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Emerging technologies for the integration of flexible electronics into Heart-on-a-Chip platforms

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Abstract

The integration of flexible and stretchable electronics into Heart-on-a-chip (HoC) platforms presents remarkable opportunities for mimicking the mechanical and electrophysiological microenvironment of native cardiac tissue. Conventional rigid electronic systems fail to accommodate the dynamic, soft, and anisotropic properties of the beating heart, resulting in poor mechanical matching and reduced signal quality. Recent advancements in flexible and stretchable electronics have led to the development of conformal interfaces that can monitor cardiac function in real-time and in situ. This review discusses new approaches to fabricating mechanically compatible devices that match with the elasticity, curvature, and continuous deformation of cardiac tissue. We focus on two major functional readouts: cardiac contractility and electrophysiology. Key technologies including strain sensors, crack-based devices, hydrogel electrodes, and nanomaterial-integrated microelectrode arrays are discussed in the context of their biointegration. While intracellular recording methods are briefly addressed, emphasis is placed on the scalable and minimally invasive approaches for extracellular signal acquisition. This review investigates recent interdisciplinary strategies that combine bioelectronics, materials science, and cardiac tissue engineering, highlighting how soft electronics promote the development of physiologically relevant *in vitro* cardiac models for drug screening and disease modeling.

Keywords

Flexible electronics, Stretchable electronics, Cardiotoxicity, *In vitro* platform, Heart-on-a-Chip, Organ-on-a-Chip, Cardiac contractility, Cardiac potential, Sensors, Biointerface

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1. Introduction

Cardiovascular disease continues to be the main cause of death around the world, with heart failure and arrhythmias presenting major obstacles in clinical treatment and drug development (1). A key hurdle in pharmaceutical research is an increasing incidence of drug-induced cardiotoxicity, indicating an important aspect of late-stage drug development (2). Conventional preclinical models, such as animal studies, often fail to accurately predict human-specific cardiac responses because of physiological and species-specific differences (3). Consequently, there is an immediate demand for advanced *in vitro* platforms that accurately replicate human cardiac physiology and offer predictive insights during early-stage screening (4).

Heart-on-a-Chip (HoC) systems have emerged as powerful platforms that bridge the gap between traditional cell cultures and *in vivo* models (5). These microengineered devices integrate living cardiac cells with biomimetic scaffolds and microfluidic architectures to emulate the structural, mechanical, and electrophysiological microenvironment of native heart tissue. A key problem still exists: the inability to accurately monitor functional outputs, especially electrical activity and mechanical contraction, in real time and over long periods of time.

Conventional sensing methods, such as optical imaging or rigid planar electrodes, offer partial solutions but have substantial limitations (6). Optical methods often require complex post-processing and lack the depth to probe electrical properties, while rigid electrodes suffer from mechanical mismatch, poor tissue-electrode adhesion, and limited adaptability to 3D or dynamically moving organs (7). These limitations hinder the accurate acquisition of cardiac signals, reduce device-tissue interface quality, and may even compromise cell viability.

In this context, flexible and stretchable electronics have emerged as innovative tools for HoC platforms. By utilizing materials and structures that closely mimic the mechanical properties of cardiac tissue, such as ultrathin films, soft elastomers, and serpentine design, these devices can seamlessly interface with beating, curvilinear tissues (8). Flexible electronics not only maintain the integrity of the cardiac microenvironment but also allow for high-resolution, long-term monitoring of both extracellular action potentials and contractile forces. Their conformability ensures low-impedance contact with tissue surfaces, while their biocompatibility and mechanical matching minimize inflammatory responses and recording artifacts.

This review aims to explore the emerging technologies enabling the integration of flexible electronics into HoC platforms (Figure 1). In section 2, we examine the key material and mechanical features of soft electronics, including modulus matching, cell alignment guidance, flexibility and ultrathin conformability, stretchability, and biocompatibility. Section 3 focuses on functional sensing mechanisms, including recent advances in the real-time measurement of cardiac contractility and electrophysiological activity. We emphasize the use of strain sensors and impedance-based detection for reliable and high-quality data

acquisition. Finally, section 4 discusses current challenges and future perspectives, highlighting the need for improved biocompatibility, scalability, and integration with organoid systems and machine learning-based data analysis.

