Large Language Model Agents Enable Autonomous Design and Image Analysis of Microwell Microfluidics

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1. Introduction

Microwell-microfluidic platforms enable the high-resolution isolation and analysis of biological samples in nanoliter to picoliter volumes, allowing for the study of individual cells in controlled microenvironments and high-throughput screening. The successful implementation of these studies depends critically on the CAD design of microfluidic microwell devices. However, being slow, error-prone, and dependent on specialized expertise, manual CAD workflows for microfluidic microwell devices make design modifications tedious and poorly reproducible, creating significant barriers to throughput, collaboration, and innovation. Furthermore, accurate classification of microwells by single cell or microbead occupancy, whether single, multiple, or empty, becomes essential; while single-bead wells enable discrete molecular analyses with minimal signal ambiguity, multiple-bead wells introduce risks of cross-reactivity, barcode collisions, and compromised quantification.

LLMs are rapidly reshaping a broad range of fields, including biomedical research [1-4], mechanical design [5,6], material science [7-13], chemistry [14-18], biology [19-23] and medicine [24-29] by enabling new avenues for scientific discovery and technological advancement [30-33]. Despite their growing impact in other domains, the application of LLM agents and MLLMs into microwell microfluidic systems remains limited, highlighting a compelling opportunity for technological advancement. Comparing traditional automated design frameworks for the automation and validation of microfluidic devices reveals that they are typically implemented as closed, rule-based systems [34-36], LLM Agents are capable of integrating complex tasks into autonomous, closed-loop digital discovery platforms such as literature synthesis, hypothesis generation, autonomous design, execution in self-driving laboratories [37-46], analysis of results, and the generation of new hypotheses.

In this study, we propose an LLM-driven framework for microwell design (Fig. 1), which integrates a mixture of LLM agents to generate CAD scripts for microwell geometries. Using this framework, we designed microwells of diverse shapes and dimensions prior to fabrication and subsequently loaded them with microbeads. Only through the use of state-of-the-art MLLMs were we able to classify microwell images directly, distinguishing between occupancy states (empty, single-bead, or multiple-bead) as well as their geometrical configurations. By integrating MLLMs with logistic regression, we designed a simplified classification approach that, in its final form, delivered marked improvements in accuracy. This study highlights the broader potential of LLMs and MLLMs in offering autonomous, scalable, cost-effective, and interpretable solutions for device prototyping and biomedical image analysis. This LLM Agents-driven framework (Fig.2) enables a more adaptive and scalable framework, paving the way for accelerated innovation in microfluidic research.

2. Methods

LLM-driven microwell design framework (Fig. 1)

The framework used a mixture of agents strategy [47], integrating a reviewer and a rivisor. The mixture of agents comprised LLAMA3.1, MISTRAL, DEEPSEEK-R1, and GEMMA2, which captures a diverse spectrum of model capabilities and linguistic priors. The QWEN3-driven aggregation layer is to perform semantic synthesis by resolving inconsistencies and integrating partial or competing code fragments into a unified, executable representation. Beyond aggregation, the framework is distinguished by a recursive feedback mechanism through which the synthesized script undergoes iterative assessment and refinement by QWEN3 until predefined correctness, completeness, and quality criteria are achieved. The completed script undergoes a rigorous, multi-step validation process. Initially, it is executed within a live AutoCAD environment to verify both syntax and functional performance. Subsequently, human experts assess the script

to ensure it aligns with domain-specific constraints, design objectives, and safety standards before fabrication. This approach establishes a hybrid validation framework that combines automated execution with expert review, effectively addressing the limitations of relying solely on LLM-based systems.

Direct inference with MLLMs for classification of microwell occupancy and shape.

MLLM-logistic regression classification framework.

3. Results

Since the use of LLMs and MLLMs in microwell microfluidics has not been systematically explored, despite their broad applicability, we developed a framework that utilizes LLMs to automate CAD script generation, enabling rapid microwell fabrication with varied geometries, followed by microbead loading. We achieved significant improvements, *exceeding 0.92 for occupancy classification and 0.99* for shape classification, across all evaluated MLLMs, *compared with 0.50 and 0.55*, respectively, when relying solely on direct classification (Fig. 3&4). The MLLM-logistic regression framework is a scalable, efficient solution for high-throughput microwell image analysis. Our study demonstrates an autonomous design microwell platform by translating natural language prompts into optimized device geometries, CAD scripts and image analysis, facilitating the development of next-generation digital discovery by integration of literature mining, autonomous design and experimental data analysis.

