Perspective

Lexicography of Kinetic Modeling of Complex Reaction Networks

Linda J. Broadbelt and Jim Pfaendtner
Dept. of Chemical and Biological Engineering, Northwestern University, Evanston, IL 60208

DOI 10.1002/aic.10599

Introduction

Complex reaction networks are ubiquitous. Reacting systems consisting of hundreds or thousands of species and reactions are common in many different types of seemingly disparate chemistries. Pyrolysis, oxidation, polymerization, amino acid biosynthesis, silicon nanoparticle growth and catalytic cracking all involve complex reaction networks that can originate in different ways. For example, hydrocarbon conversion processes in the petrochemical industry, such as catalytic cracking, reforming and hydrocracking, involve the transformation of complex mixtures of molecules via a large number of gas-phase and catalytic reactions, largely because petroleum feedstocks themselves are multicomponent mixtures.[1,2] Complex reaction networks can also manifest themselves for conversion of single components or simple mixtures of reactants, where the complexity is not derived from the feed but from the nature of the reactions. Oxidation and pyrolysis are classic examples of chemistries that create complex reaction networks of $O(10^2\text{-}10^4)$ of species from even simple molecules, such as methane[3] or ethane,[4] because of the nonspecificity of the free-radical intermediates. Polymerization conditions are typically controlled such that only radical addition reactions are favored, but reaction networks for polymerization or depolymerization are indeed complex because of the thousands of possible chain lengths.[5,6] Similarly, silicon nanoparticle production in the homogeneous phase starts with very simple reactants, silane and hydrogen, but thousands of different species are possible as particles grow to nanometer sizes that are of significance in semiconductor contamination.[7] Even with the specificity of enzymes, biochemical systems also involve numerous reactions of a large number of different species because of the wide range of functions that different enzymes perform.[8-11]

Although the chemistries enumerated here are seemingly diverse, they share many common features that can be uncovered by lexicography of kinetic modeling. A "dictionary" detailing the language of quantitative kinetic modeling can help unify the chemical principles underlying this wide array of systems, much in the same way that a dictionary unifies speakers of a common language. Chemical engineers are uniquely qualified to develop kinetic models of complex reaction systems that offer a quantitative framework to synthesize the efforts of chemists, biologists, mathematicians and other engineers. We understand the underlying physical sciences, and also have the mathematical tools and modeling expertise to deconvolute the behavior of chemical and biochemical systems through kinetic models. It is, thus, important that we continuously refresh and refine our dictionary of kinetic modeling so that state-of-the-art methods can be brought to bear on the ever-widening array of reacting systems of interest to our discipline and that advances in quantitative analysis in one area — for example, metabolic engineering — that is seemingly disjoint from another — for example, silicon nanoparticle production — are seamlessly translated.

The lexicography of kinetic modeling of complex reaction networks begins with a definition of the key words. As illustrated in Figure 1, the building blocks of complex reaction networks are species (the nodes) and reactions (the edges). Foremost, it is necessary to know or postulate which species are involved as reactants, products and reactive intermediates. It is then essential to define how they are connected, that is, what the reactions are. The topology of the reaction network is essential, but it is not enough. In order to obtain quantitative insight from the reaction network, thermodynamics must be quantified to ensure microscopic reversibility and consistency with the thermodynamics of the overall reaction. The final, and most challenging, step is to specify a rate coefficient for each reaction. While analytical rate expressions still can provide tremendous insight into the controlling chemistry and are more compatible with process models because of their simplicity,[12] we focus here on mechanistic kinetic, or microkinetic,[13] modeling. Mechanistic models have the greatest potential for extrapolation and also allow the power of techniques such as computational quantum chemistry to be exploited.

Great success has already been achieved in kinetic modeling of homogeneous, gas-phase chemistries, such as oxidation and pyrolysis. For example, reaction mechanisms have been proposed for a wide range of hydrocarbon substrates in combustion,[14-18] and understanding of the underlying chemistry is quite mature. Reaction networks that capture the essential reactions have been developed, and even adaptive kinetic mod-

---

Correspondence concerning this article should be addressed to L. J. Broadbelt at broadbelt@northwestern.edu.

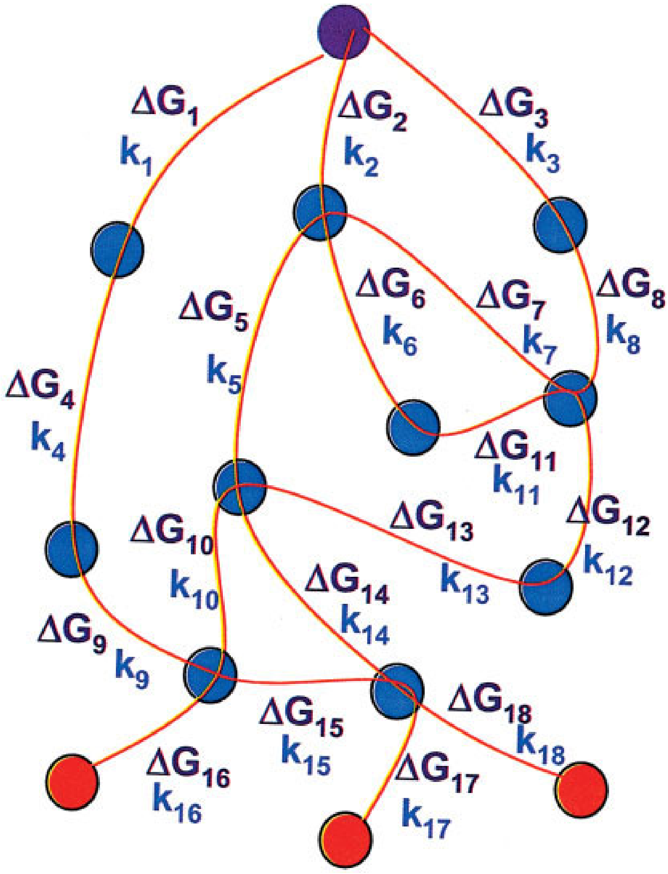

Figure 1. Complex reaction networks are composed of species as the nodes and reactions as the edges.

The species can be global lumps, molecules, or reactive intermediates, such as free radicals. For example, the network above might represent a reaction mechanism with the reactant represented as a purple circle, the products shown as red circles, and reactive intermediates denoted as blue circles. The reactions are characterized by thermodynamics through free energies of reaction (ΔG_i) and kinetics through rate coefficients (k_i).

eling[19,20] can be performed so that coupling the reaction mechanisms with computational fluid dynamics models is facilitated. One reason that kinetic modeling has been so successful for these types of chemistries is that extensive experimental studies have been carried out to identify key reactive intermediates and even measure individual rate coefficients. Databases have been developed that summarize reactions and rate coefficients and "gold-standard" mechanisms are even available. These accomplishments underscore the importance of experimentalists and modelers working together and represent decades of concerted effort to develop quantitative pictures of complex chemistries.

