points [13], methods for computing free energy surfaces [14–16], stochastic simulation algorithms [17], transition path sampling methods [18,19], and the recently developed reaction coordinate identification methods [19]. The book concludes with a discussion of free energy relationships, powerful tools for discovering and explaining trends across series of similar reactions [20,21].
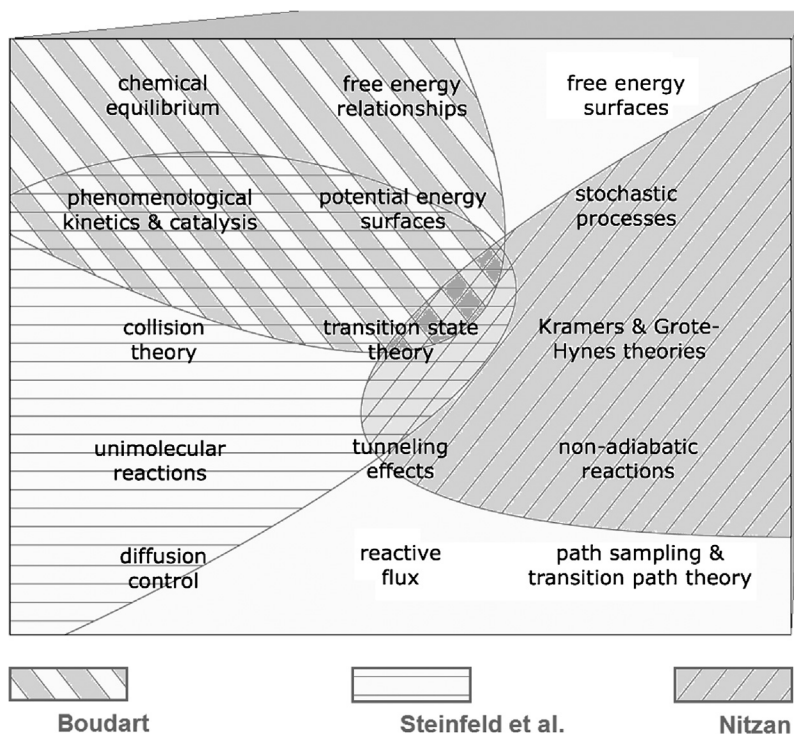


**Figure 1.1.1: The shaded areas show included topics which are covered by some previous books. These include the Boudart (engineering) text "Kinetics of Chemical Processes," the Steinfeld et al. (chemistry) text "Chemical Kinetics and Dynamics," and the Nitzan (physics) text "Chemical Dynamics in Condensed Phases." This book spans longstanding gaps between these three branches of the literature on reaction rate theory and rare events.**

Some preliminary topics that are included in many traditional books were omitted and/or abridged. For example, this book assumes a basic understanding of physical chemistry, equilibrium statistical mechanics, and some familiarity with non-equilibrium statistical mechanics. The book also assumes an understanding of basic computational chemistry ideas and basic simulation methods like molecular dynamics [22,23] and Monte Carlo methods [24,25]. Additionally, the book assumes some familiarity with basic mathematical techniques like Laplace transforms, eigenfunction expansions, and statistical regression procedures. All algorithms in

the book are presented in language-independent pseudo-code. There are no computer codes or scripts in the book because prevalent programming styles and languages vary over time and between communities.

Several important topics were omitted or abridged because they are extensively discussed in other books. For example, there is no discussion of experimental methods for measuring rates of reaction, nucleation, folding, and electron transfer [26–28]. This book does not address molecular beam experiments [29], femtosecond spectroscopy [30], or quantum scattering theories [26]. A single introductory chapter combines acid base catalysis [31], enzyme catalysis [32], homogeneous catalysis [33,34], and heterogeneous catalysis [21,35,36]. Powerful tools for systematic reduction of complex reaction networks to simple rate laws are only briefly introduced [33,37,38]. We do not discuss classical electrostatic solvation models [39–42] nor the continuum solvation models for *ab initio* calculations [43–46]. Unfortunately, it was not possible to cover these and many other important topics.