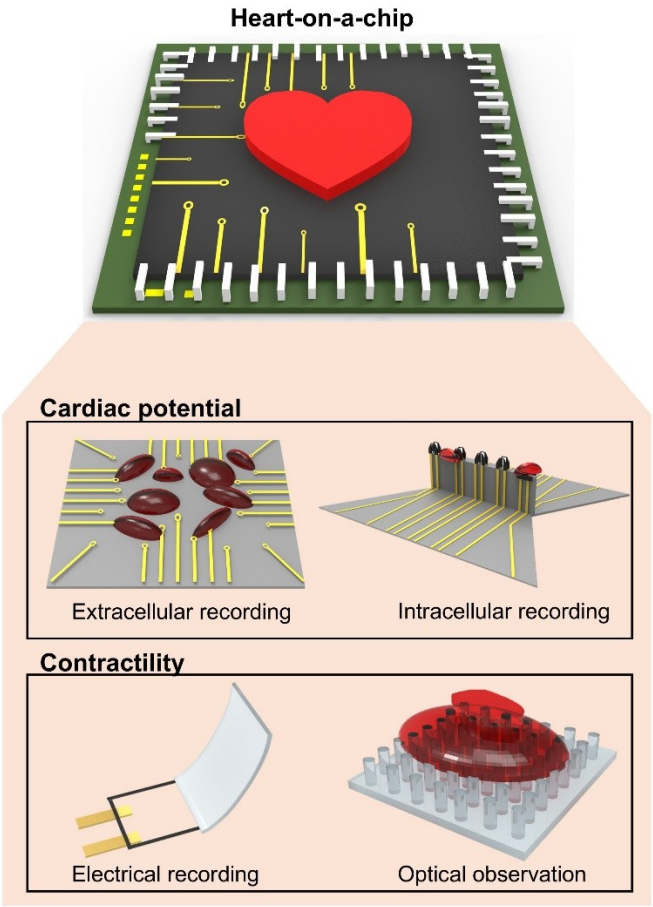

Figure 1. Integration of flexible electronics into heart-on-a-chip.

2. Material and structural design of flexible electronics for cardiac interfaces

The incorporation of flexible and stretchable electronics into HoC depends on the development of materials and device designs that correspond to the dynamic and soft nature of cardiac tissue. Unlike conventional rigid electronics, these bioelectronic components are required to perform constantly under continuing strain, curvature, and micro-motion while maintaining both signal quality and cell viability. This section outlines essential features for the integration of flexible electronics into HoC. It emphasizes concepts such as mechanical modulus matching, designs for cell alignment and conformal contact, strategies for ultrathin and stretchable structures, and biocompatibility (Figure 2). The combination of these characteristics establishes the technological foundation that enables seamless, real-time monitoring in engineered cardiac models.

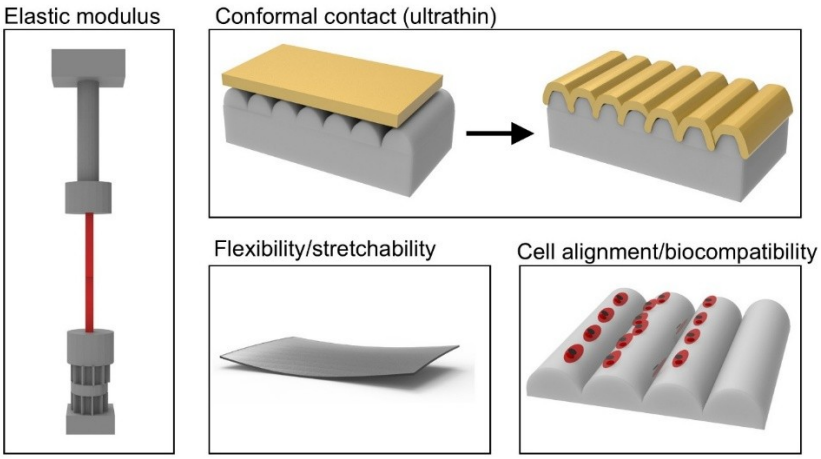

Figure 2. Key features of flexible electronics for heart-on-a-chip.