Tremendous progress has also been made in heterogeneous catalytic systems in recent years, which are inherently more challenging than homogeneous, gas-phase systems because of the complexity of typical solid catalysts. Dumesic and coworkers helped spark this progress by demonstrating the power of microkinetic modeling for a number of different systems.[13] For example, microkinetic modeling has been extremely valuable in developing a deep understanding of ammonia synthesis.[21-26] Another example is the work of Vlachos and coworkers [27] who have recently demonstrated the ability to capture a wide array of different experimental studies for reactions of relatively small molecules (e.g., CO and H_2) on metal surfaces using a multiscale approach for specifying rate parameters. The ability to develop these microkinetic models has been greatly aided by computational quantum chemistry, which has allowed different configurations of surface intermediates to be interrogated in detail.[28-35]

On the cusp of the transformation of chemical engineering to chemical and biological (or biomolecular) engineering, an interesting question is what techniques and methods applied to "conventional" chemistries in the past can be exploited for applications to biochemical systems. If one adopts the viewpoint that quantification and understanding of the kinetics of complex biochemical reaction networks is in the same stage as combustion chemistry in the 1970s, and factors in the tremendous advances in computational techniques and power in recent years, it is conceivable that complex biochemical reaction systems can be reliably modeled at the mechanistic level in the next two decades. One starting point for realizing this goal is to identify what commonalities exist that can be exploited and outline what new challenges must be overcome. To this end, this Perspective article describes the general elements of kinetic modeling of complex reaction networks, with an emphasis on computational techniques that have recently emerged. Techniques for uncovering the species and reactions are described first. Methods for specifying thermodynamic properties and rate coefficients are then discussed. Finally, future prospects for and challenges in kinetic model development are described.

Species (spē'shēz) and Reactions (rē-ăk' shənz)

The nodes of the reaction networks are species, and the edges connecting the nodes are the reactions. Depending on the level of detail included in the reaction network, the species can be molecules or intermediates, such as free radicals or ions, and the reactions can be pathways or elementary steps. The first step in developing a kinetic model of a complex reaction network is to define its species space. One can imagine a species space that encompasses every possible permutation of every possible atom in the periodic table. However, it is clearly more practical to restrict the species space to the likely molecules and intermediates for the chemistry of interest and ultimately, the important species that are chiefly responsible for the observed chemical behavior.

The most obvious starting point for figuring out which species are involved in a particular reaction system is to observe and measure them experimentally, and the role of experimental methods in uncovering the details of complex reaction networks is certainly not discounted here. Rather, this Perspective focuses on computational techniques that can serve as a complement or indeed, as a possible substitute, to experimental approaches. Quantum chemistry is becoming the kinetic modeler's computational method of choice to uncover details of species and reactions that are part of a complex reaction network. The approach is to use quantum chemistry to map the potential energy surfaces (PES) to determine the stability of

Table 1. Glossary of Terms Relevant to Computational Quantum Chemistry

Word(s)	Abbreviation	Definition
Ab initio		From first principles. Used to denote molecular orbital methods that invoke a minimal number of approximations for solution of the Schrödinger equation.
Basis function		A function used in building up the description of molecular orbitals. Often, atomic orbitals are used but not always. Common forms of basis functions are Gaussians, planewaves, or numerical.
Basis set	3-21G, 6-311G*, LanL2DZ, cc-pVDZ, cc-pVTZ, cc-pVQZ	Complete set of basis functions that is used to represent the molecular orbitals. Gaussian functions are the most commonly used. The basis set simply consists of the relevant exponents and coefficients of the functions.
Configuration interaction	CIS, CISD	Introduces electron correlation by mixing in an optimum amount of different electronic configurations. The "weightings" of these electronic configurations are called the CI coefficients.
Coupled cluster	CCSD, CCDT	Expresses the wavefunction using many determinants to include electron-electron correlation. Higher excitations are partially included, but the fact that their coefficients are determined by the lower order excitations helps reduce the computational demand.
Density functional theory	DFT	An approach for solving the Schrödinger equation that describes an interacting system of electrons via its density and not via its many-body wave function.
Functional	BP86, BLYP, B3LYP, PW91, XLYP	Relevant to density functional theory. In DFT, the exact exchange for a single determinant is replaced by a more general expression, the exchange-correlation functional, which can include terms accounting for both exchange energy and the electron correlation that is omitted from Hartree-Fock theory.
Gaussian-3 theory	G3	A composite technique in which a sequence of well-defined ab initio molecular orbital calculations is performed to arrive at a total energy of a given molecular species.
Hartree-Fock	HF	A method that seeks to approximately solve the electronic Schrödinger equation. It assumes that the wavefunction can be approximated by a single Slater determinant made up of one spin orbital per electron. An electron is assumed to move in a mean field of the other electrons, i.e., electron-electron correlation is not included.
Møller-Plesset perturbation theory	MP2, MP4	Improves upon the Hartree-Fock solution by expanding the wavefunction in a Taylor series in a perturbation parameter. The X in MPX refers to the order of the expansion.
Semi-empirical method	PM3, AM1	Class of methods that solve the Schrödinger equation via parameterization against experimental data.

intermediates and the likelihood that a reaction between proposed set of species will take place. The potential energy landscape is revealed by solving the electronic Schrödinger equation, $\hat{H}\Psi = E\Psi$, where $\hat{H}$ is the Hamiltonian, E is the electronic energy, and ψ is the wavefunction, for a number of nuclear configurations. This Perspective is not meant to be a comprehensive review of computational quantum chemistry since there are several excellent texts and reviews available.[36-38] Rather, we focus here on defining the important terms in the dictionary of kinetic modeling of complex reaction networks. To this end, a brief glossary of terms relevant to quantum mechanical methods is provided in Table 1. The essential message provided here is that the energy of a configuration of atoms can be calculated, and minimum energy structures on the PES can be identified. These structures are likely stable intermediates along a reaction coordinate and provide some insight into the likely reactants and products of elementary steps.

Solution of the Schrödinger equation has been brought into the hands of chemical engineers with the explosion of software packages[39] that are readily available. The awarding of the Nobel Prize in Chemistry in 1998 to John Pople and Walter Kohn was in recognition of their accomplishments of putting computational chemistry in usable form. It is important, however, that the software not be treated as a "black box" since it is easy to obtain meaningless results. On the contrary, the user must be very prudent about selecting the method to solve the Schrödinger equation, as approximations must be made for all systems of practical interest. The different approaches for solving the Schrödinger equation are broadly classified as *ab initio* methods, density functional theory, and semiempirical methods. The *ab initio* method to which other methods are often compared is Hartree-Fock (HF). The wavefunction is assumed to be a combination of molecular orbitals described as Slater determinants. Furthermore, it is assumed that the molecular orbitals are expanded linearly in terms of atomic orbitals with fixed coefficients. Solution is carried out self-consistently, with the coefficients of the molecular orbitals optimized until the electronic energy is minimized. Each electron is assumed to move in a mean field of the other electrons, such that the motion of the electrons is not correlated. It is this assumption upon which other *ab initio* methods seek to improve. These post-Hartree Fock methods include configuration interaction, coupled cluster and Møller-Plesset perturbation methods. As higher degrees of correlation are included, the computational demand increases. Hybrid methods, such as G3,[40] seek to mitigate this by using a lower level of theory to carry out geometry optimization and then use energies for a fixed nuclear configuration from a variety of different higher-level methods.