## 1.2  Why are rare events important?

A colleague once heard me say that nucleation is a rare event, to which he objected: "Nucleation isn't a rare event. It happens all the time." Indeed, my colleague is correct. Many of the processes that theorists call rare events do happen all the time. Measured rates of nucleation range from $10^{-10}$events/$cm^3$/$s$ (slow and rare) to about $10^{20}$events/$cm^3$/$s$ (which seems quite fast). Measurable chemical reaction rates can be even faster. For example, a gas phase reaction with rate constant $10^{10}$/$s$ at standard conditions occurs at a blistering rate of $10^{30}$events/$cm^3$/$s$. Similarly, rare events like electron transfer, protein folding, bimolecular reactions, etc. often exhibit high frequencies and/or extremely fast rates.

Why do we refer to these processes as rare events even when they are fast? The reason lies in their rates *relative to other relaxation processes*. $10^{10}$/$s$ is a fast reaction, but typical bond vibrations are much faster with frequencies on the order $10^{13}$/$s$. Thus before a molecule reacts, its chemical bonds will oscillate thousands of times, exchanging energy with each other and with the surroundings and entirely forgetting the initial conditions before a chance fluctuation funnels the required activation energy into the reaction coordinate. The story is similar for nucleation: thousands of nuclei will form and redissolve before a chance fluctuation creates a nucleus that is large enough to grow. In fact, across all rare events in chemical physics the mechanism is essentially the same: small and inconsequential excursions along the reaction coordinate happen all the time, but larger and more infrequent excursions along the reaction coordinate lead to new products and intermediates with qualitatively different structures and properties from the reactants.

Most experiments cannot directly see the reaction coordinate or track its fluctuations. Likewise, experiments cannot anticipate when or where a spontaneous reaction or nucleation event will occur, and thus they cannot directly observe the barrier crossing event. Rare events that occur at the molecular scale are only *indirectly* evident from macroscopic observations of new products, conformations, and/or phases. Because reaction coordinates, transition states, and free energy profiles elude direct observation, research in rare events and reaction rate theory has some unusual characteristics. In many other disciplines, simulation and computation are "third wheels" of the scientific method, but in kinetics they are vital components. To understand mechanisms of reactions and other rare events we rely heavily on a judicious combination of evidence from rate theories, experimental kinetics, *and* simulations. Indeed, first principles computation and simulations often provide the most direct evidence for or against molecular-level mechanistic hypotheses.

Note, however, that studying rare events with simulation is far more difficult than running a standard molecular dynamics simulation. Figure 1.2.1 shows the (approximate) time scales and length scales which are accessible by different simulation methods. These diagrams are common in the multiscale simulation literature, but they only show methods along the diagonal (the gray circles). Each method moving up the diagonal hierarchy sacrifices some detail and accuracy from the Hamiltonian to access longer time scales. However, the most prevalent methods in the coarse graining [47,48] hierarchy do not preserve the spectrum of time scales [49], especially for chemical reactions, electron transfer reactions, and nucleation and growth where the slowest time scales are associated with processes at very short length scales.
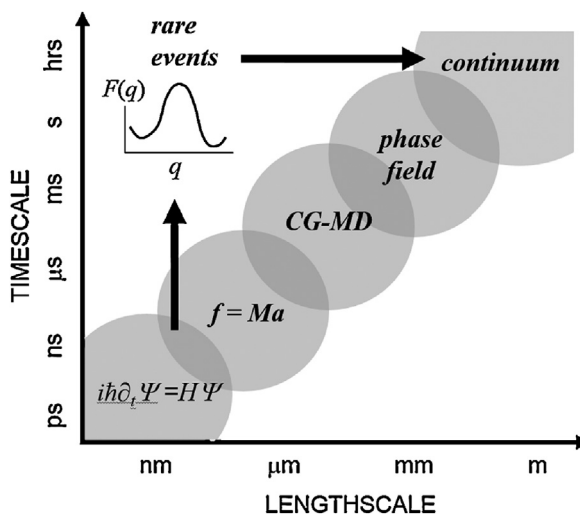


**Figure 1.2.1: Multiscale simulation attempts to reach long time and length scales with a hierarchy of increasingly coarse grained methods. Rare events approaches obtain rates and rate laws without altering the Hamiltonian or the natural dynamics by taking advantage of natural time and length scale separations. The rate laws then become the species generation terms in continuum scale models.**