2.1 Mechanical modulus matching with cardiac tissue

The mechanical mismatch between conventional rigid electronic devices and the soft, dynamic nature of cardiac tissue represents a fundamental barrier in developing bioelectronic interfaces for HoC systems. Typically, rigid electronic materials such as silicon or metals possess elastic moduli in the gigapascal range, whereas cardiac tissue exhibits a much lower modulus ~ 10 to 15 kPa (9). This disparity generates chronic mechanical stress at the interface, resulting in inflammation, fibrotic encapsulation, and eventual degradation of signal quality and device performance. Although much of the current literature focuses on reducing static modulus mismatch, cardiac tissues are not purely elastic (10). They exhibit viscoelastic behavior, meaning their mechanical response depends on both strain and time. Ignoring these dynamic properties limits the reliability of *in vitro* models and of long-term electrophysiological monitoring.

To mitigate these issues, several materials have been adopted for use as mechanically compliant substrates. Polyimide (PI) has long been a staple in flexible electronics due to its chemical stability and compatibility with standard microfabrication (11). However, even in thin-film form, PI remains stiffer than cardiac tissue. Recent strategies have focused on microstructuring PI into porous mesh networks to enhance its flexibility and reduce interfacial stress. For instance, Viventi et al. demonstrated that rigid silicon-based electronics can be adapted into mechanically compliant formats by integrating silicon nanomembrane transistors onto flexible PI substrates. Their system consisted of a 288-electrode array, built with 1.5 µm spin-coated PI insulation layers. When applied to a porcine heart, the device enabled high-resolution cardiac wavefront mapping at 800 µm with a signal-to-noise ratio (SNR) of ~34 dB, validating the feasibility of combining high-performance electronics with flexible, tissue-compatible materials for stable, high-resolution cardiac sensing (12).

Parylene C (a polymer of repeating para-monochlorobenzenediyl rings connected by

1,2-ethanediyl bridges) is another widely used substrate that offers low cytotoxicity, high chemical resistance, and compatibility with photolithography. Its modulus is still on the order of 1 to 3 GPa, but because it can be deposited as conformal, ultrathin coatings, it provides improved flexibility without compromising biocompatibility (9). In one study, kirigami-patterned parylene substrates were engineered to stretch over 800 percent while maintaining stable electrical recordings from a beating mouse heart (13). This approach illustrates how structural engineering can overcome intrinsic material limitations by allowing stiff materials to deform in a controlled and reversible manner.

Polymers such as PET (Polyethylene terephthalate) and PEN (Polyethylene naphthalate) offer excellent chemical and thermal stability and have been used as substrates for multielectrode arrays. However, their high Young's moduli (2.9 GPa for PET and 5.5 GPa for PEN) make them suitable mainly for applications where moderate flexibility is sufficient (14). A notable example is the work by Lee et al., who developed a 1.5-micrometer-thick PET-based multielectrode array for cardiac monitoring in rats (15). The authors integrated a polyvinyl acetate hydrogel coating to promote soft tissue adhesion, which resulted in reduced noise levels and improved signal stability. Although PET is not intrinsically soft, its thin-film form factor and the addition of hydrogel interfaces allowed effective physiological integration.