Density functional theory (DFT) is an alternative to HF and post-HF methods that formulates solution of the Schrödinger equation in terms of the electron density instead of the wavefunction. However, the problem of an approximate wavefunction is traded for the fact that the relationship between the electron density and the electronic energy is not known exactly. Specification of these relationships, or functionals, is one important controlling parameter of using DFT. There are also hybrid DFT functionals, where a small portion of the total energy is calculated via the HF methodology. Pure DFT is more computationally efficient than HF and has accuracy that is comparable to post HF methods.

For all of these methods, the user must also select the way in which the molecular orbitals are represented in terms of atomic orbitals, which is referred to as the basis set. Broadly, there are four major types of basis sets: Gaussian-type, numerical, effective core potentials and plane waves. Gaussian, or Pople-type, basis sets are used most frequently because of their ease of integration, particularly for multicentered overlap integrals. Effective core potentials treat valence electrons in detail and represent the core electrons in the form of a potential. These are appropriate for systems with heavy atoms with many electrons, such as transition metals, since they can make the calculation easier. Plane wave basis sets work well for extended periodic systems, such as metals.

Successful demonstrations of the use of quantum chemistry to uncover details of reaction intermediates and reactions are growing. Quantum chemistry is an important entry in the dictionary of kinetic modeling of complex reaction systems because it can, in theory, be applied to any type of reaction system, from gas-phase pyrolysis and oxidation[3,41] to heterogeneous catalysis[28-30,42-49] to enzyme-catalyzed biotransformations.[50,51]

An alternative computational approach to studying reactions individually using quantum chemical calculations is to use prior, often minimal, knowledge about likely chemical transformations to construct rules and reaction types that can be applied systematically to reactants to create products. This is the central concept of automated network, or mechanism, generation. The underlying tenet is that complex reaction networks are simply the manifestation of a small number of reaction types being applied to a large number of species. Knowledge of the appropriate reaction types is gained through experimental studies or complementary theoretical investigations of the system of interest and then translated into a form that the computer can utilize to generate networks automatically.

A variety of research groups have developed algorithms for generating reaction networks via the computer in the past 15 years,[3,7-9,52-64] and they all have common features. A representation of the constituent atoms and their chemical environment in a molecule is needed. A method for transforming reactants into products via an operator with a convenient computational representation is included. Finally, approaches for telling molecules apart and determining their uniqueness must be incorporated. The specific implementation that will be highlighted here is that of Broadbelt and coworkers which has been applied to a wide range of chemistries, including hydrocarbon pyrolysis,[52-55,64] silicon hydride clustering,[7] Fischer-Tropsch synthesis,[59] and amino acid biosynthesis.[8,9]

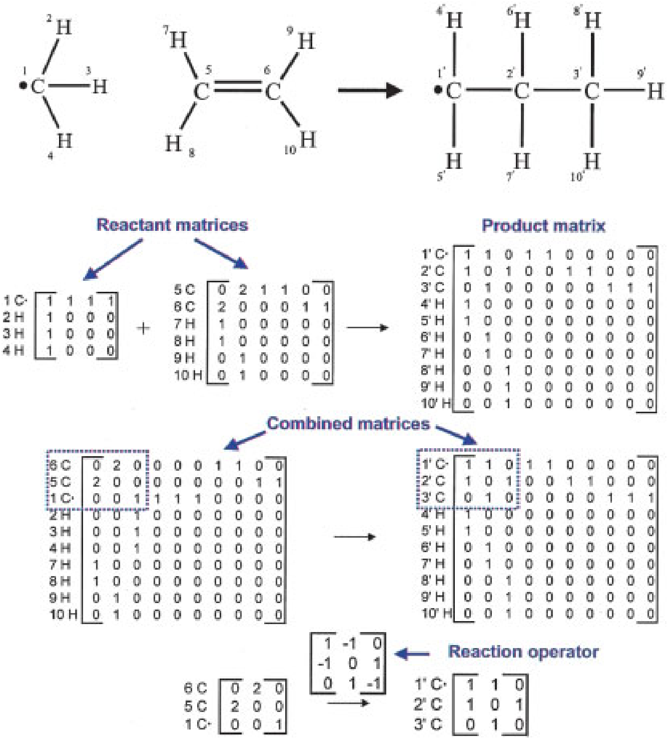

Figure 2. Development of a reaction matrix for radical addition.

Atoms in reactants and products are numbered and converted into BE matrices. The matrices are combined and the atoms that are affected are moved to the top. The matrices for the affected atoms are separated and a reaction matrix is calculated.

The species are represented in the computer as graphs, thereby unleashing all of the powerful algorithms that graph theory has to offer. A graph representation of a molecule is comprised of a finite set of vertices and edges and a set of rules describing the edge/vertex connectivity. A substantial amount of information about the species can be stored with or determined from the connectivity information, including formal charge, nonbonded electron count, stereochemistry, aromaticity, oxidation state and even three-dimensional (3-D) structure given an appropriate conversion algorithm.[65,66] To tell species apart, their connectivity is transformed into an appropriate canonical representation which is typically a string code[67,68] that allows for easy comparison in the computer.

Given a graph theoretic representation of species, chemical reaction is then implemented by applying rules for changing properties of the vertices, and their connectivity. A simple way to illustrate this is using the concept of bond and electron (BE) matrices [69] to represent species. The diagonal element *ii* of the BE matrix gives the number of nonbonded valence electrons of atom *i*, and off-diagonal entries *ij*, provide the connectivity and bond order of atoms *i* and *j*. An example BE matrix for 1-propyl radical is shown in the upper righthand portion of Figure 2. The rows of the BE matrix correspond to the atoms in the order in which they are numbered in the picture on the left. Chemical reaction may then be carried out via simple manipulation of the BE matrices of reactant species which are temporarily created from species' graph representations. Because the number of atoms whose connectivity and electronic environment changes as a result of reaction is small, chemical reaction can be carried out by operating on a small, dense sub-matrix. To carry out a particular reaction type, the reaction matrix that quantifies the change in the electronic configurations and the connectivity among the atoms affected by reaction is determined. The reaction matrices can then be identified by simple matrix subtraction of the reactant and product matrices. This is illustrated in Figure 2 for a radical addition reaction. First, the reactants, methyl radical and ethylene, and products, 1-propyl radical, are represented by their BE matrices. The two matrices for the reactants are combined into one matrix, and the same is done for the products. The matrices are then permuted in a consistent manner so that the atoms that will experience the bond breaking, bond formation, or change in number of nonbonded electrons are moved to the upper left-hand corner. The reaction matrix for radical addition is then calculated by the difference between the reactant and product matrices. The reaction matrix obtained is general and can now be applied to any combination of a radical and a substrate with an unsaturated bond.

Generation of a complex reaction network is, thus, distilled into specification of the set of reaction matrices, or operators, that the user deems likely based on chemical knowledge and rules for their implementation. For example, if the user desires to build a reaction network for amino acid biosynthesis, reaction matrices can be formulated for the generalized enzyme actions as defined using the third-level of the enzyme classification system. In fact, the Broadbelt and Hatzimanikatis groups have proposed that biochemical reactions, either known or novel, can be generated using the small number (~200) of known enzyme actions in the Kyoto Encyclopedia of Genes and Genomes.[8,9] Note that automated network generation is faithful to the reaction matrices that are provided by the user, i.e., new types of transformations are not suggested by the software. However, application of the reaction matrices to the reactants and their progeny does create species and reactions that are new to the user's current understanding of the reaction system because of the user's inability to conceive of all of the combinatorial possibilities.

