MIT Chemical Engineering Department

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Computer Assistance in Organic Synthesis Planning and Execution

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ABSTRACT: In the discovery and development of new small molecule drugs, there are two critical phases where synthesis is often a bottleneck. The first is during lead optimization, where iterative design-synthesis-test cycles require many "singleton" (one-off) compounds to be made. The second is when a candidate progresses past initial screening and must suddenly be made at the ~kg scale, rather than the ~mg scale, and the efficiency of a synthesis pathway becomes more important. In this talk, I will describe my efforts to address both of these challenges.

Machine learning and data science techniques have enabled new approaches to computer-aided synthesis planning. First, we discuss how the recursive expansion and search strategy can be learned, leveraging the information contained in hundreds of years of published chemical reactions. Second, we discuss the challenge of *in silico* reaction validation, which can be addressed by solving the inverse problem of forward reaction prediction. I will summarize supervised learning approaches we have taken to develop neural network models that can anticipate the major products of a chemical reaction given the reactants and reaction conditions. These techniques for retrosynthesis and forward prediction are integrated into an overall workflow that, for a given molecular target, predicts a rank-ordered list of reaction paths that connect the target to purchasable starting materials via a series of plausible reaction steps.