

Chip-Sized Biosensor for Multiparametric Monitoring

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Summary: A chip-sized biosensor based on lensless digital holographic microscopy is introduced for continuous, in-incubator monitoring of *in vitro* models. The system integrates a CMOS sensor and a micro-LED display, enabling compact, label-free imaging, and quantitative parameter extraction across biological systems. Its capabilities were validated through angiogenesis and muscle-on-chip models, enabling quantification of both morphological parameters (network formation metrics), and functional parameters (contractile displacement). This work establishes a scalable, multiparametric biosensing platform for tissue monitoring.

Keywords: chip-sized microscopy, holography, angiogenesis, muscle-on-chip.

Background, Motivation and Objective

Continuous, non-invasive monitoring of cellular and tissue dynamics is critical for advanced *in vitro* assays. Conventional live-cell imaging typically depends on large, costly benchtop microscopy systems that are frequently shared and situated outside incubator environments. This arrangement restricts experimental flexibility, scalability, and the ability to maintain uninterrupted observation under physiological conditions.

To address these limitations, we present a compact chip-sized biosensing platform based on lensless digital holographic microscopy for continuous monitoring directly within standard incubator environments. It incorporates a CMOS sensor and a micro-LED array in an in-line configuration, allowing simplified optical architecture and parallel deployment of multiple devices within standard CO₂ incubators.

Existing lensless systems often rely on additional optical elements [1–2], increasing system complexity and limiting scalability. In contrast, the proposed platform uses a simplified illumination scheme and compact design, enabling robust operation within standard incubator environments.

The platform was validated across distinct biological models to demonstrate its capability for both morphological and functional biosensing. In angiogenesis assays, this approach provides continuous monitoring of vascular network formation and remodeling, which has been shown

to be critical for capturing dynamic angiogenesis processes that cannot be resolved by endpoint analyses [4–5].

The platform is further applied to muscle-on-chip systems for the extraction of functional parameters under electrical stimulation. Contractile behavior in engineered skeletal muscle tissues is typically evaluated by measuring force, deformation, or displacement [6]. In the present study, contractility is quantified by tracking tissue displacement between flexible anchoring pillars providing a readout of muscle activity.

Description of the New Method or System

The platform has three acquisition modes: endpoint, time-lapse and video. For angiogenesis monitoring (Fig. 1), time-lapse imaging was performed every 30 min over 18 h and quantitative metrics were extracted using a custom image analysis pipeline.

For muscle-on-chip experiments (Fig. 2), video sequences were acquired at 60 frames per second during electrical stimulation using the Myo-Moves system [7], to induce twitch (low-frequency) and tetanic (high-frequency) contractions. Tissue displacement was quantified by tracking pillar deflection using a custom algorithm, yielding time-resolved contractile dynamics.

The key innovation lies in a unified biosensing approach that extracts both morphological and functional parameters across distinct *in vitro* systems.

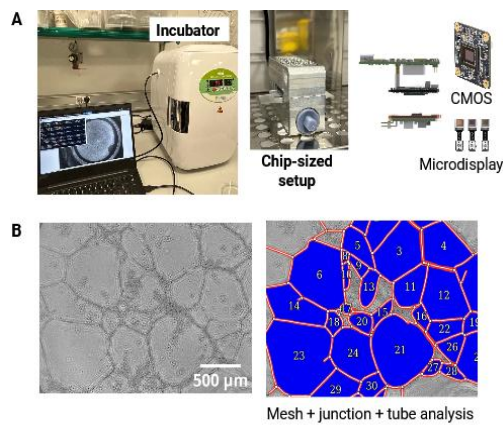


Fig. 1. (A) Chip-sized system inside incubator. (B) Example of a capture and its analysis.

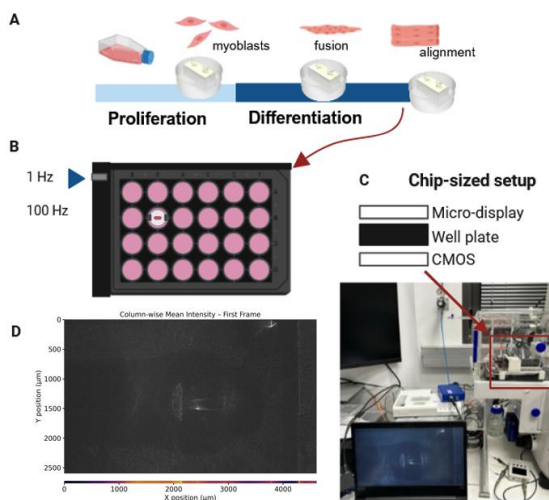


Fig. 2. (A) 3D muscle generation. (B) Electrical stimulation configuration. (C) Chip-sized system within a controlled chamber. (D) Representative analyzed frame of muscle contraction.

