Resource-efficient Bayesian optimization for self-calibrating liquid handling

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1. Introduction

Automated liquid handlers (ALH) perform the foundational task of liquid transfer in modern self-driving labs (SDLs), where experiments are executed and optimized autonomously through closed-loop control. Reliable liquid handling is therefore essential for experimental validity and reproducibility. Despite widespread adoption of ALHs, poor accuracy and consistency are still the norm when handling non-ideal liquids such as viscous, volatile, or biologically complex solutions [1].

Manufacturer-provided profiles are typically optimized for aqueous fluids, leading to suboptimal performance with customized solutions, which require extensive manual adjustment to adopt new liquids, volumes, or devices [2]. This manual calibration process is time-consuming, difficult to reproduce, and fundamentally in conflict with the scalability and autonomy required by SDLs [3, 4]. As such, calibration involves difficult trade-offs between accuracy, repeatability, and time, with liquid-dependent errors propagating through automated workflows and reducing trust in autonomous systems [5].

2. Substantial section

To support reliable SDL operations, liquid handler calibration must be automated, data-efficient, and robust to changes in liquids, volumes, and hardware. We frame calibration as a constrained optimization problem, where device-specific parameters are tuned to minimize systematic error and variability while respecting laboratory constraints. Rather than relying on default manufacturer profiles or manual trial-and-error, we propose to utilize Bayesian optimization to iteratively select parameter sets and leverage experimental outcomes to rapidly converge on effective parameter frontiers within a fixed budget.

Our approach balances multiple objectives relevant to SDL operations, including volumetric accuracy, repeatability and execution time. Crucially, the optimization process is designed to operate under realistic conditions, adhering to limited consumables, finite iterations, and stopping criteria. By treating calibration as a workflow-driven, closed-loop learning problem, our framework enable automated, reproducible, and scalable parameter discovery, allowing for calibration reuse across experimental workflows.

2.1 System Architecture and Optimization Workflow

The system is modular by design, allowing for end-to-end calibration and validation that integrates naturally into SDL environments. Device control, experiment execution, measurement, and optimization are cleanly separated into independent functions, allowing calibration workflows to be reused across liquids and hardware with minimal configuration changes. Calibrated profiles for each liquid can be utilized in future automated workflows to ensure reliable and repeatable liquid handling.

Calibration runs follow a structured sequence to efficiently identify pipetting parameters. For each trial, parameters are selected, executed on the liquid handler, evaluated through automated measurements, and used to update the optimization state. Parameters, which are system-dependent, typically include aspirate and dispense speed, settling time, pre/post aspirate air volume, and over-aspirate volume.

Initial parameters are selected using SOBOL (pseudo-random space filling) sampling of the parameter space, before moving to Bayesian optimization (BO) for the remaining trials. Closed-loop optimization using BO takes the initial SOBOL data and applies multi-objective optimization to identify parameters that provide the best compromise between volumetric accuracy, repeatability, and time. Subsequent optimizations leverage prior trial data through transfer learning, using tested parameters as informed starting points rather than starting from scratch.

Performance is evaluated using available laboratory equipment, including plate readers or gravimetric scales, with support for additional instruments. Calibration is performed across a range of target volumes. Validation is performed through a separate workflow, assessing accuracy and reproducibility.

2.2 Related work

Existing approaches to liquid handling performance focus mainly on verification and manual calibration. Verification methods, including gravimetric and absorbance-based protocols, provide standardized mechanisms for quantifying volumetric accuracy and precision, focusing on quality control and compliance [1]. While effective for assessing performance, these methods do not provide guidance for improvement, often leading to tedious manual tuning with limited reuse across experiments [2].

More recent work has explored data-driven approaches to model and correct pipetting behaviour. Yap et al. introduced learning-based techniques to characterize liquid-dependent transfer errors, demonstrating that systematic deviations can be predicted and compensated using experimental data [4]. Complementary efforts have shown that Bayesian optimization can efficiently find acceptable pipetting parameters for challenging liquids, reducing experimental effort compared to manual calibration

[5]. However, these approaches are typically scoped to specific devices, liquids, or operating protocols, and are evaluated as optimization studies rather than reusable laboratory infrastructure.

Beyond parameter-level calibration, recent work has begun to address automation at the workflow and system level. Bao et al. demonstrated an end-to-end automated experimental workflow for surfactant critical micelle concentration determination, highlighting the importance of reliable liquid handling as a foundational component of reproducible autonomous experimentation [6]. In parallel, Angers et al. introduced RoboCulture, a general-purpose robotic platform capable of executing closed-loop biological experiments [7]. While these systems emphasize autonomy and robustness at the experimental execution level, they typically assume validated liquid handling behaviours as a prerequisite for reliable operation. This naturally motivates the development of reusable, data-efficient calibration frameworks that enable systematic adaptation of liquid handling parameters across workflows, liquids, and hardware.

