Robot-Enabled Biofabrication of Tissue Cultures with Micrometer-Scale Precision

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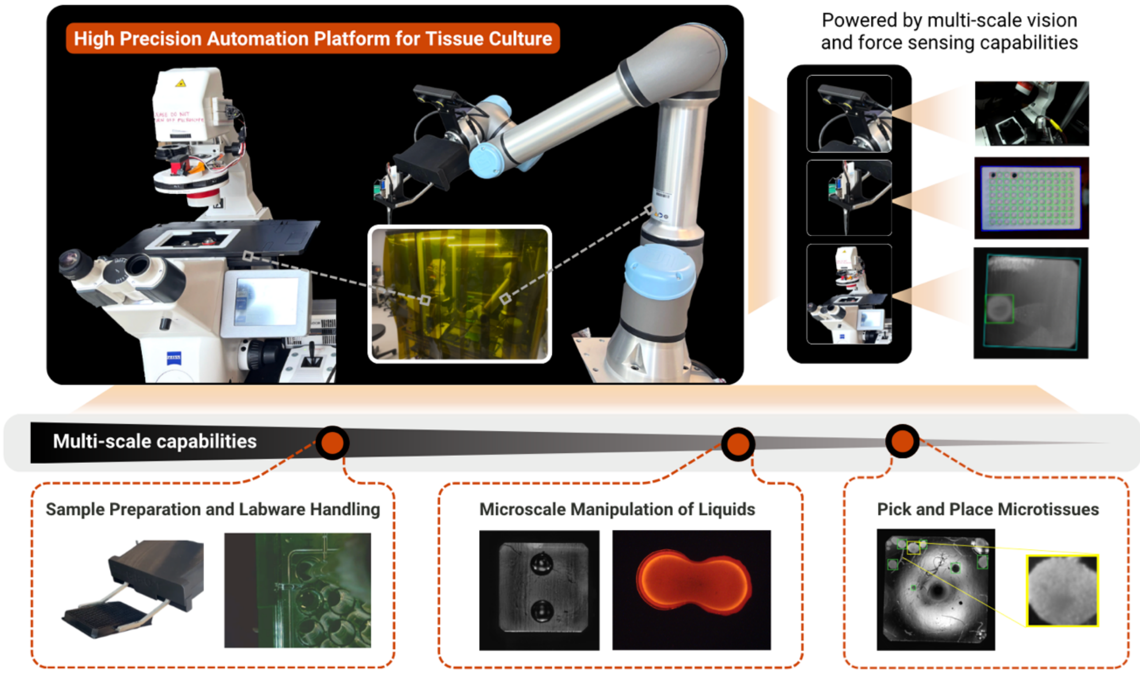

Fig 1: An outline of our platform HAPTiC (High Precision Automation Platform for Tissue Culture). Our platform specializes in high precision liquid handling tasks at the microscale, while also executing upstream sample preparation and labware handling tasks.

1. Introduction

A long-standing challenge in bioengineering is creating lab-grown tissue models that accurately mimic the microenvironment of the human body. Current drug-screening techniques often rely on simplistic 2D-cell cultures or animal models, both of which fail to capture the complexity of human physiology [1, 2]. This shortcoming has contributed to the ballooning cost of bringing a new drug to market, which currently averages 10 years and $2.5 billion [3]. Recent breakthroughs including organoids [4] and assembloids [5] that aim to accurately capture cell-cell and tissue-tissue interactions, are now being leveraged to enable a wide range of physiologically relevant platforms for drug screening and disease modelling [6-9]. Yet, a critical trend in the development of high-fidelity human tissue models, is the increasing reliance on sophisticated protocols to realize greater biological complexity. Reliable spatio-temporal control over liquid placement at the microscale, for example, is a critical enabler of many frontier tissue models [10], and a skill that often eludes a human operator's manual capabilities. To enable the use of frontier tissue models in high-throughput drug discovery pipelines, there is a critical need for specialized automation that can deliver greater precision and reliability than manual labour.

To this end, we propose High Precision Automation Platform for Tissue Culture (HAPTiC), a multi-capability platform built to handle the end-to-end fabrication of frontier tissue models. A diagram of HAPTiC and several highlighted capabilities is presented in Figure 1.

2. Related work

Several previous works have proposed automated systems to aid in tasks relevant to tissue culture, but fall short of the scope of automation we aim to achieve here. Micromanipulation techniques leveraging a live image feed from a high-magnification camera for closed loop control of a robotic manipulator have demonstrated the ability to reposition and move microtissues between vessels to facilitate testing of therapeutics [11, 12]. However, this