In contrast to these relatively stiff materials, elastomers such as polydimethylsiloxane (PDMS) and Ecoflex™ (an aromatic aliphatic copolyester obtained by polymerization of terephthalic acid, adipic acid and 1, 4-butanediol) offer elastic moduli under 1 MPa, closer to that of cardiac tissue (16). These materials can undergo large deformations and return to their original shape, making them attractive for applications involving cyclic strain, such as cardiac monitoring. However, their purely elastic response fails to replicate the viscoelastic behavior of biological tissues. To address this, researchers have begun incorporating additives such as polyethyleneimine (PEIE) into PDMS to enhance its viscoelasticity and tissue adhesion.

Hydrogels represent the next frontier in developing mechanically matched interfaces. Their water content, low modulus, and high porosity make them excellent candidates for mimicking the extracellular matrix of soft tissues (17). In a recent study, a HoC platform incorporated soft, conductive hydrogel pillar electrodes that not only matched the mechanical compliance of native myocardium but also enabled dual-functionality: electrical stimulation and non-invasive real-time monitoring of contractile force and electrophysiological signals (18). This was achieved by embedding induced pluripotent stem cell (iPSC)-derived cardiomyocytes and fibroblasts within a 3D tissue matrix constrained by the hydrogel pillars, whose deformation under contraction was optically tracked. The conductivity of the hydrogel allowed continuous electrophysiological readout, capturing drug-induced responses without disturbing tissue integrity. These developments point to the possibility of creating hybrid systems where electronic functionality is embedded within

biomimetic scaffolds, offering both electrical performance and biological fidelity.

Despite these advances, mechanical modulus matching remains a complex challenge, particularly under the dynamic and heterogeneous conditions of cardiac environments. Most existing studies rely on short-term or static evaluations, which do not fully capture the effects of long-term mechanical loading, tissue remodeling, or biofouling (19). Developing more advanced HoC systems will require substrate materials that combine tunable viscoelasticity, fatigue resistance, and adaptable microstructures. These capabilities are essential for maintaining stable interfaces between devices and tissues during extended physiological operation.

2.2 Engineering cell alignment

Spatial alignment of cardiomyocytes is a cornerstone of functional myocardium and a critical design consideration in HoC systems. *In vivo*, cardiomyocytes are organized anisotropically within laminar layers supported by an ExtraCellular Matrix (ECM), enabling directional action potential propagation and coordinated mechanical contraction (20). Without replicating this highly ordered structure *in vitro*, engineered cardiac tissues often lack physiological accuracy in disease modeling and drug screening. Yet, many platforms continue to rely on isotropic two-dimensional (2D) cultures, which fail to capture the structural complexity and electromechanical integration found in the native heart.

To guide anisotropic tissue formation, researchers have employed surface microengineering strategies that impose topographical cues on cell substrates. Among these, microcontact printing has emerged as a reliable method to control cellular organization by spatially patterning ECM proteins. In a representative study, Camelliti et al. used a fabricated PDMS mold to stamp 30 μm wide collagen lines onto a culture substrate (21). Neonatal Rat Ventricular Myocytes (NRVMs) seeded on these tracks aligned parallel to the collagen patterns and developed well-organized sarcomeres, closely mimicking the structural anisotropy of native myocardium.

However, planar microcontact printing inherently lacks the capacity to reproduce the depth-dependent mechanical gradients, fiber curvature, and vascular architecture of three-dimensional (3D) cardiac tissue. Addressing this gap, recent efforts have shifted toward 3D hydrogel molding approaches. For example, Bian et al. developed a PDMS mold that recapitulated epicardial fiber orientation by embedding in-plane micro-post arrays into which NRVM-laden hydrogels were cast (22). The resulting constructs, over 200 μm thick, not only demonstrated region-specific cell alignment but also contained interconnected pores that facilitated oxygen diffusion and supported high cell viability. These designs represent a significant improvement over planar constructs by enabling structural anisotropy and metabolic support in thicker engineered tissues.