2.3 *Experimental Results and Validation*

The iterative learning process over successive optimization trials is illustrated in Figure 1. Early SOBOL trials exhibit significant deviation from the target volumes, reflecting high variability across explored parameter configurations. As optimization proceeds, measured volumes increasingly cluster around the targets, indicating convergence towards parameter sets that reduce volumetric deviation. This trend is most pronounced for the initial target volume, where a large number of trials are performed and the densest concentration of low-deviation results is observed. When optimization transitions to additional target volumes, convergence occurs more rapidly, with fewer trials required to reach comparable accuracy, demonstrating that parameter structures identified earlier provide key information at subsequent volumes.

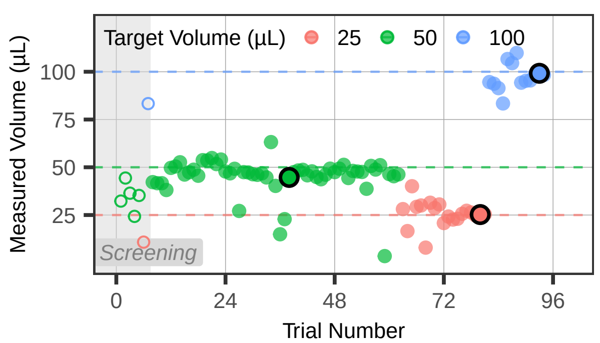

Fig. 1: **Measured volume across optimization trials for glycerol calibration.** Points are colored by target volume (25, 50 and 100 µL), dashed lines indicate targets, and the shaded region marks the initial screening phase. Circled points denote the best-performing trials.

Figure 2 presents validation results of the optimization parameter set on a later date, comparing measured and target volumes across both calibrated and non-calibrated volume ranges. Measured volumes remain closely aligned with the target line, with all tested volumes falling within ±10% accuracy. Notably, volumes outside the original calibration range showed similar performance to directly calibrated values, indicating the optimized parameter set retains performance beyond the original experimental setup. Together, these results demonstrate that optimization outcomes observed during the trial phase translates into stable liquid handling parameters that can be generalized for experimental workload.

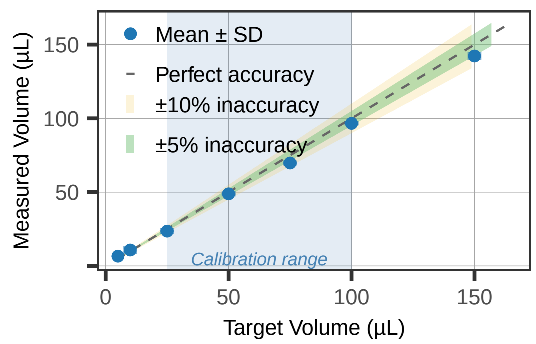

Fig. 2: **Validation of glycerol dispensing accuracy.** Data are shown as mean ± standard deviation from triplicate measurements.

Alginate was successfully calibrated across target volumes ranging between 2μl and 50μl in two experimental configurations. Similar calibration workflows were evaluated on water, ethanol, DMSO, and representative biomaterial solutions, demonstrating robustness and generalization capabilities of the system across liquids with diverse physical properties.

3. Conclusions

In this work, we presented a data-efficient, closed-loop calibration framework for automated liquid handling, addressing key bottlenecks regarding the deployment of liquid handlers in self-driving laboratories. Using Bayesian optimization under realistic experimental budgets, the approach systematically improves volumetric accuracy and repeatability while accounting for execution time.

Results show significant systematic learning in the early stages of optimization, with subsequent volumes converging more rapidly. Validation performed on a later date confirms that optimized parameters maintain transfer accuracy, even when tested beyond the calibrated range. These findings demonstrate a practical and reusable calibration strategy suitable for scalable SDL workflows.

Acknowledgments

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Appendix A. Experimental Setups

The system supports standalone execution and integration into orchestration frameworks such as Prefect, enabling scheduling and distribution across machines. The system can also be containerized to ensure platform compatibility. New devices can be incorporated through lightweight configuration files without having to change the backend optimization logic.

