

Abstract

Heart-on-a-chip (HoC) platforms represent a convergence of microfluidics and cellular biology, designed to imitate the complex physiological, electrical, and mechanical environments of a human heart. HoC devices culture and observe cardiac cells in a customizable environment with real-time observation. However, current HoC systems face critical translational bottlenecks. Most notably, laboratory-grown cardiomyocytes exhibit structural and functional immaturity and lack cellular complexity. This review evaluates recent strategies to address these limitations. We dissect advancements in multicellular co-culture, biomimetic electrical/mechanical stimulation, and microvascular fabrication aimed at driving functional maturation. Finally, we highlight cardiac model applications, challenges, and future perspectives.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide [1]. Limitations of clinical trials, animal research, and laboratory models have driven interest in in vitro cardiac models such as 3D engineered heart tissues, cardiac organoids, 2D monolayers, scaffolds, and HoCs. HoCs are microfluidic devices that culture and observe cardiac cells while recreating the heart's physiological, electrical, and mechanical systems [2,3]. They allow control of stimulation, contractility, and oxygenation with real-time observation [4]. They suit drug testing, patient-specific studies, and disease modeling. This review covers heart models, applications, challenges, and future perspectives.

Methods

Databases: PubMed
Keywords: heart-on-a-chip, organ-on-a-chip, heart model, cardiomyocytes, electrical stimulation, mechanical stimulation
Number of Articles: A total of 103 articles were identified.
Analysis: After reading the full-text, the findings of each paper were categorized into fabrication/stimulation methods, current models, applications, and limitations.

Findings

Figure 1: Roadmap for heart-on-a-chip development

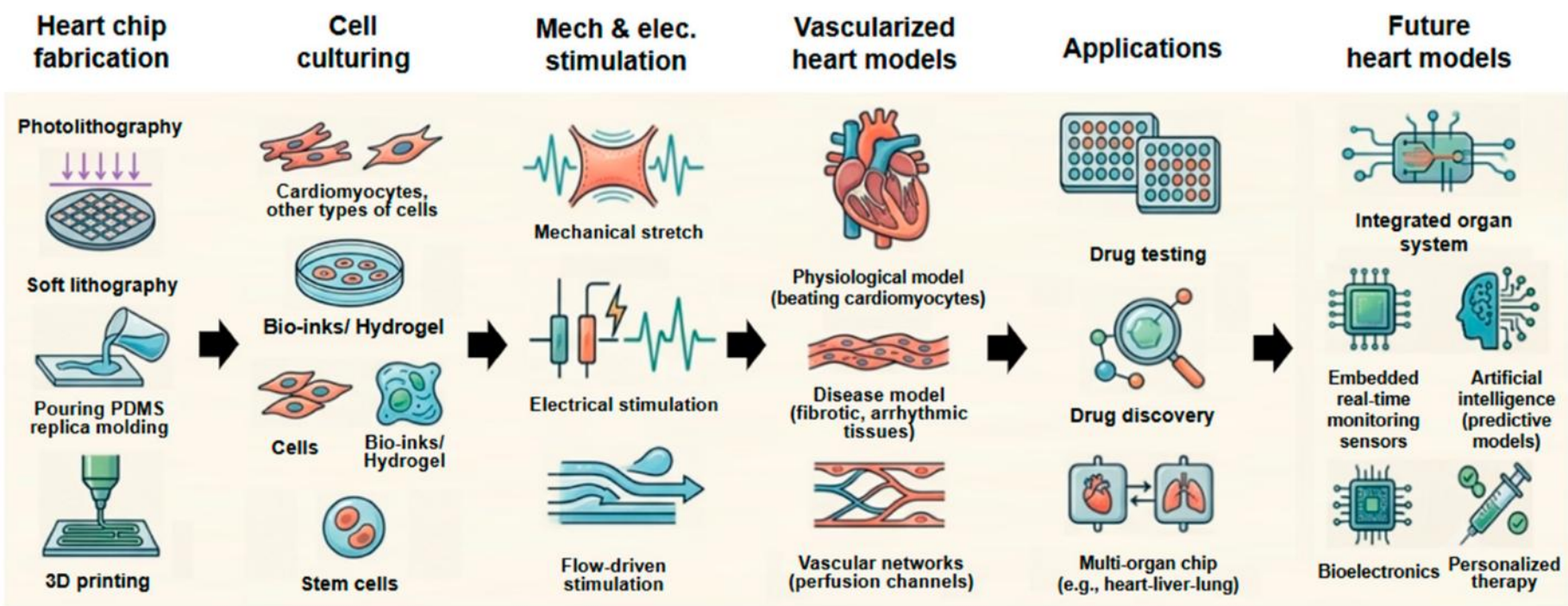


Table 1: Fabrication methods of heart-on-a-chip & their assessments

	Advantage	Disadvantage
Photolithography	High sub-micron precision	Expensive cleanroom facilities; poor direct biocompatibility
Soft lithography	Accessible, biocompatible, rapid	May absorb hydrophobic molecules
3D bioprinting	Directly deposits living cells and bio-inks into 3D structures	Lower resolution; slower manufacturing
Laser cutting	Rapid, maskless patterning	Localized thermal damage; surface roughness
CNC milling	Rapid, low-cost prototyping	Limited size by cutting-tool dimensions
Hot embossing	High-throughput, low per-unit cost	High upfront tooling cost