Beyond molding, additive manufacturing has introduced new paradigms for constructing spatially guided tissues. Three-dimensional microfibrous scaffolds with alternating filament orientations have been used to

engineer multilayer cardiac constructs with layer-specific cell alignment, reflecting the rotational fiber architecture observed *in vivo* (23). Optical bioprinting techniques, such as microscale continuous optical printing, now allow for precise 3D shaping of cardiomyocyte-laden hydrogels. These approaches yield constructs that not only maintain high spatial resolution but also exhibit long-term contractile behavior and phenotypic alignment akin to native myocardium.

While current strategies have significantly advanced the control of cellular alignment in engineered cardiac tissues, many still rely predominantly on structural cues, often overlooking the influence of biochemical gradients, stiffness heterogeneity, and dynamic mechanical feedback. Moreover, the integration of soft bioelectronics into anisotropic tissue constructs remains limited, restricting the capacity to monitor functional maturation in real time. To better replicate the complexity of native myocardium, future HoC systems should incorporate composite hydrogels with spatially controlled ECM patterning, tunable mechanical properties, and embedded flexible electronics. Such multi-modal platforms would support both structural organization and functional analysis, offering improved fidelity in modeling cardiac physiology and disease.

2.3 Flexibility and conformal contact

Achieving stable and high-quality sensing in HoC systems requires more than just mechanical compliance at the macroscale. It demands intimate, conformal contact between electronic devices and the microscopically textured, continuously moving surfaces of cardiac tissues. Flexibility refers not only to the ability of devices to bend, but also to their capacity to maintain mechanical invisibility during deformation, ensuring signal accuracy without perturbing natural tissue behavior (24).

The bending stiffness of a material scales with its elastic modulus and the cube of its thickness, which means that significant flexibility can be achieved through miniaturization. This principle has driven the development of ultrathin electronic systems, often with thicknesses < 5 μm, that are capable of wrapping tightly around biological surfaces. For instance, Miyamoto et al. demonstrated a substrate-free nanomesh sensor composed of gold-coated PolyVinyl Alcohol (PVA), which achieved exceptional conformal contact through ultrathin geometry and open mesh design (25). The structure maintained intimate adhesion to irregular and moving skin surfaces such as fingertips, without adhesives, while offering high gas permeability and mechanical durability. Even after 10,000 cycles of 40% elongation, the sensor preserved its function, highlighting the critical role of geometry-driven flexibility in enabling long-term, low-irritation integration with soft biological tissues.

However, flexibility alone is not sufficient to ensure mechanical and physiological compatibility. Conformal integration must also consider substrate roughness, organ curvature, and dynamic deformation. For example, the RMS surface roughness of skin (~10–50 μm) and the beat-induced deformation of the heart (~20% strain) present significant mechanical challenges for electronics, particularly when conventional

inorganic materials like silicon or gold exhibit rupture strains below 1% (26). Without sufficient conformability, these devices risk impairing tissue function or inducing inflammatory responses.

Transfer printing has become the fabrication backbone of such systems. Through kinetic control of adhesion strength via elastomeric stamps such as PDMS, thin-film electrodes can be cleanly transferred from rigid wafers to soft substrates (27). This technique allows for precise assembly of ultrathin devices on pre-curved or prestrained elastomers, facilitating the construction of multilayered, stretchable electronic arrays compatible with cardiac curvature.

Together, these advances underscore that flexibility and conformal contact are not simply structural enhancements but functional necessities for integrating electronics with the mechanically active surfaces of cardiac tissues. As HoC platforms evolve toward more complex and physiologically accurate models, future designs must move beyond static thin-film strategies and adopt adaptive interfaces that can accommodate continuous tissue motion and maintain long-term biological compatibility. By combining ultrathin geometries, tunable adhesion strategies, and integrated stretchable electronics, next-generation HoC systems can support stable and high-resolution sensing under cyclic mechanical strain, offering improved performance for *in vitro* cardiac diagnostics and drug screening.