Two separate setups were used in this study: a) North Robotics N7 Robot in Polymer Self-Driving Laboratory (Acceleration Consortium) (**Figure A1**) and b) Hamilton STARlet in Human Organ Mimicry Self-Driving Laboratory (Acceleration Consortium) (**Figure A2**).

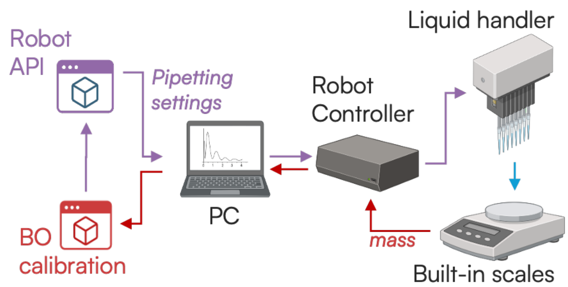

Fig. A1: **North Robotics N7 Robot Setup.** Purple arrows depict the flow of robot pipetting parameters. Red arrows depict the flow of measurements.

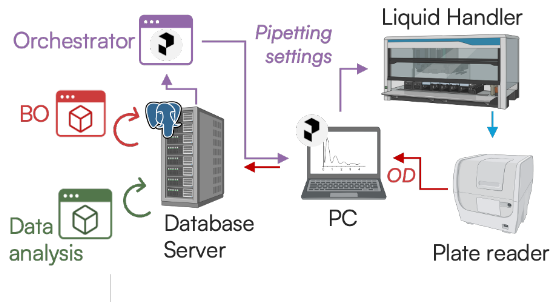

Fig. A2: **Hamilton STARlet Setup.** Purple arrows depict the flow of robot pipetting parameters. Red arrows depict the flow of measurements. Green arrow depicts data manipulation.

Appendix B. Optimization parameters

We optimized liquid-handling parameters across multiple target dispense volumes; therefore, target volume itself was not treated as a decision variable in the Bayesian optimization campaign. The optimization space instead consisted of aspiration- and dispensing-related parameters that directly influence volumetric accuracy, repeatability, and throughput. These parameters were defined over bounded continuous ranges informed by hardware constraints and prior empirical knowledge. Aspiration-related parameters included aspirate flow rate, aspiration settling time, blowout air volume, transport air volume, and optional over-aspirate volume. Dispensing-related parameters included dispense flow rate, dispense settling time, swap speed, and tip retract speed. The explicit specification of parameter bounds ensures safe operation while enabling efficient exploration of the calibration space (**Figure A3, Table A1**).

Initial glycerol pipetting experiments exhibited substantial variability in volume dispensed across parameter configurations, with measured deviations spanning a wide range even at comparable execution times. Notably, parameter sets with comparable throughput exhibited markedly different accuracy and repeatability.

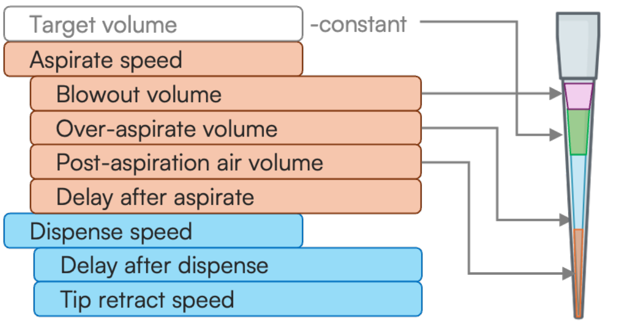

Fig. A3: **Optimization parameters**. The target dispense volume is fixed and not considered a parameter in the BO campaign. Optimization was performed over aspiration parameters (aspirate speed, blowout volume, over-aspirate volume, post-aspiration air volume, and delay after aspiration) and dispensing parameters (dispense speed, delay after dispense, and tip retract speed).

Table A1: Liquid handling parameters optimized using Bayesian optimization and their corresponding bounds.

Parameter	**Description**	**Range**
flow_rate_aspirate	Aspirate flow rate	1 – 500
settling_time_aspirate	Delay after aspiration (s)	0.0 – 9.9
blowout_air_volume	Blowout air volume (μL)	0.0 – 25.0
transport_air_volume	Air volume used during liquid transport (μL)	0.0 – 25.0
overaspirate_vol[†]	Additional aspirated volume (μL)	0.0 – 20.0
flow_rate_dispense	Dispense flow rate	1 – 500
settling_time_dispense	Delay after dispense (s)	0.0 – 9.9
swap_speed	Speed of tip movement between steps	0.3 – 160.0
tip_retract_speed	Speed of tip withdrawal	Device-defined

[†]Included conditionally depending on the liquid and protocol configuration.