Progress toward a molecular understanding of rare events began with simple rate theories and models that helped to understand observed rates and kinetic trends. Prominent examples are

harmonic transition state theory [5], classical nucleation theory [50], and Marcus theory [7,51]. These do not always predict accurate rates, but they are extremely useful for understanding and correlating experimental data [52]. Computational rare events methods emerged later, enabled by advances in computational quantum chemistry [53,54], molecular simulation [22,24], and stochastic simulations [55–58]. As depicted in the upper left off-diagonal region of Figure 1.2.1, rare events methods exploit natural time scale separations to compute rates without simulating the waiting time between events. The rate constants and rate laws can then be used in species balance equations or population balance models to predict kinetics and dynamics at extremely long time scales. The rare events strategy thus bypasses the hierarchy of methods on the diagonal, and it does so with remarkable efficiency and without sacrificing *any* molecular-level resolution. Amazingly, these "too-good-to-be" claims are true. Of course, there are challenging aspects of these calculations. The predictions are only as good as the force fields and model chemistries, and often the most efficient rare events methods require an accurate reaction coordinate, i.e. an *a priori* mechanistic understanding. Fortunately, the past few decades of rare events research have led to powerful methods for computing free energy surfaces, for finding saddle points, for optimizing minimum free energy paths, for simulating reactive trajectories, for identifying reaction coordinates, and for computing accurate rates even without a complete mechanistic understanding.

Selecting the most appropriate rare events method or rate theory for a particular application can be a major pitfall even for veteran practitioners. This book outlines the strengths and limitations of the most practical theoretical frameworks and rare events methods – discussions which are often muted in the literature. In some cases the advantages of one theory over another are indisputable. For example, inertial rate theories like transition state theory are appropriate for chemical reactions, while overdamped theories are more appropriate for nucleation and protein folding. In other cases, the advantages of one method over another are more subtle issues of computational efficiency or ease of implementation. In general, two considerations should be weighed when choosing a computational method or theory:

1. *Correct and definitive answers*. The foremost merit criteria is a method's capacity to correctly answer the most important and interesting questions, and to do so with minimal uncertainty in the conclusions.
2. *Ease of implementation and computational efficiency*. These are also important (but secondary) criteria. Sometimes ease of implementation and efficiency considerations oppose each other, and in these cases their balance depends on available computational power and human expertise.

Computing power continues to grow and some supercomputers now boast petaflop/s performance. Additionally, enormous effort has been invested to develop accurate *ab initio* model

chemistries and molecular force fields. Several software packages now implement state-of-the-art electronic structure methods and force fields so that users can bypass the difficult tasks of developing and implementing model chemistries. These developments have dramatically increased the system sizes, the time scales, and the breadth of different processes that can be studied in simulations. But despite advances in hardware and software, the time scales that are accessible to a straightforward simulation are still far too short for analysis of rare events. Let us now consider the types of questions which can be posed and answered with theoretical analyses, simulations, and rare events methods.

## 1.3  The role of computation and simulation

In the most literal sense, a simulation is a model that resembles a real process. Some computational studies of rare events basically report snapshots from long unbiased simulations and then anecdotally relate the observations. There are a few situations where long unbiased simulations are useful in studies of rare events. First, long unbiased trajectories are useful for characterizing the properties of reactant and product states. Second, a long unbiased trajectory sometimes discovers unexpected intermediates or new pathways, and these discoveries (while impossible to plan) can inspire important new areas of inquiry. Third, long time scale trajectories are useful for constructing Markov state models [59] and diffusion maps, but only when barriers are relatively small.

Rare events analyses more typically use simulations only as devices to compute averages, free energy barriers, and dynamical prefactors. Some rare events methods modify the dynamics to sample parts of phase space that would otherwise be rarely visited. Often we learn the most from simple models that explain trends and/or from analyses of static equilibrium properties like free energy landscapes. Those rare events methods which do require realistic dynamical simulations will only require extremely short trajectories.