Kinetic (kə-nĕt′ ĭk) and Thermodynamic (thûr′ mō-dī-năm′ ĭk) Parameters

Once the reaction network is in hand, it is critical to specify thermodynamic and kinetic parameters for every reaction in the network. These parameters are required for model solution, and even if model reduction is the ultimate aim, rate parameters are needed to allow sensitivity analysis to be performed. Specification of rate parameters and thermodynamic properties for every reaction is a challenging task, particularly since automated network generation can easily generate $O(10^4)$ reactions or more. However, the advent of computational techniques that have recently emerged has made estimation of these quantities a practical reality.

Figure 3 summarizes a hierarchical approach for estimating kinetic and thermodynamic parameters that seeks to maximize accuracy, while minimizing computational effort. To estimate rate coefficients, experimental values that are available in databases or in individual research articles and that are deemed reliable are at the top of the hierarchy. However, experimental values of rate coefficients for individual elementary steps or reactions are limited. It is an experimental challenge to detect and measure intermediates, and it is difficult to isolate an individual reaction of interest. Furthermore, many reactions are carried out in a complicated reaction environment, including solvents or catalysts. The second choice in the hierarchy is to use kinetic correlations. The idea is that rate coefficients, which are hard to measure or estimate, can be related to a reactivity index, such as thermodynamic quantities, that is easier to measure or predict. Kinetic correlations are the perfect complement to automated network generation since they can be derived from a small set of reactions that are well characterized, accessed quickly on-the-fly and applied to a broad set of related reactions. The final choice in the hierarchy for estimating rate coefficients is transition state theory. Transition state theory can be widely applied to a number of different reaction systems, but it is currently too computationally intensive and requires substantial manual intervention to be realized on-the-fly.

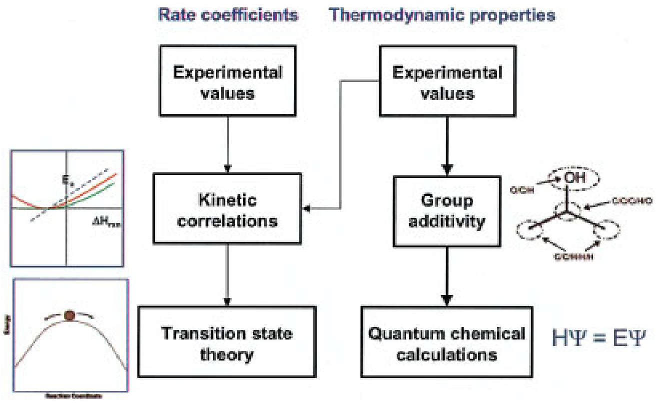

Figure 3. Hierarchical approach for estimating thermodynamic and kinetic parameters of complex reaction networks.

A similar hierarchy is proposed for thermodynamic properties. Thermodynamic quantities are used to estimate equilibrium constants to ensure that reactions are thermodynamically consistent, and thermodynamic properties are one common choice as reactivity indices in kinetic correlations. The first choice for specifying thermodynamic quantities is experimental data. Although these data are more plentiful than experimental data for rate coefficients, tabulated data that have been well curated are restricted to certain systems. For example, gas-phase heats of formation for molecules are widely available, but values for radicals, ions, or surface intermediates are more rare. The next option in the hierarchy is to estimate properties using group additivity schemes. Group additivity estimates properties of a species via summation of the contributions from its constituent groups. Finally, quantum chemical calculations can be used to calculate thermodynamic properties or other reactivity indices directly.

The following sections discuss computational approaches for calculating thermodynamic quantities and rate coefficients. Examples of the application of the various approaches from the literature will be provided so that their applicability to different types of chemistries will be highlighted. At this point, our dictionary of kinetic modeling expands rapidly, as there are many different techniques with which the kinetic modeler should be familiar.

Thermodynamics

Group additivity offers a rapid and reliable way to calculate thermodynamic and other properties. Pioneered by Benson,[70] a group is typically defined as a central atom and all of its ligands. Species are decomposed into groups, and then the property of the species is obtained as the summation of the constituent group values. Group additivity can be used to calculate heats of formation, entropies and heat capacities as a function of temperature for compounds that contain a wide range of atoms, including carbon, hydrogen, oxygen, nitrogen, phosphorous, halogens, and sulfur. Groups for intermediates such as free radicals are even available. Values are typically defined for the gas-phase, but some liquid-phase and solid-phase values are available. More recently, the concept of group additivity was extended to biochemical compounds to calculate free energies at biologically relevant conditions.[71] Group values can be easily organized in a computer database for facile lookup during automated network generation. Accuracies of less than 1 kcal mol^{-1} for heats for formation of gas-phase hydrocarbons, for example, are achieved.

It is important that all groups present in all molecules that might be encountered in a complex reaction network be available. Thus, there are continued efforts to derive new group values.[72-76] Unknown groups can be regressed against experimental data, but it is becoming increasingly common to use quantum chemical methods to calculate properties of species from which new group values can be regressed. Hybrid methods such as G3[40] that can achieve accuracies comparable to that of experimental data have made this approach a viable one.

Calculation of thermodynamic properties from quantum chemistry has been used with increasing frequency. The approach is to optimize the geometry of a species, calculate vibrational frequencies by evaluating the Hessian matrix, and use statistical mechanics to calculate the enthalpy, entropy and heat capacity.[77] Heats of formation are often the desired thermodynamic quantity, but these are not obtained directly from an individual quantum chemical calculation. Rather, a series of calculations involving the atomization energy components or reactants and products of isodesmic reactions, in which the bond types on either side of the reaction, is carried out. Typically, the harmonic oscillator approximation is used, but there are methods for identifying and treating hindered and free rotors[78] to obtain more accurate values. Geometry optimization can be challenging for large molecules because of the presence of many low-energy conformations, but approaches that facilitate conformational searching are available.[79]

Rate coefficients

Prediction of rate coefficients is more challenging than estimating thermodynamic properties, yet there are computational methods that can predict values in good agreement with experiment (for a nice review see Sumathi and Green (2002) [80]). Furthermore, even with the advent of high throughput screening methods, one can envision that computational methods are the most viable choice for estimating individual rate coefficients for systems of $O(10^4)$ or more reactions. In accord with the hierarchy of Figure 3, we first focus on kinetic correlations, in which a property that can be estimated more easily than the rate coefficient itself is used to predict reactivity.

