# An End-to-end, Autonomous Platform for Liquid-liquid Extraction Optimization

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## Introduction

Automating the optimization of process chemistry workflows can dramatically accelerate the industrial deployment of new chemistries. However, current robotic and automation solutions tend to be rigid, cost prohibitive, and require highly trained personnel to operate. Furthermore, there are still no standardized approaches for transferable solutions to various unit operations, particularly in the process purification space. Specifically, liquid-liquid extraction (LLE) is an essential and ubiquitous post-reaction unit operation implemented for enhanced purity in several small molecule chemical transformations. The understanding of process parameters and the optimization of extraction conditions is an extremely time- and labour-intensive task, often considered non-innovative. Recent advances in high-throughput experimentation and automated LLE platforms have primarily focused on accelerating screening processes to identify promising extraction conditions. However, these platforms largely do not address the robustness or reliability of extraction conditions under varying process parameters. [1-4]

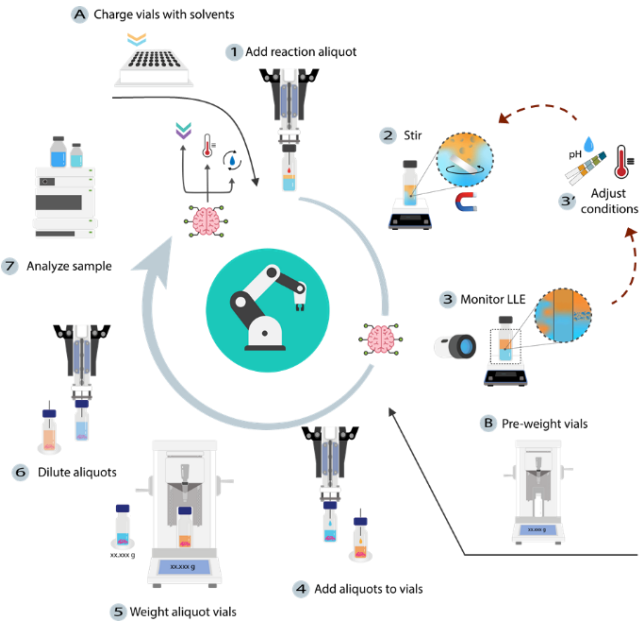


Figure 1 Example autonomous LLE workflow with decision making point depicted

In this work we propose an approach focused on LLE process optimization that leverages computer vision for analysing multiple visual cues and flexible automation for enabling rapid reconfiguration during the platform development. The self-driving lab (SDL) platform was developed in partnership with Bristol Myers Squibb (BMS) and two SDL groups in the Acceleration Consortium, namely the organic chemistry lab (SDL2) at the University of Toronto and the scale-up lab (SDL7) at the University of British Columbia. This new tool enables both optimization and deeper understanding of process characterization parameters for LLE such as purity, yield, and sustainability. Beyond improved screening, the platform can enable testing for scalability and transferability of LLE conditions for broader applications, while its modularity allows for reconfigurability and adaptability of the developed workflows and instrumentation.

## Experimental Methods

The multidisciplinary and multi-site team developed an end-to-end autonomous liquid-liquid extraction robotic platform for process characterization and optimization. The workflow is built upon a flexible automation platform and utilizes end-of-reaction samples, carrying out several crucial steps including: the addition of appropriate organic solvent(s) or aqueous solution(s); the efficient stirring of the biphasic mixture; the live monitoring, identification, and quantification of phase layers; the control of pH and temperature of the sample during the extraction; the physical separation of relevant liquid layers; the sampling, using a mobile liquid handler, and analytical quantification of both layers for recovery and purity assessment, Figure 1.

The novelty in the workflow stands in the two main decision-making points and the autonomy they provide in the execution of LLEs. The first focuses on whether a successful separation was achieved or if any challenging physical pitfalls were encountered (e.g., persistent emulsion, rag layer, etc.). The monitoring unit

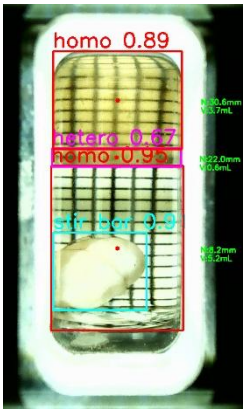


Figure 2 Example output form CV model for 1st decision making point

relies on a custom computer-vision (CV) model, inspired by HeinSight [5], designed to interpret visual cues from the sample in real time, both during the stirring and separation stage of the extraction. The model tracks, analyses, and quantifies visual indicators, providing real-time feedback for scoring and decision-making, Figure 2. The CV model output is not only used to determine the number and the quality of the layers, but also their volume and inform the mobile liquid handler by adjusting the sampling depth. This ensures more reliable operations and allows for variations in volume fractions and samples compositions. Furthermore, instead of relying on predefined time-based actions (e.g., fixed time for phase separation prior to sample the layers), the system can adapt based on observable conditions (e.g., wait until separation is achieved) which can be used to inform how long to stir the sample for and determine its split time. By mimicking expert-level assessments, the system ensures reliable, autonomous operation without the need for constant human oversight. The latter decision-making point concerns the analytical tracking and quantification of components' partition in the different layers, if the extraction was successful, enabling the acquisition of knowledge associated with mass-balance and impurity rejection.

Finally, to ensure long-term use of the platform, the source and execution code were built with modularity and usability in mind, where operations mimic those found in a standard operating procedure. This, coupled with a hardware-agnostic user interface, IvoryOS [6], enables lowering the barrier of entry for the implementation and use of the platform by non-experts and new users. Collectively, these features shift the chemist's role from hands-on execution to oversight and innovation, aligning with prioritization of efficiency, cost reduction, and resource saving. The team has also demonstrated dynamic adaptability of the automation modules by deploying parallel SDL platforms on collaborative sites. Outcomes from this project approach augment cross collaborations between research groups, protocol and workflow exchange, as well as help fostering academia-industry partnership.

**Acknowledgments**

We acknowledge the support of Bristol Myers Squibb and the Natural Sciences and Engineering Research Council of Canada (NSERC) (ALLRP 602689 – 24). This research was undertaken thanks in part to funding provided to the University of Toronto's Acceleration Consortium from the Canada First Research Excellence Fund (CFREF-2022–00042). Additional support was provided by NSERC (Discovery Grant – RGPIN-2021-03533 and Canada Research Chair – 950-230935), Canada Foundation for Innovation (CFI) (Project No. 35261), Ontario Research Fund, and the University of Toronto to S.A.L.R; and NSERC (Discovery Accelerator – RGPIN-2021–03168), CFI (Project No. 44843), the BC Knowledge Development Fund, and the University of British Columbia to J.E.H.

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