### Quantitative rate predictions

A 2010 US National Academy report estimated that a heat of formation measurement is 100 times more expensive than a heat of formation calculation of similar accuracy [60]. Because of these capabilities, computational thermochemistry is widely viewed as an inexpensive alternative to experimental measurements. However, the situation is different in kinetics. Rates are more difficult to compute for several reasons:

1. Rate calculations exponentially magnify small errors in activation barriers. *Ab initio* calculations and force fields are typically calibrated to match equilibrium properties, but precise transition state properties are rarely available for calibration.

2. Tunneling, spin crossings, and electron transfer processes require a correct description of quantum effects and excited states.
3. In systems where the dynamics deviate from those assumed by transition state theory, computing the kinetic prefactor can be highly non-trivial task.
4. The most practical rate theories require selection of a reaction coordinate, and identifying the reaction coordinate can be a major challenge.
5. Correctly predicting the observed kinetics often requires careful analysis of large reaction networks or catalytic cycles, e.g. using pseudo-steady states or other approximations. A computational error in just one elementary step may severely compromise the predicted kinetics.

In certain cases, state-of-the-art *ab initio* calculations and force fields can predict absolute rates, but for many systems accurate rate calculations are not yet possible. The fact that rates depend on so many factors makes it difficult to pinpoint the most important sources of error. Thus predicting rates continues to pose challenges, even for systems where predicting the thermodynamics has become straightforward.

### Two types of kinetic trends, two different applications

In many applications we cannot accurately predict absolute rates, but we can often predict *trends* in the rate as a function of composition, temperature, or molecular characteristics. The reason that we can accurately predict trends even when we cannot predict rates is a rather unglamorous cancellation of errors. Fortunately, the trends are often more important than the absolute rates anyway. First, engineering better catalysts, drugs, crystal growth modifiers, etc. requires understanding kinetic trends as a function of composition, temperature, pressure, pH, solvent dielectric, etc. Second, the trends implied by computational analysis of a hypothesized mechanism can be used to refute or confirm the mechanism.

Note that there are actually two different types of trends and that they are used in different types of analyses. First, there are trends in the rate of one reaction across a family of related reactants and/or catalysts. In recent years, these trends have been widely pursued in computational studies of heterogeneous catalysts [21]. Many recent catalysis studies do not even attempt to compute rates, instead focusing on descriptor correlations that relate activation energies to adsorbate binding energies and other catalyst properties. Descriptor correlations are powerful ways to discover cheap and active catalyst materials from the vast possibilities in the periodic table. However, these trends describe the kinetics of one specific reaction, usually with a well-understood mechanism, occurring on different metal surfaces.

To test a new mechanistic hypothesis for a poorly understood reaction, we must instead cross-examine the observed and predicted activation parameters, rate laws, and reaction orders. Some

would argue that trends are more important than quantitatively correct activation parameters or rate laws, but this viewpoint misses the fact that reaction orders and activation parameters **are** trends. Specifically, the activation parameters are trends in the rate vs. temperature, and the reaction orders are trends in the rate vs. concentration, partial pressure, etc. Reaction orders and activation parameters follow directly from the mechanism, and as such they are important fingerprints for identifying the mechanism. Where possible, one can also test predictions about abundant intermediates, spectra, molecular weights, etc. [61]. Ideally, one should cross-examine a comprehensive suite of properties and kinetic trends to provide many points of comparison to experiment. Each comparison is an opportunity to refute the hypothesized mechanism [62], and the more tests a hypothesis passes, the more confidently we can assert its veracity. Finally, note that the ideal starting point to identify a mechanism in computational work is a single well-defined catalyst and/or specific reactant(s). We should not *a priori* assume that the mechanism will be preserved across a family of catalysts, reactants, adsorbates, etc. Accordingly, we cannot build reliable descriptor correlations without first developing an understanding of the mechanism and establishing its validity for a family of catalysts and/or reactants.

### In silico experiments

Simulations are often viewed as a branch of theory, but in some ways simulations are more like experiments. The role of simulations as idealized experiments was recognized at the dawn of molecular dynamics simulations by Fermi, Pasta, and Ulam (FPU) who described their study as an "experiment" to test a theory [60,63]. Theories are often oversimplified to facilitate analysis, whereas a simulation can retain all of the essential physics and sometimes reveal surprises. Experiments also retain all of the physics, but changing one variable in an experiment can inadvertently change other variables. The often messy nature of real experiments calls to mind the quote from Einstein: "A theory is something nobody believes, except the person who made it. An experiment is something everybody believes, except the person who made it." A simulation provides absolute and independent control over all parameters, even parameters that could never be changed in a real experiment. For example, we can turn off quantum effects, change the sizes of atoms, choose any masses we like, turn off dispersion interactions, add friction to the natural dynamics, etc. In this manner, simulations can be devised to perform proper controlled experiments that test hypotheses about these factors.