2.4 Stretchability and stability

HoC systems must operate under highly dynamic mechanical conditions, where cardiac tissues undergo continuous stretching, compression, and torsion during each beat. Unlike simple flexibility, which allows devices to bend along a single axis, stretchability requires multidirectional strain, often exceeding 10–20% biaxially without compromising electrical function or mechanical durability (28). Since conventional electronic materials such as gold, silicon, or indium tin oxide are intrinsically brittle, stretchability must be engineered geometrically. The following structural strategies represent key advances in transforming rigid materials into deformable, high-performance components suitable for integration with the moving heart.

The wavy or buckled structure is one of the earliest and most accessible strategies for achieving stretchability through out-of-plane deformation (29). By bonding an ultrathin device onto a pre-stretched elastomeric substrate, such as PDMS, and subsequently releasing the prestrain, a periodic buckling pattern forms spontaneously. This sinusoidal geometry absorbs tensile strain as the wave flattens under load. The degree of stretchability is proportional to the pre-strain applied during fabrication and can be fine-tuned by adjusting material thickness, modulus, and bonding configuration. While this approach preserves electrical performance under moderate deformation, it is inherently limited by the pre-strain threshold and can suffer from mechanical failure under large or repeated strains.

The island-and-bridge design was developed to localize strain away from sensitive components. In this approach, rigid "islands"

containing electrical components are physically separated by stretchable "bridges" composed of thin metal interconnects (30). Under mechanical stress, these bridges arch upward or deform in-plane, relieving strain from functional regions. Among all strategies, serpentine interconnects have emerged as the most versatile and widely adopted solution. By replacing straight conductive lines with arc-shaped or horseshoe-like geometries, strain is distributed along the curved path, reducing localized stress and enabling elongation far beyond the material's intrinsic limit (31). These designs can be customized through geometrical tuning of arc radius, segment length, and trace width. When combined, the island-and-bridge layout with serpentine interconnects forms a robust and adaptable architecture that supports both high mechanical compliance and reliable electrical performance in stretchable electrode circuits.

A more recent and sophisticated variant of strain engineered geometry is the 3D coil structure, which departs from planar designs to achieve uniform stress distribution through volumetric deformation (32). Helical coils are formed via controlled out-of-plane buckling or direct 3D assembly, allowing devices to extend by hundreds of percent without inducing localized failure. The 3D coils distribute load evenly across the structure, enhancing fatigue resistance. Figure 3 shows the structures.

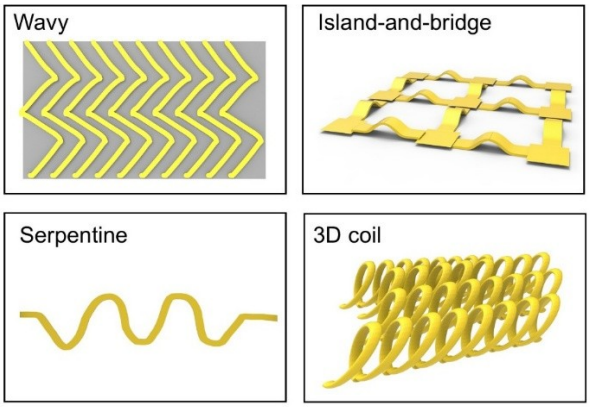

Figure 3. Design strategies for stretchability.

In contrast to out-of-plane strategies, mesh design offers stretchability through in-plane rotation and expansion. These systems comprise interconnected networks of polymer or metal traces that deform via hinge-like motion at their junctions. Because they do not rely on elastomeric substrates, mesh devices can be fully self-supporting and fabricated entirely from high-modulus materials such as PI or gold. In one study, an open mesh structure with PI-gold interconnects withstood uniaxial strains exceeding 1400%, enabled by rotational freedom at the nodes (33).

Despite the promise of these strategies, several challenges remain. Many stretchable systems still depend to a significant extent on elastomer substrates, which are susceptible to creep, delamination, and hydrolytic degradation over time. Moreover, thermal dissipation becomes increasingly critical as

device density and power consumption rise, especially in closed-loop HoC systems with active stimulation. The future of stretchable electronics will depend on hybridizing multiple strategies such as combining serpentine traces with 3D coils or embedding mesh networks within hydrogels to balance electrical performance, mechanical compliance, and biological compatibility.