Historically, kinetic correlations with thermodynamic properties as the reactivity indices have been most widely used. One classic example is the Evans-Polanyi relationship, $E_a = E_o + \alpha \Delta H_r$, where E_a is the activation energy, E_o is the intrinsic barrier, α is the transfer coefficient and ΔH_r is the heat of reaction. The underlying idea is that the Evans-Polanyi relationship will hold for reactions that have similar reaction coordinates such that the differences in the entropic changes during the reaction for all members of the reaction family are zero or proportional to the enthalpic changes. As a result, all members of the reaction family share the same Arrhenius pre-exponential factor, and E_a can be calculated by knowing only the heat of reaction. Variations of or improvements upon the Evans-Polanyi relationship include the Blowers and Masel correlation for atom transfer reactions.[81] Originally developed for intermolecular hydrogen transfer reactions, the Evans-Polanyi relationship has been extended to intramolecular cyclization reactions of hydroperoxyl radicals,[82] radical addition/β-scission reactions,[83] catalytic cracking,[84] and reactions relevant to silicon nanoparticle production.[7]

The Evans-Polanyi relationship is not a panacea, however, and thermodynamic properties are not always an appropriate reactivity index. For example, Hemelsoet et al.[85] showed using density functional theory calculations that hydrogen abstraction reactions by methyl radical from polynuclear aromatics were not well described by an Evans-Polanyi correlation when a series of polyaromatics was studied. Instead, they showed that the principle of hard and soft acids and bases and the related concept of the Fukui function were good predictors of the activation barrier. In the same work, they also showed that the kinetics of cyclization reactions involving aromatic moieties were well correlated with magnetic susceptibility and proton chemical shift.

The majority of the kinetic correlations that have been developed in recent years are relying on performing a set of quantum chemical calculations on select reactions in a particular family and using transition state theory to predict energy barriers. The hope is that performing select calculations at a high level of theory that are computationally demanding but accurate will allow the kinetics of related reactions to be easily predicted. Alternatively, one can envision, with sufficient computational resources, that transition state theory can be used directly to estimate a rate coefficient for every reaction in a complex network. It is, thus, important to understand the foundation of transition state theory and how quantum chemical calculations are used in conjunction with it as we add it to our dictionary of kinetic modeling.

The underlying concept of transition state theory is that a reaction proceeds via an activated complex that is located at a saddle point on the potential energy surface as illustrated in Figure 4. The reactants and the activated complex are assumed to be in equilibrium, and the activated complex, or transition state, decomposes with a rate constant equal to $k_B T/h$, where k_B is Boltzmann's constant, T is temperature, and h is Planck's constant. The transition state theory rate constant, k_{TST}, is thus

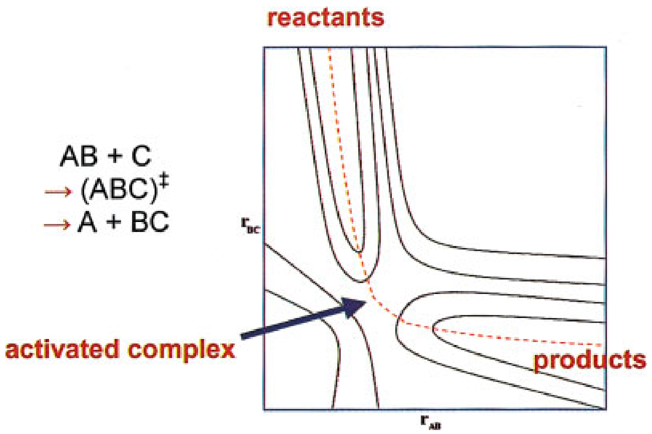

Figure 4. Transition state theory estimates rate coefficients by identifying and characterizing an activated complex that lies at a saddle point along the minimum energy path between reactants and products (shown as the dotted line).

$$k_{TST} = (c^{o})^{1-n}\,\frac{k_B T}{h}\,e^{-\Delta G^{\dagger}/RT} \tag{1}$$

where $\Delta G^{\pm}$ is equal to the change in free energy between the reactants and the transition state, n is the molecularity of the reaction, and c^{o} is equal to a standard state concentration, which is typically set equal to 1 M. Effects of quantum mechanical tunneling can also be taken into account using the transmission coefficient.

The role of quantum mechanics in calculating rate coefficients using transition state theory is to calculate $\Delta G^{\dagger}$. In its conventional formulation, this involves locating and characterizing the reactants and the transition state on the electronic energy surface and using statistical mechanics to calculate free energies. The transition state is located at a saddle point on the potential energy surface, so it is characterized by having one negative eigenvalue of the Hessian matrix. There are different approaches to locating transition states. Most simply, a reaction coordinate is postulated, and the potential energy surface is scanned at fixed values of the reaction coordinate to map the energy until a maximum is observed. The structure at the maximum can then be refined to ensure that it is a true saddle point. There are also methods in typical quantum chemical software that facilitate location of transition states, such as QST2 and QST3, but they are often not successful. The nudged elastic band method[86] is another popular approach for mapping reaction coordinates that has even been improved and extended to optimization of reaction paths for enzymatic systems[87] that have many flexible degrees of freedom. String methods and growing string methods[88] have also been developed.

Applications of transition state theory to estimate rate coefficients via quantum chemistry are growing, and many of these reports underscore the importance of choosing a sufficiently high level of theory and a large enough basis set to achieve results of desirable accuracy. For example, Wijaya et al.[82] showed that CBS-QB3 agreed well with limited experimental data for cyclization of various hydroperoxyl radicals to form cyclic ethers, but a high level of theory that is commonly used, B3LYP, underestimated barrier heights by as much as 8 kcal mol^{-1}. There is also value in using transition state theory to estimate which intermediates on surfaces are not kinetically significant, even if reaction barriers with accuracy comparable to experiment are not obtained, since quantum chemistry does a very good job of ranking the relative stabilities of species. For example, Alcala et al.[29,30] calculated transition state structures for reactions of ethanol-derived intermediates on platinum and platinum-tin catalysts, and showed that they could predict the relative likelihood of different carbon-carbon and carbon-oxygen cleavage reactions. Transition state theory is also being used successfully in conjunction with molecular orbital methods to study enzyme kinetics[50].

Methods to facilitate the use of transition state theory and improve its accuracy are also available. Recently, Saeys et al.[72] and Sumathi and coworkers[89-91] have developed an approach for estimating the thermodynamic properties of activated complexes. They proposed that the energy of a reactive center in an activated complex may be calculated via group additivity through the introduction of "supergroups" which were obtained from quantum chemical calculations. Variational transition state theory[92] and other dynamical methods[93] seek to improve upon conventional transition state theory. Variational transition state theory (VTST) uses the concept of a generalized transition state that is a hypersurface in position and momentum space that divides reactants and products, which is varied to minimize the flux coefficients. A further basis of VTST is that a more accurate barrier to the reaction can be obtained by considering an energy surface of the Gibbs free energy, rather than the electronic energy.

Future Prospects

Although chemical engineers work on a large array of different reacting systems that can be characterized as complex, this Perspective aims to reveal the links among them through the lexicography of kinetic modeling of complex reaction systems. Key entries have been defined that encompass computational techniques for the elucidation of species and reactions and characterization of the associated thermodynamic and kinetic parameters. While chemistries such as pyrolysis, combustion, polymerization, glycolysis, amino acid biosynthesis, silicon nanoparticle growth and Fischer-Tropsch synthesis may appear discordant, revelation of their common elements suggests harmony, and even synergy, among them.