### Mechanistic hypothesis testing

For many decades the principal way of testing a mechanistic hypothesis was to fit data to a phenomenological model. A sequence of elementary steps would be proposed along with assumptions about pseudo-steady-state behavior, quasi-equilibrium steps, rate determining steps,

irreversible steps, etc. All rate constants in the resulting rate law would then be used as adjustable parameters in fitting the model to the experimental data. The rate law would then be accepted or refuted according to analysis of residual variance from the best fit. Classic hypothesis testing approaches are still valuable, but computational chemistry and molecular simulation have dramatically expanded the arsenal of hypothesis tests.

- In addition to checking for quality of a fit to experimental data, we can now ask whether the fitted rate constants are approximately consistent with independent estimates from *ab initio* computational chemistry. First principles calculations can also cross-examine the predicted and observed abundances of hypothesized intermediates.
- Classic phenomenological analyses like those of Hinshelwood, Hougen and Watson invoked abstract symbolic entities like "*" for an active site. Computational chemistry techniques now allow us to propose and test specific molecular models of the active site structure.

Hypothesis testing procedures based on first principles calculations are primarily useful for understanding chemical reactions and catalysis. In these applications, questions about mechanisms primarily concern the sequence of elementary steps and models of the active sites. Once transition states have been found for all elementary steps, the individual rates are easily computed, e.g. using harmonic transition state theory.

For processes like nucleation, self-assembly, and protein folding, simulations face many additional challenges. Are mechanistic conclusions robust to changes in the force field? Are the designated bath variables sufficiently fast relative to designated slow variables? Do dynamical trajectories really lose memory between the adopted milestones? Is the transmission coefficient small because of intrinsic friction in the dynamics or because of a poorly chosen dividing surface? The answers to these questions depend upon which reaction coordinate was selected for computing barriers and rates. There are now several methods for discovering reaction coordinates, for testing their accuracy, for using them to compute rates, and for constructing simple rate theories [19,52]. These new tools are conclusively answering mechanistic questions and pointing the way to simple theories for new types of reactions and rare events.

## 1.4  Polemics

This section addresses some of the occasional abuses, misuses, and misconceptions that appear in the rare events literature. It is not intended as a targeted critique of any specific work, but rather as a list of precepts and best-practices.

### Units

Units are extremely important in scientific research, and yet we (engineers in particular) always try to eliminate them. Consistency of units is the foremost hurdle that must be passed by any successful theory or quantitatively meaningful statement. Nonsensical comparisons between quantities with incompatible units are all too common in the literature. Statements like "...the growth rate surpasses the nucleation rate..." or "...the reaction is faster than diffusion..." do not have a proper meaning. To compare quantities with different units, they must first be multiplied/divided by additional time scales, length scales, areas, volumes, concentrations, etc. to obtain an equivalent units. Proper comparisons and dimensional analyses often reveal important lengthscales and time scales apart from the intrinsic kinetics. As such, units are invaluable guides *in the early stages of model formulation*.

On the other hand, the units are a nuisance in mathematical manipulations and data analysis. Furthermore, dimensionless groups reduce the number of independent parameters that are needed to make quantitative predictions. Systems with different barriers, temperatures, frictions, concentrations, etc. might follow an equation with just one or two dimensionless parameters. In many cases, dimensional analyses identify certain factors in a model that can be entirely omitted. Finally, dimensionless equations and parameters suggest compact ways to correlate data across a diverse set of conditions.

