Revolutionizing Bioanalysis through Automation: Overcoming Challenges and Unlocking Potential

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Introduction

- Integration of multiple bioanalytical instruments at both hardware and software levels including liquid handlers, plate washers, shaking incubators, and plate readers to create a total laboratory automation (TLA) system for ligand binding assays.
- Optimization of system settings (e.g., liquid class, labware definition, and script design) to ensure high-quality assay results, such as consistency, accuracy, precision, and high throughput.
- Comprehensive assessment of factors influencing assay precision and accuracy, including sample mixing, incubation duration, sample transfer sequence, and plate reading settings, leading to the identification and optimization of key parameters.
- Development of a master script that accommodates various types of assay tests without compromising assay quality, significantly reducing assay timeline from months to just weeks or days.

Materials & Methods

TLA System Installation

The Total Lab Automation (TLA) system was assembled by integrating several key components: the MSD SQ 120, BioTek ELS405 Microplate Washer, and the HIS plate shaking incubator were paired with the Hamilton MicroLab Star liquid handler. The systems were coordinated using Methodical Minds (1.0.38) from MSD and Liquid Handling Control (V2.22.7), both of which were linked to the Hamilton Venus system through Application Programming Interfaces (APIs). The incubators were also connected directly via APIs. Venus is equipped with libraries developed for each piece of equipment, allowing seamless connection, control, and disconnection of all the components involved.

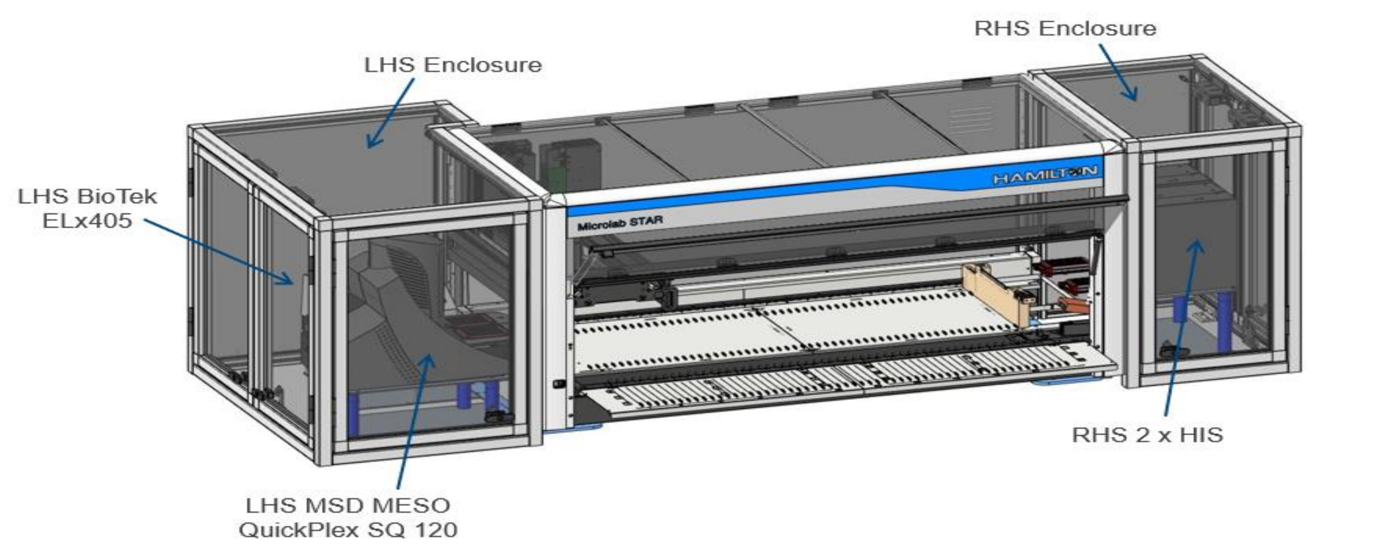

Figure 1: Total Lab Automation System. Situated on the right side are two incubation units, equipped with both shaking and temperature control features. The central area is dedicated to liquid handling operations, which facilitate sample preparation, treatment, and transportation. The left area houses a Plate Washer and an MSD Reader, forming a bioanalytical automation suite.