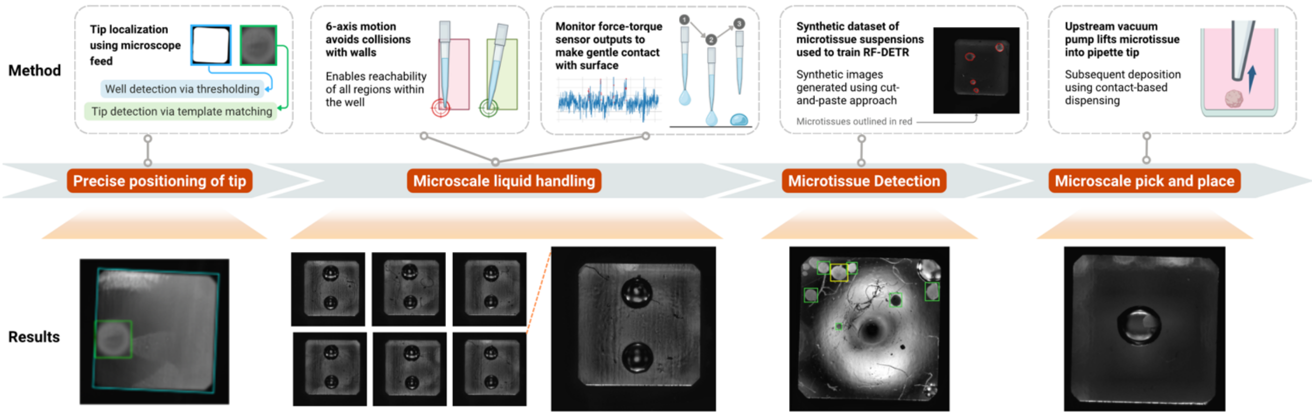

Fig 2: Diagram of the core capabilities of the HAPTiC system and the methods used to achieve them. Precise positioning of the pipette tip is achieved by localizing the tip in an image feed provided by a microscope and subsequently repositioning to the target pose. Microscale liquid handling is achieved through six-degree of freedom motion planning and contact-based dispensing. Results show example droplet depositions of Fibrinogen, and demonstrate spatial and volumetric consistency. Microtissue detection using an RF-DETR [15] object detection model finetuned on a synthetic dataset [16] of microtissue images, and leveraged to enable microtissue pick-and-place.

approach has not yet been applied to advanced tissue culture techniques such as the spatially precise seeding of organoid cultures or the formation of assembloids. Further, the use of micromanipulators constrains the applicability of the system to high precision tasks only, leaving macro-level tasks such as sample preparation to human operators to complete manually. Since many high-precision tasks in tissue culture are time-coupled to upstream sample-preparation steps, (such as fibrin preparation where seeding must occur quickly before gelation occurs), gaps in platform capabilities greatly impede protocol translation. In recent years, self-driving labs [13] have emerged to propose an alternative vision, where laboratory tasks are handled by multi-capability systems which provide holistic automation, reducing the need for human operators to intervene during protocol execution. RoboCulture [14] demonstrates an early vision for how self-driving systems can be used to handle a diverse set of tasks relevant to cell culture but lacks the ability to handle the high precision tasks most critical to advanced tissue culture.

3. Methods

Our platform integrates robust sample preparation capabilities with high precision pipetting skills to provide a suite of capabilities uniquely suited to executing tissue culture workflows. The automation capabilities we implement (Fig. 2) are driven by a synergistic approach to hardware and software development.

3.1 Materials

We combine a six-degree-of-freedom robot arm (UR5e, Universal robots) with a two-finger microplate gripper (lab-hand, 8-bot robotics) and demonstrate how we can perform a comprehensive suite of actions enabling end-to-end protocol execution for tissue cultures. By grasping and manipulating a commercially available vacuum pipette (DHOE, Festo), the system can perform all required sample preparation steps as well as subsequent high precision seeding in an aseptic customized enclosure.

3.2 Feedback-driven control

We present a multimodal feedback loop leveraging vision and force-torque observations to enable a suite of microscale manipulation capabilities. Combining real-time localization of pipette tip and tissue aggregates in a well, six-degree-of-freedom motion planning and soft-contact detection, we demonstrate sub-millimeter spatiotemporal control over tissue culture seeding, and the ability to pick-and-place tissue aggregates as small as 200 microns. These capabilities collectively enable frontier use cases including the spatiotemporally controllable seeding of multiple tissues in a single well, the repositioning of tissues to support tissue integration in a previously established 3D-vasculature, and the positioning of organoids in close-proximity to facilitate assembloid formation [10].

4. Conclusion

Overall, HAPTiC addresses a critical need in modern tissue culture. By performing microscale material handling operations, the platform is poised to support frontier tissue culture efforts currently bottlenecked by the limitations of human labour. Amid rapid advancements in self-driving labs [13], HAPTiC also holds the potential to be a pivotal component of large-scale tissue culture automation setups.

Acknowledgments

We would like to thank Rosanna Jiang, Canner Dykol, and Kelvin Chow for their insightful discussions. We would also like to thank Kelvin Chow for supporting the development of CAD models and providing the design for the well plate storage tower. This research was undertaken thanks in-part to the University of Toronto's Acceleration Consortium, from the Canada First Research Excellence Fund, grant number CFREF-2022-00042. Graphics created with Biorender.com.

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