Non-dimensionalization is ubiquitous in engineering, but less so in chemistry and physics. Scientists instead use different unit conventions in different areas, e.g. there are atomic units, cgs units, natural units, SI units, etc. [64]. Cussler quips [65] "Dimensionless numbers are weapons that engineers use to confuse scientists." but perhaps scientists have the more confusing system. For example, polymer scientists, quantum chemists, and non-equilibrium statistical mechanicians all solve similar Schrodinger equations, but their equations *look* different except for those cases where they are non-dimensionalized. This book discusses both formulation and analysis stages of kinetic modeling. Accordingly, some discussions involve quantities with units, and others are non-dimensionalized.

### On the value of results that disagree with experiment

The reaction pathways and mechanisms that we investigate are often based on some preconceived ideas about the mechanism. Anyone can fail to anticipate the correct mechanism, but among those mechanisms that are investigated, computational results should be used and interpreted in an unbiased manner. Unfortunately, some investigators view *ab initio* calculations as a tool "to validate" their mechanistic hypotheses. Note the subtle bias in that phrase – we should embark on a calculation with the goal of performing an unbiased test, not to achieve

a validation. The problem goes beyond semantics. A bias toward results that validate the hypotheses has led some investigators to excuse results that clearly and conclusively refute their mechanistic hypothesis as "expected errors from DFT".

If we believe that *ab initio* computational evidence can support a mechanistic hypothesis, then we must also believe that *ab initio* evidence can refute a mechanism [62]. Computational chemistry cannot accurately predict experimental results, but most computational methods are associated with some typical range of errors. When disagreements with experiment exceed the plausible range of computational errors, the theorist should revise his mechanistic ideas, re-interpret experimental results, consider new active site models, etc. Revisiting the mechanistic assumptions and hypotheses because of some discrepancy often leads to the most important discoveries: revised mechanisms, new interpretations for experiments, new insights about the active site, etc. In this sense, computational results that disagree with experiment are often more exciting than results which agree.

On the other hand, if implausibly large discrepancies are just brushed aside, then there really is no value in performing calculations at all. Unfortunately, studies that promote a mechanism despite strong computational counter-evidence are easy to find. In some cases, the computational counter-evidence is even presented as supporting evidence for a mechanism [61]. One scathing critique [66] concluded that *ab initio* calculations cannot predict anything and even described computational chemistry as a "dartboard". It should be noted that the most egregious errors cited in their critique resulted from (i) calculations that were done incorrectly (e.g. by ignoring entropy in association steps), or (ii) investigating the wrong mechanisms or active sites. It seems likely that many of the most egregious errors are not actually due to computational chemistry itself, but rather to human errors; i.e. to flawed analysis, applications, and interpretations of computational chemistry results.

### Quests of questionable value

As computers and software for massively parallel simulations become more powerful, it is increasingly common to see fully atomistic simulations of processes that involve highly disparate length and time scales.[1] In some cases, large scale atomistic simulations have been used to model phenomena where there are very good continuum models. Some examples include atomistic simulations of solidification (where there are exquisite and accurate continuum scale models) [67,68], atomistic simulations of boundary layer transport and catalysis (despite rigorous continuum equations for coupling boundary layer resistances to surface kinetics) [69,70]

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[1]   These efforts are not to be confused with multiscale simulation methods, where phenomena at different scales are studied with different methods.

and sophisticated rare events analyses of water evaporation (which is accurately described by coupled heat and mass transfer equations) [65,71].

Each of the above examples involves gradients in temperature, composition, or fluid velocity coupled to molecular scale interfacial processes. Perhaps these seem like complicated situations which require multiscale simulation or (even less desirably) atomistic simulations with billions of atoms to span multiple scales. But before embarking on a massive simulation effort, one should ask whether the problem might be broken into separately soluble but coupled parts. We should also ask which molecular level details (if any) are needed to advance technology or fundamental understanding. When there is no need for molecular level detail, then an accurate continuum theory is superior to an atomistic simulation. This statement is not a matter of opinion or personal preference. Simple theories, by construction, omit thousands of molecular details, and when the details are irrelevant they should be omitted.

Consider, for example, the overall rate of a heterogeneous surface reaction. The intrinsic kinetics at the surface depend only on the concentrations of reactants immediately above the surface. Mass transfer from the bulk depends on concentrations in the bulk and concentrations at the surface. The problem can be rigorously broken into two parts: (1) determine the rate law as a function of concentration near the surface, and (2) self-consistently match the continuum mass transfer rate to the rate law. Matching reveals the concentrations at the surface and therefore the overall rate. The problem can be rigorously solved without simulating any part of the mass transfer process at atomistic resolution. The model that we obtain from the coupled analytic analysis is simpler than the results from a massive simulation. Importantly, the analytic model is also more useful. It immediately predicts the overall rates at many different bulk concentrations, whereas the massive simulation just gives the overall rate for the one concentration that was simulated.