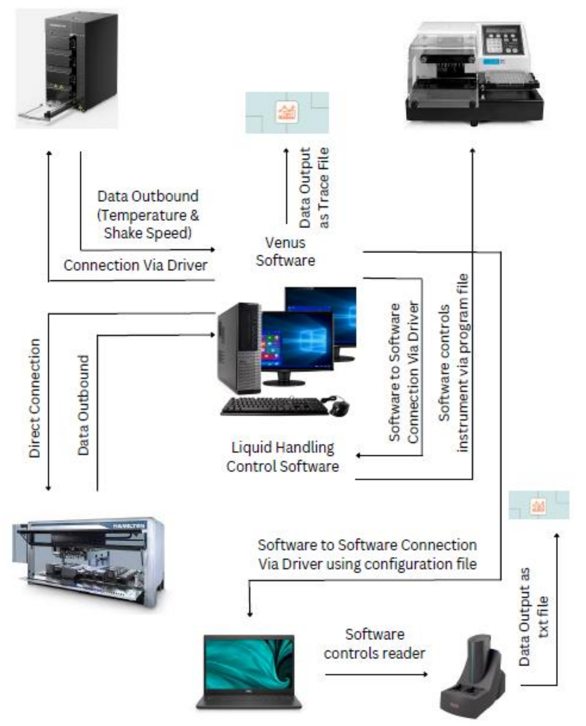

Figure 2: TLA data flow map

Sample Preparation

The sample preparation was evaluated by preparing a diluted pembrolizumab standard curve and Quality Controls (QCs) in serum, which were subsequently diluted tenfold in a LowBinding assay buffer. To measure the accuracy of the liquid transfer process, the Hamilton Liquid Verification Kit was employed. Adjustments were made to the liquid class and/or the correction curve to ensure an accuracy rate of less than 3.7% for all liquid transfers. To evaluate the overall intra- and inter-accuracy and precision, multiple PK assays were conducted using the TLA system.

Labware Teaching

Labware positioning was configured using the Venus Software, ensuring the system accurately recognized the precise location (x, y, and z coordinates) of integrated equipment, tubes, and plates.