Computational approaches are currently at hand for unraveling the species and reactions comprising complex reaction networks. Our lexicography starts with **quantum chemistry**, a general approach for uncovering details in reacting systems. Potential energy, or even free energy, surfaces can be mapped in detail, thereby revealing what reactive intermediates are stable and how one intermediate may be transformed into another. Quantum chemistry offers precise control over what reactions are explored, as it is possible to interrogate individual elementary steps.

Automated network generation is another important entry in the dictionary of complex kinetic modeling. It provides a framework for expressing chemical knowledge that can be universally applied to disparate reacting systems. It removes the tedium of developing complex reaction networks by hand, and it allows one to rapidly and reliably test hypotheses about possible reaction types and their rules. It even has the potential to reveal novel compounds and suggest new routes for their synthesis.[8] It can even be argued that a software package for performing automated network generation is as essential to kinetic model development as a stiff differential-algebraic equation solver is to model solution or a graphing program is to visualizing results.

The prospects for estimating thermodynamic properties for a wide variety of complex reaction systems are excellent. The key entries in the dictionary of kinetic modeling are **group additivity** and **quantum chemistry**. Group additivity databases are continually being developed and expanded and even encompass molecules in biochemical environments. In theory, quantum chemistry is a very general approach that can even be used to predict new group additivity values. It is much more computationally expensive, but its application to heterogeneous, liquid-phase, and biological systems has been demonstrated.

Estimation of rate coefficients is more difficult, but it is now possible to predict kinetic parameters within experimental accuracy by using transition state theory or its extensions. The use of **transition state theory** has increased with the advent of computational **quantum chemistry** for locating and characterizing activated complexes. Accurate results require high levels of theory and corrections to the conventional formulation. The development of **kinetic correlations** has also exploded with the growth of quantum chemistry, because it is possible to predict kinetic parameters such as activation barriers while at the same time calculating other properties that may serve as appropriate reactivity indices. Emerging **group additivity** schemes for activated complexes demonstrate great promise to estimate rate coefficients quickly and reliably and offer an alternative to more conventional kinetic correlations. While it is still challenging to include the effects of the reaction environment, such as solvents, catalysts, or enzymes when calculating rate coefficients, the theoretical foundation is in place, and the arsenal of computational approaches for including realistic reaction environments is growing at a rapid pace.

Acknowledgments

The authors appreciate fruitful discussions with Vassily Hatzimanikatis, Mark Swihart and Robin Hutchinson in formulating the ideas reflected in this Perspective. The financial support of the National Science Foundation and Department of Energy for funding is also gratefully acknowledged.

Literature Cited

1. Froment GF. Single event kinetic modeling of complex catalytic processes. *Catalysis Reviews-Sci and Eng*. 2005; **47**:83-124.
2. Narasimhan CSL, Thybaut JW, Marin GB, Denayer JF, Baron GV, Martens JA, Jacobs PA. Relumped single-event microkinetic model for alkane hydrocracking on shape-selective catalysts: Catalysis on ZSM-22 pore mouths, bridge acid sites and micropores. *Chem Eng Sci*. 2004;**59**: 4765-4772.
3. Matheu DM, Dean AM, Grenda JM, Green WH. Mechanism generation with integrated pressure dependence: A new model for methane pyrolysis. *J of Physical Chem A*. 2003;**107**:8552-8565.
4. Tranter RS, Sivaramakrishnan R, Brezinsky K, Allendorf MD. High pressure, high temperature shock tube studies of ethane pyrolysis and oxidation. *Physical Chem Chem Phys*. 2002;**4**:2001-2010.
5. Campbell JD, Teymour F, Morbidelli M. Production of hyperbranched polystyrene by high-temperature polymerization. *Macromolecules*. 2005;**38**:752-760.
6. Hutchinson RA. Modeling of chain length and long-chain branching distributions in free-radical polymerization. *Macromolecular Theory and Simulations*. 2001;**10**:144-157.
7. Wong HW, Li XG, Swihart MT, Broadbelt LJ. Detailed kinetic modeling of silicon nanoparticle formation chemistry via automated mechanism generation. *J of Physical Chem A*. 2004;**108**:10122-10132.
8. Li CH, Henry CS, Jankowski MD, Ionita JA, Hatzimanikatis V, Broadbelt LJ. Computational discovery of biochemical routes to specialty chemicals. *Chem Eng Sci*. 2004;**59**:5051-5060.
9. Hatzimanikatis V, Li CH, Ionita JA, Henry CS, Jankowski MD, Broadbelt LJ. Exploring the diversity of complex metabolic networks. *Bioinformatics*. 2005;**21**:1603-1609.
10. Hatzimanikatis V, Li CH, Ionita JA, Broadbelt LJ. Metabolic networks: Enzyme function and metabolite structure. *Current Opinion in Structural Biology*. 2004;**14**:300-306.
11. Holzhutter S, Holzhutter HG. Computational design of reduced metabolic networks. *Chembiochem*. 2004;**5**:1401-1422.
12. Blackmond DG. Requiem for the reaction-rate equation? (vol **83**, pg 133, 2002). *Catalysis Letts*. 2003;**89**:281-284.
13. Dumesic JA, Aparicio LM, Trevino AA, Rekoske JE, Rudd DF. *The Microkinetics of Heterogeneous Catalysis*. Washington, DC: American Chemical Society; 1993.
14. Babushok VI, Tsang W. Kinetic modeling of heptane combustion and PAH formation. *J of Propulsion and Power*. 2004;**20**:403-414.
15. Curran HJ, Gaffuri P, Pitz WJ, Westbrook CK. A comprehensive modeling study of iso-octane oxidation. *Combustion and Flame*. 2002;**129**:253-280.
16. Fournet R, Battin-Leclerc F, Glaude PA, Judenherc B, Warth V, Come GM, Scacchi G, Ristori A, Pengloan G, Dagaut P, Cathonnet M. The gas-phase oxidation of n-hexadecane. *Intl J of Chemical Kinetics*. 2001;**33**:574-586.
17. Ranzi E, Dente M, Goldaniga A, Bozzano G, Faravelli T. Lumping procedures in detailed kinetic modeling of gasification, pyrolysis, partial oxidation and combustion of hydrocarbon mixtures. *Progr in Energy and Combustion Sci*. 2001;**27**:99-139.
18. Westbrook CK, Pitz WJ, Curran HJ, Boercker J, Kunrath E. Chemical kinetic modeling study of shock tube ignition of heptane isomers. *Int J of Chemical Kinetics*. 2001;**33**: 868-877.
19. Bhattacharjee B, Schwer DA, Barton PI, Green WH. Optimally-reduced kinetic models: Reaction elimination in large-scale kinetic mechanisms. *Combustion and Flame*. 2003;**135**:191-208.
20. Schwer DA, Lu PS, Green WH. An adaptive chemistry approach to modeling complex kinetics in reacting flows. *Combustion and Flame*. 2003;**133**:451-465.
21. Dooling DJ, Rekoske JE, Broadbelt LJ. Microkinetic models of catalytic reactions on nonuniform surfaces: Application to model and real systems. *Langmuir*. 1999;**15**: 5846-5856.