### On the proliferation and testing of new methods

There are hundreds of methods for optimizing transition states, hundreds of methods for computing free energy surfaces, and scores of methods for computing dynamically accurate rate constants. Some of these methods dramatically advanced rare events research through powerful theoretical principles and innovative computational strategies. Others (perhaps most) are minor variations on the major themes with little or no practical benefit.

In the long run, the merits of a method are easily judged by its impact in actual applications. But how can merit be assessed for new methods? Ideally, new methods should resolve some deficiency in the capabilities of existing methods, or else they should provide a great leap (e.g. $>2\times$) in efficiency. In principle, publications on methodology should include difficult example problems that demonstrate truly new capabilities, but modern funding structures require that

we frequently document our progress. Thus, in practice, to require a challenging demonstration would stifle many creative, important, and ambitious new directions.

How do we balance the principled ideals against the practical realities? Ultimately, a method development effort should not be regarded as complete until its capabilities are established for rigorous and demanding test cases. There are subltle differences in the ways that new methods are tested and used in science, engineering, and mathematics. To a mathematician, assumptions have logical consequences (theorems) which can be studied apart from the properties of any real system. To the scientist, assumptions (hypotheses) have consequences that must be tested against observations of real systems. To an engineer, assumptions and models are measured by their broader impacts (technology).

The different priorities of scientists, engineers, and mathematicians are often evident in our respective contributions to the field.[2] Engineers tend to pursue important and ambitious applications, sometimes with insufficient rigor and before the available simulation methods are actually ready. Scientists tend to dwell on model systems like hard spheres and model peptides, sometimes with too little concern for discoveries with potentially practical impacts. Mathematicians tend to create test systems for which the requisite assumptions of a theorem are true by construction, and as such these tests are more properly regarded as illustrations. For example, overdamped dynamics on a low dimensional potential energy landscape is Markovian by construction, so all theorems and methods derived from that property must work perfectly well – on the system used in the illustration. After methods have been so illustrated, scientists and engineers sometimes use them on complex molecular systems with no further tests of the underlying assumptions. As Churchill has said "However beautiful the strategy, you should occasionally test the results." Clearly, scientists, engineers, and mathematicians can each learn valuable lessons from each other.

### On corrections to transition state theory

Several chapters of this book focus on methods for obtaining accurate rate constants. Many readers will already be familiar with transition state theory (TST) and perhaps also with non-TST effects like tunneling and recrossing that require more elaborate calculations. There are two schools of thought on the importance of corrections for non-TST effects. One viewpoint maintains that errors in *ab initio* calculations are unavoidable and dominant sources of error, regardless of how carefully the non-TST corrections are estimated. Some proponents of this viewpoint omit non-TST corrections and focus on trends rather than absolute rates. Indeed,

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[2] As an engineering professor, with a partial appointment in chemistry, and an undergraduate degree in mathematics, I feel less-underqualified-than-most to over-generalize.

there are many applications where non-TST effects can be ignored. There is no need to include non-TST effects in studies that examine one reaction across a series of catalysts with different adsorbate binding energies or d-band centers. Non-TST effects can also be ignored for examining trends in homogeneous reaction kinetics, e.g. trends in the rate vs. electron withdrawing characteristics of various substituent functional groups [72]. Non-TST effects can also be ignored for steps that do not control the overall rate.

On the other hand, corrections to TST can be extremely important when computational results are compared to experiment to test a hypothesized mechanism. For example, tunneling can alter the slope of Arrhenius and Eyring plots for many hydrogen and proton transfer reactions. Dynamical recrossing can lower the intercept on Arrhenius and Eyring plots. These effects cannot be "switched off" in the experiments, and accordingly they should not be switched off in computational rate predictions. The PES may well be the dominant source of error, but to omit a correction that influences the quantity being computed adds bias to an already imprecise calculation. In general, the potential impact of non-TST effects and the need for accurate rates should be assessed carefully on a case-by-case basis when justifying computational shortcuts.