Accurate Liquid Transfer

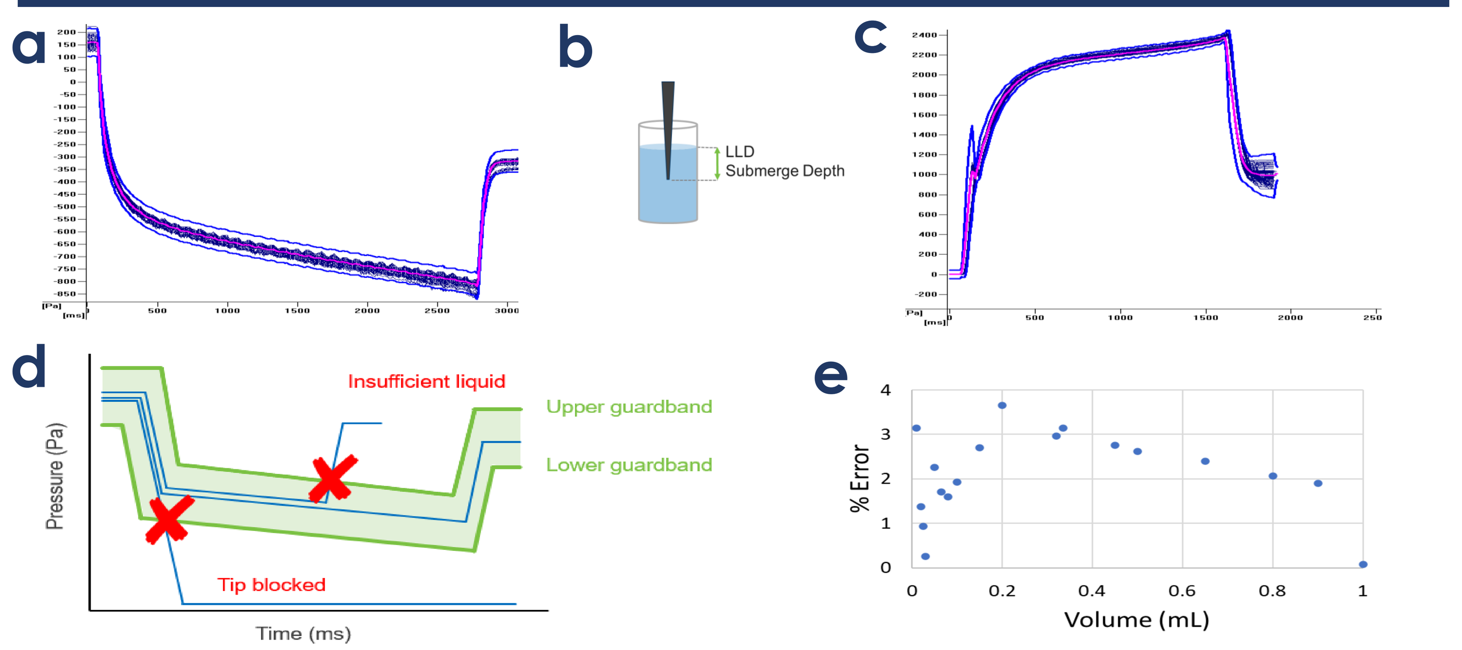

Figure 3: TLA Liquid Transfer Procedure. In order to maintain an empty tip, the tip is sustained under high pressure while the tip is submerged to a specific depth (Figure 3a & 3b). Aspiration involves the generation of negative pressure, thereby filling the solution into the tip (Figure 3a). Dispensation, on the other hand, necessitates the creation of positive pressure (Figure 3c). Any abnormal pressure conditions and their related occurrences are concisely detailed in Figure 3d. The liquid transfer is executed using varying volumes across different tip sizes. To assess accuracy, gravimetric analysis method is utilized for testing (Figure 3e).

The TLA's liquid handling system demonstrated good accuracy in handling various volumes (10 µL-1,000 µL) across different tip sizes. The error rate was within 3.1% using 50 µL, 3.7% using 300 µL tips, and 3.2% using the 1,000 µL tip. Liquid class definition is required for handling various solution especially with varying viscosity, vapor pressure, and density.

High Throughput

The Total Lab Automation (TLA) system demonstrates superior throughput compared to manual lab procedures. It is capable of efficiently processing more than 10 micro-well plate ligand binding assays, enhancing the capacity and speed of operations. With the aid of the scheduling software, the duration of sample treatment can be effectively controlled, thereby minimizing variation in assay results. In addition, the TLA system is equipped to support second shift operations that further increase lab capacity.