22. Hinrichsen O. Kinetic simulation of ammonia synthesis catalyzed by ruthenium. *Catalysis Today*. 1999;**53**:177-188.
23. Honkala K, Hellman A, Remediakis IN, Logadottir A, Carlsson A, Dahl S, Christensen CH, Norskov JK. Ammonia synthesis from first-principles calculations. *Sci*. 2005;**307**:555-558.
24. Mhadeshwar AB, Kitchin JR, Barteau MA, Vlachos DG. The role of adsorbate-adsorbate interactions in the rate controlling step and the most abundant reaction intermediate of NH_3 decomposition on Ru. *Catalysis Letts*. 2004; **96**:13-22.
25. Zupanc C, Hornung A, Hinrichsen O, Muhler M. The interaction of hydrogen with Ru/MgO catalysts. *J of Catalysis*. 2002;**209**:501-514.
26. Murzin DY. On surface heterogeneity and catalytic kinetics. *Ind & Eng Chem Res*. 2005;**44**:1688-1697.
27. Mhadeshwar AB, Vlachos DG. Microkinetic modeling for water-promoted CO oxidation, water-gas shift, and preferential oxidation of CO on Pt. *J of Physical Chem B*. 2004;**108**:15246-15258.
28. Ciobica IM, Kramer GJ, Ge Q, Neurock M, van Santen RA. Mechanisms for chain growth in Fischer-Tropsch synthesis over Ru(0001). *J of Catalysis*. 2002;**212**:136-144.
29. Alcala R, Mavrikakis M, Dumesic JA. DFT studies for cleavage of C-C and C-O bonds in surface species derived from ethanol on Pt(111). *J of Catalysis*. 2003;**218**:178-190.
30. Alcala R, Shabaker JW, Huber GW, Sanchez-Castillo MA, Dumesic JA. Experimental and DFT studies of the conversion of ethanol and acetic acid on PtSn-based catalysts. *J of Phys Chem B*. 2005;**109**:2074-2085.
31. Klinke DJ, Wilke S, Broadbelt LJ. A theoretical study of carbon chemisorption on Ni(111) and Co(0001) surfaces. *J of Catalysis*. 1998;**178**:540-554.
32. Klinke DJ, Dooling DJ, Broadbelt LJ. A theoretical study of methylidyne chemisorption on Ni(111) and Co(0001) surfaces. *Surface Sci*. 1999;**425**:334-342.
33. McMillan SA, Snurr RQ, Broadbelt LJ. Origin and characteristics of preferential adsorption on different sites in cobalt-exchanged ferrierite. *J of Phys Chem B*. 2003;**107**: 13329-13335.
34. McMillan SA, Broadbelt LJ, Snurr RQ. Effect of local framework heterogeneity on NO adsorption in cobalt-ferrierite. *J of Catalysis*. 2003;**219**:117-125.
35. Klinke DJ, Broadbelt LJ. A theoretical study of hydrogen chemisorption on Ni(111) and Co(0001) surfaces. *Surface Sci*. 1999;**429**:169-177.
36. Jensen F. *Introduction to Computational Chemistry*. New York: Wiley; 1998.
37. Leach A. *Molecular modelling: Principles and applications*. New York: Prentice Hall; 2001.
38. Santiso EE,Gubbins KE. Multi-scale molecular modeling of chemical reactivity. *Molecular Simulation*. 2004;**30**: 699-748.
39. Gorelsky S. Software for computational chemistry. In: *Comprehensive Coordination Chemistry - II*. Meyer T, McCleverty J. Boston: Elsevier; 2004.
40. Curtiss LA, Raghavachari K. Gaussian-3 and related methods for accurate thermochemistry. *Theor Chem Accts*. 2002;**108**:61-70.
41. Carstensen HH, Naik CV, Dean AM. Detailed modeling of the reaction of $C_2H_5+O_2$. *J of Phys Chem A*. 2005;**109**: 2264-2281.
42. Broadbelt LJ, Snurr RQ. Applications of molecular modeling in heterogeneous catalysis research. *Appl Catalysis A-Gen*. 2000;**200**:23-46.
43. Dooling DJ, Nielsen RJ, Broadbelt LJ. A density-functional study of the interaction of nitrogen with ruthenium clusters. *Chem Eng Sci*. 1999;**54**:3399-3409.
44. Greeley J, Mavrikakis M. Alloy catalysts designed from first principles. *Nature Materials*. 2004;**3**:810-815.
45. Heyden A, Peters B, Bell AT, Keil FJ. Comprehensive DFT study of nitrous oxide decomposition over Fe-ZSM-5. *J of Phys Chem B*. 2005;**109**:1857-1873.
46. Hinnemann B, Norskov JK, Topsoe H. A density functional study of the chemical differences between type I and type II MoS_2-based structures in hydrotreating catalysts. *J of Phys Chem B*. 2005;**109**:2245-2253.
47. Vang RT, Honkala K, Dahl S, Vestergaard EK, Schnadt J, Laegsgaard E, Clausen BS, Norskov JK, Besenbacher F. Controlling the catalytic bond-breaking selectivity of Ni surfaces by step blocking. *Nature Materials*. 2005;**4**:160-162.
48. Wells DH, Delgass WN, Thomson KT. Formation of hydrogen peroxide from H_2 and O_2 over a neutral gold trimer: A DFT study. *J of Catalysis*. 2004;**225**:69-77.
49. Wells DH, Delgass WN, Thomson KT. Evidence of defect-promoted reactivity for epoxidation of propylene in titanosilicate (TS-1) catalysts: A DFT study. *J of the A Chem Soc*. 2004;**126**:2956-2962.
50. Gao JL, Truhlar DG. Quantum mechanical methods for enzyme kinetics. *Annual Review of Phys Chem*. 2002;**53**: 467-505.
51. Rod TH, Ryde U. Quantum mechanical free energy barrier for an enzymatic reaction. *Phys Review Letts*. 2005;**94**: Article No 138302.
52. Broadbelt LJ, Stark SM, Klein MT. Computer-generated pyrolysis modeling - on-the-fly generation of species, reactions, and rates. *Ind & Eng Chem Res*. 1994;**33**:790-799.
53. Broadbelt LJ, Stark SM, Klein MT. Termination of computer-generated reaction-mechanisms - species rank-based convergence criterion. *Ind & Eng Chem Res*. 1995;**34**: 2566-2573.
54. Broadbelt LJ, Stark SM, Klein MT. Computer generated reaction modelling: Decomposition and encoding algorithms for determining species uniqueness. *Comp & Chem Eng*. 1996;**20**:113-129.
55. De Witt MJ, Dooling DJ, Broadbelt LJ. Computer generation of reaction mechanisms using quantitative rate information: Application to long-chain hydrocarbon pyrolysis. *Ind & Eng Chem Res*. 2000;**39**:2228-2237.
56. Green WH, Barton PI, Bhattacharjee B, Matheu DM, Schwer DA, Song J, Sumathi R, Carstensen HH, Dean AM, Grenda JM. Computer construction of detailed chemical kinetic models for gas-phase reactors. *Ind & Eng Chem Res*. 2001;**40**:5362-5370.
57. Iyer SD, Joshi PV, Klein MT. Automated model building and modeling of alcohol oxidation in high temperature water. *Environ Prog*. 1998;**17**:221-233.
58. Klinke DJ, Broadbelt LJ. Mechanism reduction during