Of course, one should not decide whether to add or omit terms solely to improve the agreement with experiment. Adding corrections because theoretical considerations predict they are significant is good practice. It is also good practice to add corrections when a discrepancy with experiment alerts us to unanticipated factors. But omitting a theoretically important correction because the data fits better without it is shameful. The model chemistry and the effects to be included are, in some sense, a part of the hypothesized theoretical model. In principle, the model chemistry, the approximations to be used, and the corrections which will be applied should be selected before the results are compared to experiment. When all potentially important corrections are included and the results agree with experiment, the agreement is significant. When all potentially important corrections are included and the results still disagree with experiment, the results are still useful. As elaborated above, carefully performed calculations that disagree with experiment indicate flaws in our mechanistic understanding and often lead us to new discoveries.

### *On science priority and impact metrics*

Scientists (theorists in particular) are notoriously sensitive about credit and recognition (see Figure 1.4.1). Some investigators have even written articles which are chiefly about who used their ideas and methods without appropriate credit. Concerns over science priority can be understood from the many historical examples of misappropriated credit.[3] Journal editors cannot

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3   Stigler's law of mistaken eponymy says "No scientific theory is named after the person who actually discovered it." Amusingly, Stigler's law was first stated by R. Merton. There are many examples among the topics in this

check whether our citations are accurate and complete, and typical papers are read by only a few of our peers before publication. Therefore citations are largely an honor system. Most investigators feel naturally compelled to credit others, but even the most renowned scientists are occasionally slighted [73]. Proper citations are an important component of scholarly work for several reasons: they point readers to other important papers, they dispell the myth of a single genius working in isolation, and they set an example that scientific progress requires careful attention to the work of others.

**Figure 1.4.1: Despite the stigma associated with self-promotion, all scientists, living and deceased, deserve credit for their original contributions. I have tried to give appropriate credit throughout, but I will undoubtedly forget and misdirect credit for certain important contributions. Please suggest references and topics for future editions.**
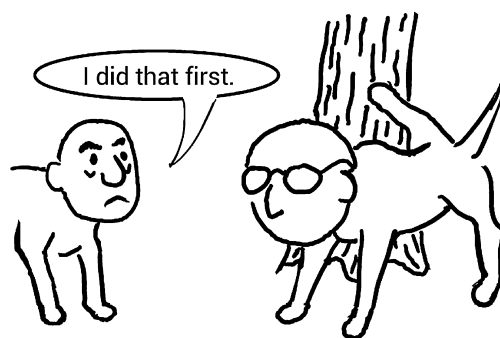


Are issues of science priority important for the advancement of science itself? Yes, because professional survival for a scientist requires some degree of recognition. The perceived impact of our prior achievements influences our ability to secure funding, to attract talented students, and to stay employed. Young investigators in particular depend on the *short term impact* of their achievements – a fledgling research program can flounder if its most innovative contributions take a decade to discover.

To some degree, all research programs depend on short term impact, and unfortunately short term metrics like journal impact factors are imperfect. Of course, any conceivable metric for judging scientific contributions would have flaws, cf. Campbell's law: "The more any quantitative social indicator (or even some qualitative indicator) is used for social decision-making, the more subject it will be to corruption pressures and the more apt it will be to distort and corrupt the social processes it is intended to monitor." The widespread pressure to publish in high impact journals does have several undesireable side effects on the quality of our literature. First, the most prestigious journals tend to attract manuscripts with hyperbolic (and sometimes fraudulent) claims [74]. Second, it is increasingly common for editorial boards – rather than true experts – to judge the importance of submitted manuscripts. These preliminary editorial reviews typically prioritize work that is new and trendy over careful, comprehensive, and consequential work on longstanding challenges. Finally, the importance of short term impact forces

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book: the Arrhenius law was put forth by van't Hoff, Fermi's Golden Rule was discovered by Dirac, Voronoi cells were first used by Descartes, the Bodenstein approximation was first used by Chapman, etc.

young investigators to pursue the hottest trends *en masse* – a feedback loop that exacerbates fads in scientific research and funding.

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