Figures and tables

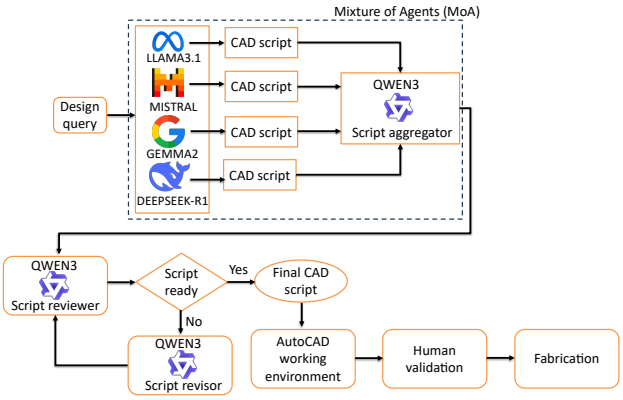

Fig. 1: LLM-driven microwell design framework

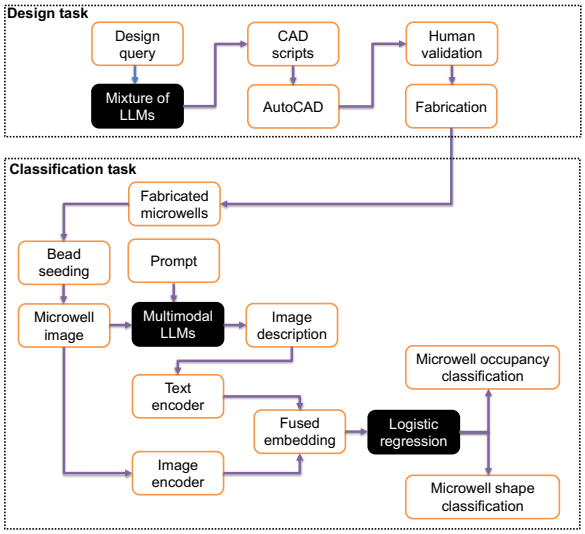

Fig. 2: Overall framework LLM Agents

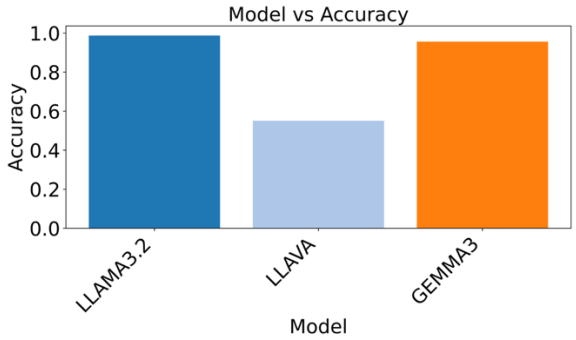

Fig. 3 Accuracy for microwell shape classification

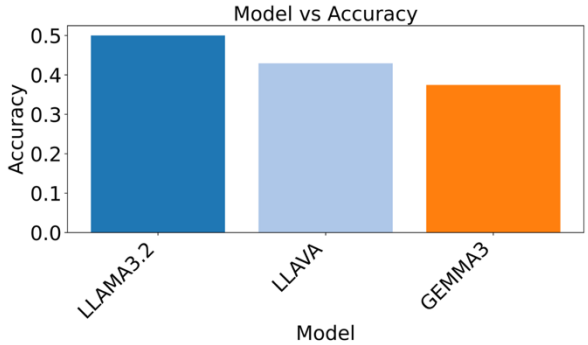

Fig. 4 Accuracy for microwell occupancy classification

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Appendix A. [Appendix Title]

[A paper may contain an unlimited number of appendices which don't count towards the page limit, but the reviewers are not required to read them. Include supplementary material, additional data, or extended methodology here.]