computer generation of compact reaction models. *AIChE J*. 1997;**43**:1828-1837.
59. Klinke DJ, Broadbelt LJ. Construction of a mechanistic model of Fischer-Tropsch synthesis on Ni(111) and Co(0001) surfaces. *Chem Eng Sci*. 1999;**54**:3379-3389.
60. Prickett SE, Mavrovouniotis ML. Construction of complex reaction systems - III. An example: Alkylation of olefins. *Comp & Chem Eng*. 1997;**21**:1325-1337.
61. Prickett SE, Mavrovouniotis ML. Construction of complex reaction systems.1. Reaction description language. *Comp & Chem Eng*. 1997;**21**:1219-1235.
62. Prickett SE, Mavrovouniotis ML. Construction of complex reaction systems. 2. Molecule manipulation and reaction application algorithms. *Comp & Chem Eng*. 1997;**21**: 1237-1254.
63. Ratkiewicz A, Truong TN. Application of chemical graph theory for automated mechanism generation. *J of Chem Info and Comp Sci*. 2003;**43**:36-44.
64. Susnow RG, Dean AM, Green WH, Peczak P, Broadbelt LJ. Rate-based construction of kinetic models for complex systems. *J of Phy Chem A*. 1997;**101**:3731-3740.
65. Gasteiger J, Sadowski J, Schuur J, Selzer P, Steinhauer L, Steinhauer V. Chemical information in 3D space. *J of Chem Info and Comp Sci*. 1996;**36**:1030-1037.
66. Sadowski J, Gasteiger J, Klebe G. Comparison of automatic 3-dimensional model builders using 639 X-ray structures. *J of Chem Info and Comp Sci*. 1994;**34**:1000-1008.
67. Wong HW, Li XE, Swihart MT, Broadbelt LJ. Encoding of polycyclics si-containing molecules for determining species uniqueness in automated mechanism generation. *J of Chem Info and Comp Sci*. 2003;**43**:735-742.
68. Weininger D, Weininger A, Weininger JL. Smiles. 2. Algorithm for generation of unique smiles notation. *J of Chem Info and Comp Sci*. 1989;**29**:97-101.
69. Ugi I, Bauer J, Brandt J, Friedrich J, Gasteiger J, Jochum C, Schubert W. New applications of computers in chemistry. *Angewandte Chemie-Int Ed in English*. 1979;**18**:111-123.
70. Benson SW. Thermochemical Kinetics. New York: Wiley; 1976.
71. Mavrovouniotis ML. Estimation of standard Gibbs energy changes of biotransformations. *J of Biological Chem*. 1991;**266**:14440-14445.
72. Saeys M, Reyniers MF, Marin GB, Van Speybroeck V, Waroquier M. Ab initio group contribution method for activation energies for radical additions. *AIChE J*. 2004; **50**:426-444.
73. Sumathi R, Green WH. Missing thermochemical groups for large unsaturated hydrocarbons: Contrasting predictions of G2 and CBS-Q. *J of Phys Chem A*. 2002;**106**: 11141-11149.
74. Sumathi R, Green WH. Thermodynamic properties of ketenes: Group additivity values from quantum chemical calculations. *J of Phys Chem A*. 2002;**106**:7937-7949.
75. Swihart MT, Girshick SL. Thermochemistry and kinetics of silicon hydride cluster formation during thermal decomposition of silane. *J of Phys Chem B*. 1999;**103**:64-76.
76. Wong HW, Nieto JCA, Swihart MT, Broadbelt LJ. Thermochemistry of silicon-hydrogen compounds generalized from quantum chemical calculations. *J of Phys Chem A*. 2004;**108**:874-897.
77. McQuarrie DA. *Statistical Mechanics*. Sausalito, CA: University Science Books, 2000.
78. Ayala PY, Schlegel HB. Identification and treatment of internal rotation in normal mode vibrational analysis. *J of Chem Phys*. 1998;**108**:2314-2325.
79. Haubein NC, McMillan SA, Broadbelt LJ. Many-body optimization using an ab initio Monte Carlo method. *J of Chem Info and Comp Sci*. 2003;**43**:68-74.
80. Sumathi R, Green WH. A priori rate constants for kinetic modeling. *Theoretical Chem Accts*. 2002;**108**:187-213.
81. Blowers P, Masel RI. An extension of the Marcus equation for atom transfer reactions. *Journal of Physical Chemistry A*. 1999;**103**:7047-7054.
82. Wijaya CD, Sumathi R, Green WH. Thermodynamic properties and kinetic parameters for cyclic ether formation from hydroperoxyalkyl radicals. *J of Phys Chem A*. 2003; **107**:4908-4920.
83. Saeys M, Reyniers MF, Marin GB, Van Speybroeck V, Waroquier M. Ab initio calculations for hydrocarbons: Enthalpy of formation, transition state geometry, and activation energy for radical reactions. *J of Phys Chem A*. 2003;**107**:9147-9159.
84. Yaluris G, Rekoske JE, Aparicio LM, Madon RJ, Dumesic JA. Isobutane cracking over Y-zeolites.1. Development of a kinetic-model. *J of Catalysis*. 1995;**153**:54-64.
85. Hemelsoet K, Van Speybroeck V, Marin GB, De Proft F, Geerlings P, Waroquier M. Reactivity indices for radical reactions involving polyaromatics. *J of Phys Chem A*. 2004;**108**:7281-7290.
86. Mills G, Jonsson H, Schenter GK. Reversible work transition-state theory - application to dissociative adsorption of hydrogen. *Surface Sci*. 1995;**324**:305-337.
87. Xie L, Liu HY, Yang WT. Adapting the nudged elastic band method for determining minimum-energy paths of chemical reactions in enzymes. *J of Chem Phys*. 2004;**120**:8039-8052.
88. Peters B, Heyden A, Bell AT, Chakraborty A. A growing string method for determining transition states: Comparison to the nudged elastic band and string methods. *J of Chem Phys*. 2004;**120**:7877-7886.
89. Sumathi R, Carstensen HH, Green WH. Reaction rate prediction via group additivity, part 2: H-abstraction from alkenes, alkynes, alcohols, aldehydes, and acids by H atoms. *J of Phys Chem A*. 2001;**105**:8969-8984.
90. Sumathi R, Carstensen HH, Green WH. Reaction rate prediction via group additivity part 1: H abstraction from alkanes by H and CH_3. *J of Phys Chem A*. 2001;**105**:6910-6925.
91. Sumathi R, Carstensen HH, Green WH. Reaction rate predictions via group additivity. Part 3: Effect of substituents with CH_2 as the mediator. *J of Phys Chem A*. 2002; **106**:5474-5489.
92. Truhlar DG, Garrett BC. Variational transition-state theory. *Annual Review of Phy Chem*. 1984;**35**:159-189.
93. Peters B, Bell AT, Chakraborty A. Rate constants from the reaction path Hamiltonian. I. Reactive flux simulations for dynamically correct rates. *J of Chem Phys*. 2004;**121**: 4453-4460.