2.5 Biocompatibility

Biocompatibility and long-term stability are foundational requirements for soft electronic systems used in HoC platforms. Since these systems are designed to operate in direct contact with living cardiac tissues, materials and device architectures must be engineered to prevent cytotoxicity, minimize immune responses, and maintain consistent performance despite repeated mechanical deformation and biochemical exposure. The core materials used in soft bioelectronics, such as PDMS, Ecoflex™, PI, parylene-C , and hydrogels, are selected not only for their mechanical tunability but also for their biocompatibility (19).

For materials that serve as active sensing or conductive layers (e.g., gold nanomesh, graphene, Carbon NanoTubes (CNTs), and PEDOT:PSS(Poly (3,4 - ethylene dioxythiophene: Polystyrene sulfonate)), numerous studies have demonstrated their *in vitro* safety under controlled conditions. For example, PEDOT:PSS exhibits minimal inflammatory response and is often used in cardiac electrodes due to its mixed ionic/electronic conductivity and low modulus (34). Graphene based electrodes have also shown good cell viability and long-term signal stability when encapsulated to reduce oxidative stress (35). Therefore, the integration of flexible and stretchable electronics into *in vitro* cardiac models demands a careful balance between electrical functionality, mechanical resilience, and biological safety.

3. Monitoring of cardiac function

In HoC systems, the ability to quantitatively assess cardiac function is essential for evaluating tissue maturation, modeling disease phenotypes, and conducting high-throughput drug screening. Two of the most fundamental functional parameters of cardiac tissues are contractility and electrophysiological activity. Contractility reflects the mechanical output of cardiomyocytes during systole and diastole, while electrophysiological signals provide insights into the electrical conduction pathways and rhythmic integrity of the tissue (36). These parameters are not only indicators of cellular health and viability, but also serve as sensitive markers of pharmacological effects and cardiotoxic responses.

HoC integrated with electronic devices allow real-time, non-invasive monitoring of these cardiac signals within a microphysiological environment. This section introduces the current state of sensing technologies for cardiac function, focusing on methods to measure cardiac contractility (section 3.1) and cardiac electrical activity (section 3.2), and discusses how these techniques contribute to the physiological relevance and analytical resolution of *in vitro* cardiac models.

3.1 Cardiac contractility

Cardiac contractility is the ability of

cardiomyocytes to generate mechanical force during contraction and relaxation. In other words, cardiac beating is the indicator of cardiac tissue maturity, viability, and functionality (37). Accurate and dynamic measurement of contractility in HoC platforms enables quantitative assessment of pharmacological responses, tissue remodeling, and disease phenotypes. In recent years, a wide array of sensing strategies has been developed to monitor contractile behavior across different levels of tissue complexity, ranging from single cardiomyocytes to 3D cardiac organoids (38). Among these, optical and electrical sensing methods represent two major approaches, each with distinct advantages and limitations.

Optical methods have been widely employed to evaluate cardiac contractility by visualizing cell or substrate deformation during beating, ranging from direct imaging of sarcomere length to more advanced techniques such as Traction Force Microscopy (TFM) and micropost deflection analysis (39). While TFM tracks bead displacement within elastic substrates and micropost arrays quantify force based on pillar bending, both approaches offer valuable spatial resolution but require complex imaging setups and intensive post-processing. Other optical or semi-optical techniques, including calcium imaging, cantilever-based laser sensors, and colorimetric readouts, provide indirect measures of contractility.

While optical techniques offer high spatial resolution and are widely used for academic validation, they often require labor-intensive image analysis and are limited in throughput. In contrast, electrical sensing strategies provide scalable, real-time, and non-invasive platforms that are better suited for high-throughput HoC systems.