Results

Figure 3 presents the temporal evolution of angiogenesis metrics across two experiments. Tube length and junction number increase during early stages and decrease after reaching its peak.

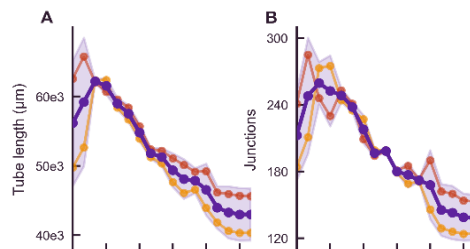


Fig. 3. Evolution of angiogenesis over an 18h experiment. Tube length, and number of junctions trends. Experiment 1, 2, and Mean $\pm$ SD (yellow, orange, purple plots).

Figure 4 shows displacement curves recorded during stimulation. At low-frequency stimulation, periodic displacement peaks correspond to

individual twitch contractions, which are characterized by complete relaxation and low-amplitude responses. In contrast, high-frequency stimulation induces tetanic contractions, resulting in sustained, higher-amplitude displacements and slower relaxation dynamics due to temporal summation.

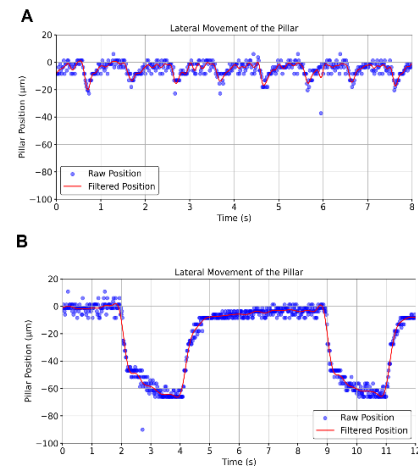


Fig. 4. Analysis of muscle contraction under (A) 1 Hz and (B) 100 Hz stimulation.

References

- [1] S.V. Kesavan, F. Momey, O. Cioni, B. David-Watine, N. Dubrulle, S. Shorte, E. Sulpice, D. Freida, B. Chalmond, J.M. Dinten, X. Gidrol, C. Allier, High-throughput monitoring of major cell functions by means of lensfree video microscopy, *Sci. Rep.* 4, 5942 (2014); doi: 10.1038/srep05942.
- [2] J.A. Picazo-Bueno, K. Trindade, M. Sanz, V. Micó, Design, Calibration, and Application of a Robust, Cost-Effective, and High-Resolution Lensless Holographic Microscope, *Sensors* 22, 553 (2022); doi: 10.3390/s22020553
- [3] H. Lee, K.T. Kang, Advanced tube formation assay using human endothelial colony forming cells for *in vitro* evaluation of angiogenesis, *Korean J. Physiol. Pharmacol.* 22, 705-712 (2018); doi: 10.4196/kjpp.2018.22.6.705.
- [4] Z. Li, H. Zhang, Y. Sun, Z. Feng, B. Cui, J. Han, Y. Li, H. Liu, T. Sun, Live-cell imaging-based dynamic vascular formation assay for antivasculardrug evaluation and screening, *iScience* 26, 106721 (2023); doi: 10.1016/j.isci.2023.106721.
- [5] C. Vesga-Castro, J. Aldazabal, A. Vallejo-Illarramendi, J. Paredes. Contractile force assessment methods for *in vitro* skeletal muscle tissues, *elife* 11, e77204 (2022); doi: 10.7554/eLife.77204.
- [6] M. Ruiz-Gutiérrez, A. Tejedera-Villafranca, S. Pujol-Pinto, J. Ramón-Azcón, J. M. Fernández-Costa, Myo-MOVES: a custom electrical stimulation system for functional studies of 3D bioengineered muscle, *Lab Chip* 25, 5677-5690 (2025); doi: 10.1039/d5lc00614g