Automated Execution and Optimization of Flow Chemistry on a Robotic Platform with Integrated Analytics

by

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Technical Summary

The development, optimization, and characterization of chemical processes for the synthesis of organic compounds, which play a key role in society as medicines and materials, is currently an expensive and laborious enterprise. These inefficiencies are driving efforts to develop automated, data-rich experimentation (DRE) platforms and methods designed to maximize the amount of useful data generated per unit time and raw material expended.

In this thesis, a modular robotic platform for continuous flow synthesis was utilized for machine-assisted organic reaction development. An improved version of the platform was built with new capabilities including a Cartesian robot for fast and reliable pick-and-place, integrated process analytical technology (PAT) for online reaction monitoring, and closed-loop feedback optimization of reaction conditions using a Bayesian optimization algorithm.

In the first case study, multi-objective optimization aided in specifying both continuous (e.g., temperature) and categorical (e.g., reagent choice) process parameters for a computer-proposed multistep synthetic route. In multistep flow processes where downstream residence times are physically constrained by upstream flow rates, the platform's modular, robotically-reconfigurable reactor volumes were leveraged to introduce an independent degree of freedom. Deployment of multiple PAT tools facilitated thorough process understanding.

In the second case study, the platform's toolkit was further expanded with the addition of an LED array to perform light-driven photochemical reactions. This new capability enabled the development of two photochemical steps that lead to an important class of drugs.

Finally, the design of data-rich dynamic flow experiments, where continuous reactors are operated under controlled transients in input variables, was computationally studied using transport equations and experimentally validated on the robotic platform. A mathematical criterion to guide the design of dynamic trajectories was developed.

Overall, this thesis demonstrates how machine assistance in the repetitive aspects of experimental execution and data collection can help us focus on the application of domain knowledge, critical interpretation of data, and creative problem-solving.

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