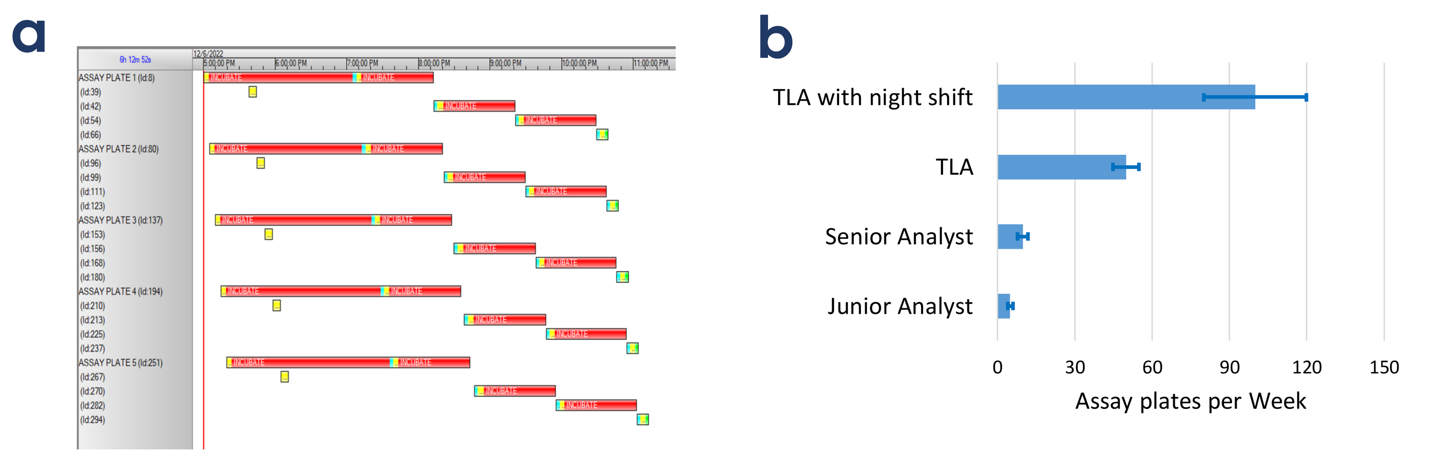

Figure 4: TLA run schedule (a) and productivity (b)

TLA is equipped with a real-time monitoring system, which enables lab work to be supervised remotely via a dual camera system. The lab procedures can be tracked in real-time through remote control, providing greater oversight and operational control.

