Algorithmic reaction explorations based on transition state searches can now routinely predict relatively short reaction sequences involving small molecules across a variety of chemical domains, including materials degradation, combustion chemistry, battery performance, and biomass conversion. Mature quantum chemistry tools can comprehensively characterize the reactivity of species with efficiency and broad coverage, but consecutive characterizations quickly encounter prohibitive costs of reactant proliferation, spurious characterization of irrelevant intermediates, and compounding uncertainties of quantum chemical calculations deep in a network. Application of these algorithms to deeper chemical reaction network (CRN) exploration still requires the development of more effective, comprehensive, and automated exploration policies.

This dissertation addresses the challenge of exploring deep chemical reaction networks (CRNs) in complex and chemically diverse systems by introducing Yet Another Kinetic Strategy (YAKS), an automated algorithm designed to minimize the computational costs of deep exploration and maximize coverage of important reaction channels. YAKS demonstrates that microkinetic simulations of the nascent network are cost-effective and able to iteratively build deep networks. Key features of the algorithm are the automatic incorporation of expanded elementary reaction steps, compatibility with short-lived but kinetically important species, and the incorporation of rate uncertainty into the exploration policy. The automatically induced expansion of reaction mechanisms gives YAKS access to important chemistries that other algorithms ignore, while also maintaining the ability to limit expensive forays into kinetically irrelevant regions of the CRN that would stymie previous methods. Instead of conducting a greedy exploration, YAKS biases network topography to probe beyond short-lived but kinetically important species, which enables YAKS to explore important endergonic reactions deep into the CRN. YAKS further induces rate uncertainty into an ensemble of microkinetic simulations, which positively influences intermediate prioritization deep in a network.

Algorithm effectiveness was validated in a case study of glucose pyrolysis, where the algorithm rediscovers reaction pathways previously discovered by heuristic exploration policies and also elucidates new reaction pathways to experimentally obtained products. The resulting CRN is the first to connect all major experimental pyrolysis products to glucose. Additional case studies are presented that investigate the role of reaction rules, rate uncertainty, and bimolecular reactions. These case studies show that na\"ive exponential growth estimates can vastly overestimate the actual number of kinetically relevant pathways in physical reaction networks. The excellent performance of YAKS demonstrates the ability of automated algorithmic methods to address the gaps outlined above.

The power of YAKS was then demonstrated on radically distinct chemistry from the validation study, chemical warfare agents (CWAs). Despite the almost uniform ban on the use of chemical warfare agents (CWAs) and the widespread neutralization of stockpiles due to treaties, CWAs continue to pose a grave threat around the world. Rogue states, terrorist organizations, and lone wolf terrorists have all conducted CWA attacks within the past few decades. These circumstances make it necessary to prepare against and forensically evaluate the use of CWAs without direct experimentation. YAKS was applied to elucidate degradation reaction networks

of three prominent CWAs, mustard gas (SM, HD), sarin (GB), and VX, and identified a range of possible degradant products of real world use cases. This dissertation also computationally interpreted the most common mechanism of action (MoA) associated with each CWA and examined their hydrolysis networks as a method to neutralize these agents. Additionally, agent stability was evaluated during extended microkinetic modeling in arid and humid scenarios, highlighting the potential for computational simulation approaches to fill a capability gap in the broader field of chemical defense.

This dissertation advanced automated CRN exploration, but considerable gaps remain. Future research directions include the accuracy gaps of both density functional theory and conformational sampling on energy calculations. Incorporation of machine learning (ML) methods can accelerate the costly reactivity characterization process, but ML models still require vast amounts of data. A recently released dataset comprehensively explored over 175,000 graphically defined reactions of moderately-sized C, H, O, and N containing molecules. While models trained on such data could readily be applied to glucose pyrolysis systems, chemical agents involve a much wider array of chemistry including Cl, S, P, and considerable quantities of radical and charged species. More comprehensive datasets are required to train a general ML model capable of accelerating geometry or energy calculations. Additionally, microkinetic modeling is hindered by software implementations that are unable to explore diverse chemistry such as multiphase reactions. In light of this, further improvements in exploration policies, reaction prediction algorithms, and simulation software make it feasible that CRNs might soon be routinely predictable in many additional contexts.