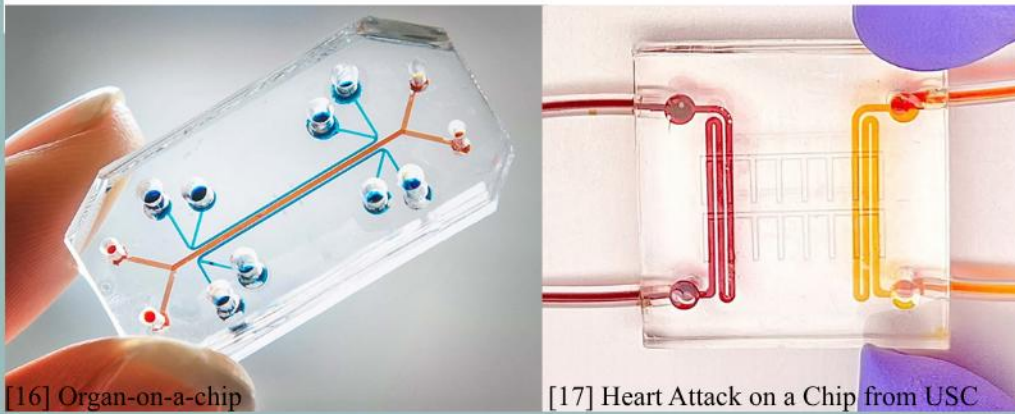
Table 2: Approaches to mechanical & electrical stimulations

	Definition	Research Examples/Approaches
Mechanical	Applies controlled stretching, compression, or other controlled mechanical deformation to cardiac tissue to recreate the mechanical environment of the heart	[5] Abulati, et al. & [6] Kong, et al.: external mechanical actuation [7] Lind, et al.: sensor-integrated mechanical stimulation [8] Visone, et al.: mechanical simulation and electrical monitoring [9] Sheehy, et al. & [10] Morimoto, et al.: architecture-based mechanical stimulation [11] Kolodziejek, et al.: magnetically controlled mechanical stimulation
Electrical	Applies electrical signals to promote mature function and synchronized beating of heart cells. Effectiveness depends on frequency, pulse amplitude, and duration.	[12] Liu, et al.: used microelectrode array (MEAs) or other patterned electrodes [13] Esmacili, et al.: made conductive hydrogels, which are hydrogen scaffolds containing gold nanorods or carbon nanotubes [7] Lind, et al.: used 3D printing electroconductive inks, including liquid metal like silver-polyamide, on the chip
Both E&M	Integrates both electrical and mechanical stimulation systems for more complete replication of cardiophysiology.	[14] Zhang, et al.: Gold electrodes with two hydrogel pillar electrodes. Platinum wires deliver electrical stimulation. Cardiomyocyte contraction against hydrogen pillars produces uniaxial mechanical stretching. [15] Manjua, et al.: Made electromagnetic scaffolds. Platinum electrodes for electrical. Indirect mechanical stimulation of hydrogel through neodymium magnet.

Sensing and detection methods exist to evaluate the functional responses of engineered cardiac tissues on HoCs. Two main types of methods:
1) **In situ detection:** real-time monitoring of the cardiac tissue without removing it from the device
Tissue displacement, deformation/strain, contractile force, piezoresistive sensing, microelectrode array, μ ECG, electrochemical impedance spectroscopy
2) **Offline testing:** analysis performed after the real-time operation of the device
Microscopy, immunostaining, gene/protein expression analysis

Current Models

Modern HoC systems frequently support multi-layered structures, complex triple co-cultures, stem-cell-derived cardiomyocyte integration, long-term 3D spheroid cultivation, and active mechanical and electrical stimulation to better mimic the native heart.



Applications

- physiological cardiac modeling
- complex heart disease modeling (e.g., ischemia, fibrosis)
- drug screening/delivery
- multi-organ-on-a-chip human body simulations

Limitations

- low reproducibility
- high manufacturing costs
- overly simple or complex fabrication methods
- stem-cell immaturity
- suboptimal cell density
- inadequate electrical or mechanical stimulation
- limited cellular and therapeutic diversity.

Conclusion

We reviewed a number of studies on HoC platforms that demonstrate considerable potential to be used as precise, physiologically relevant cardiac models for cardiovascular research, but remain limited by several factors. Continued improvements in these areas can further enhance these HoC platforms.