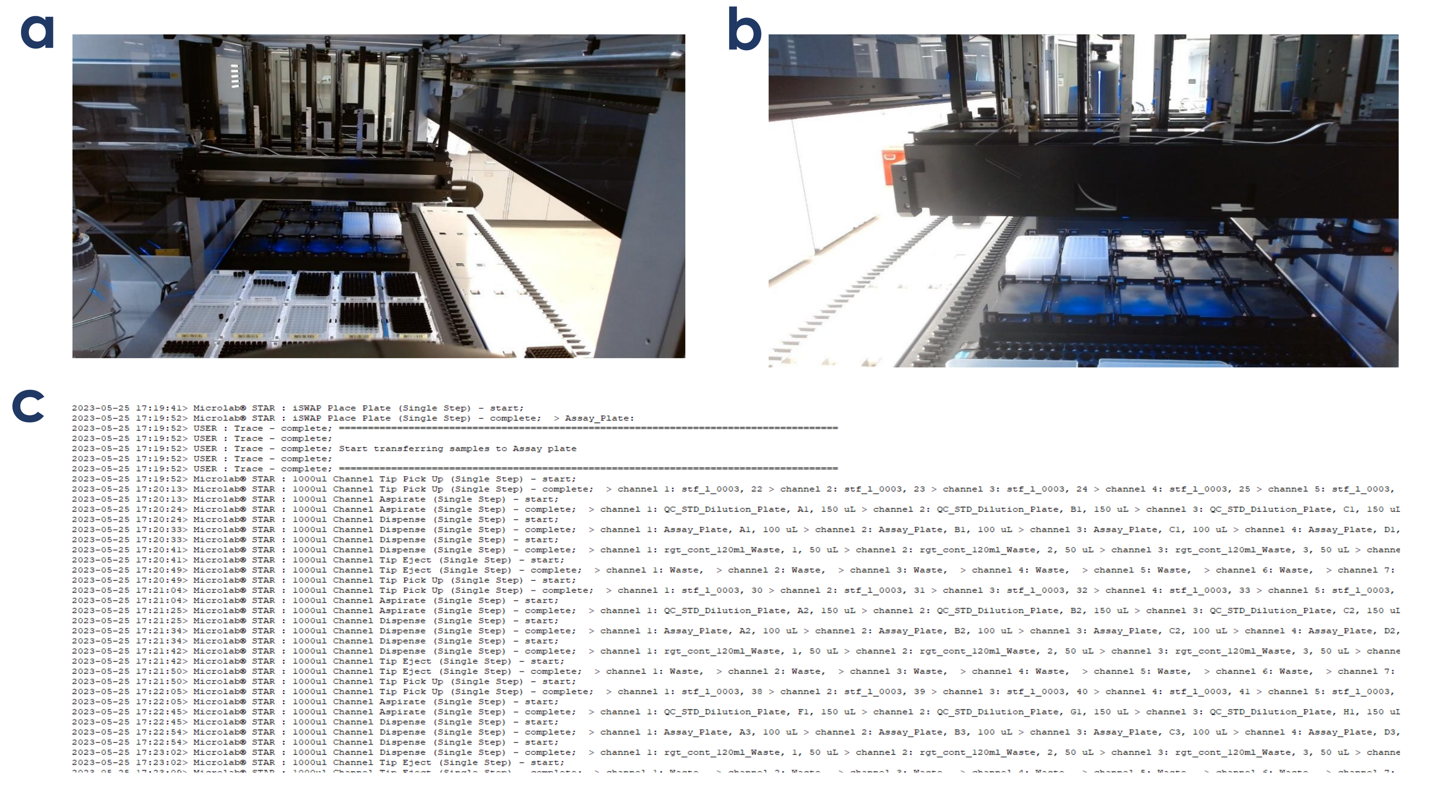

Figure 5: TLA dual camera system(a & b) and real-time assay procedure monitoring system (c)

The system also boasts a sophisticated alarm feature. It sends out notifications when labware and/or reagents are depleted or in case of any errors, alerting users through both email and text messages. This preemptive notification system ensures issues can be swiftly addressed, maintaining high productivity.

Outstanding Data Quality

TLA development revealed that various factors influence the precision and accuracy of assay tests. These include sample mixing, the duration of incubation, the sequence of sample transfer, and the settings for plate reading. Following the optimization of these parameters, the TLA system consistently displayed high levels of accuracy and precision across the tests.

Despite a few outliers, TLA managed to maintain assay precision within 5% for the majority of the samples. Furthermore, the data for accuracy showed a tightly clustered dispersion, contained within a 10% range. In contrast, the data derived from manual assays demonstrated a significantly higher variation in both assay precision and accuracy, underscoring the advantages of TLA in maintaining consistency and reducing variability in the testing process.

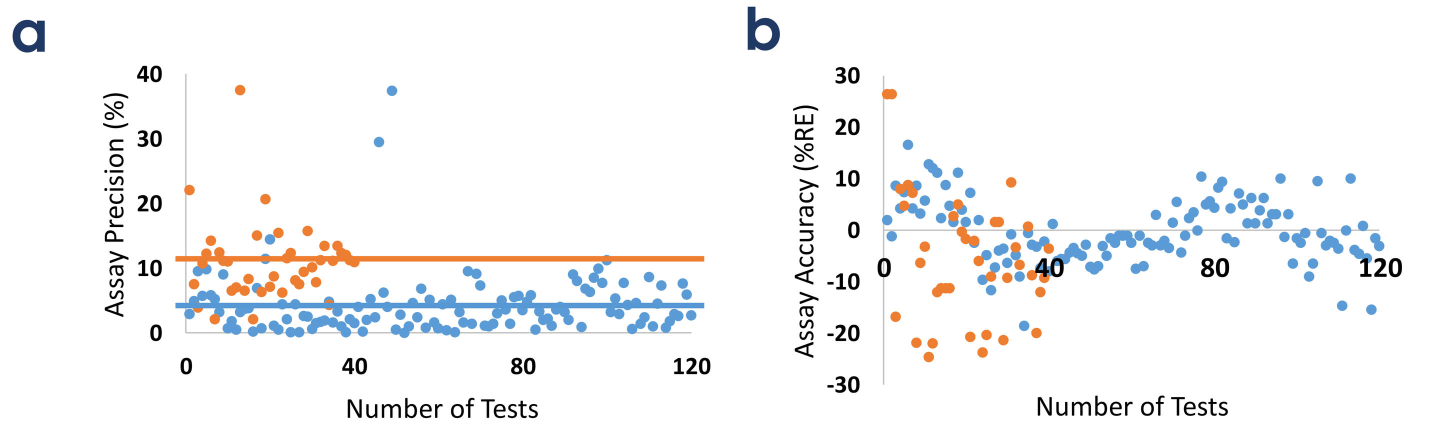

Figure 6: The comparison of TLA and manual runs in assay precision and accuracy. 40 manual and 120 TLA tests were performed. The manual tests were executed by a team of three analysts over a span of two weeks. The TLA tests were conducted across three months. The average precision of TLA and manual test results were represented by the blue (4.36%) and orange lines (10.95%), respectively (Figure 6a). The data set of TLA results exhibits a narrower dispersion, confined within a 10% range. Conversely, the manual results display a broader distribution (Figure 6b).

References

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