Among electrical sensing methods, strain sensors are particularly well-suited for monitoring contractile deformation. Wang et al. embedded CNT strain sensors into a microdevice platform and validated its performance using five cardiac drugs, including isoproterenol and verapamil (40). The CNT-based strain sensors exhibited higher resistance changes in response to contractile force compared to traditional impedance sensors, allowing for improved signal clarity. The device's ability to detect drug-induced modulation in contractility positions it as a viable tool for on-chip cardiotoxicity screening.

Lind et al. advanced this approach by integrating a strain sensor directly into a 3D-printed cantilever structure, which also incorporated a cardiomyocyte culture well and micropattern-ed groove for alignment (41). As cardiomyocytes contracted, the cantilever deflected and the embedded carbon black strain gauge converted this mechanical deformation into a measurable electrical signal. The device enabled simultaneous monitoring of contractile amplitude during systole and diastole, providing continuous readouts over extended culture periods. This all-in-one scaffold design highlights the advantage of combining structural, biological, and electrical elements for efficient and longitudinal cardiac studies.

Crack-based sensors have emerged as a highly sensitive alternative. These devices exploit nanoscale crack propagation in thin

metallic films to produce significant resistance changes under minute strain. One study demonstrated a crack sensor capable of resolving the systolic and diastolic phases of cardiomyocyte contraction with a signal-to-noise ratio over 600 times higher than conventional piezoresistive sensors (42). Notably, the crack sensor retained mechanical and electrical stability after 26 days of continuous immersion in culture medium, indicating its suitability for long-term cardiac monitoring.

Impedance-based sensors, while historically used to monitor cell attachment and proliferation, have also been adapted for contractility assessment (43). By tracking changes in electrical impedance as cardiomyocytes contract and relax over an electrode array, researchers have been able to correlate impedance fluctuations with mechanical activity. However, concerns remain about potential cytotoxicity due to direct current exposure, making alternative strategies such as passive strain sensing more favorable for chronic applications.

The electrical sensing strategies of cardiac contractility, including strain gauges, crack sensors, and impedance electrodes, are transforming the landscape of contractility monitoring in HoC platforms. Future advancements may focus on hybrid sensor systems that combine the high sensitivity of crack sensors with the integration capabilities of 3D-printed scaffolds, paving the way toward robust, multiplexed, and miniaturized platforms for comprehensive cardiac assessment.

3.2 Cardiac potential

Monitoring the electrophysiological behavior of cardiac tissue is central to evaluating functional maturation, arrhythmogenic potential, and drug-induced cardiotoxicity in HoC systems. Cardiac electrical activity originates from transmembrane ion fluxes in cardiomyocytes, propagating across tissues through gap junctions and manifesting as extracellular action potentials (44). These signals provide insight into parameters such as beat rate, conduction velocity, field potential duration, and depolarization amplitude which are key indicators of cardiac function and drug responsiveness. Electrical recordings are typically divided into extracellular and intracellular recordings. While intracellular recording offers detailed waveform information, it often involves invasive techniques incompatible with long-term, soft-tissue integration (45). Therefore, most flexible HoC systems prioritize extracellular recording, with emphasis on materials and interfaces that support high-quality and stable measurements under dynamic beating motion.

Conventional MicroElectrode Arrays (MEAs), often fabricated on planar substrates, have been widely adopted to record field potentials from monolayer cardiac cultures (46). While effective for basic rhythm tracking, their rigid format limits their utility in dynamic or 3D environments. To address this, Kalmykov et al. introduced a self-rolling biosensor array that wraps around spheroidal cardiac tissues (47). The device, composed of SU-8 polymer (an epoxy based negative photoresist) and gold microelectrodes, enables 3D multisite recording, allowing conduction velocity (~12.45 cm/s) to be measured across the

curved surface of cardiac spheroids. Their system not only improved signal coverage but also enabled construction of isochronal maps that captured spatial differences in electrical activation, a step toward physiologically realistic modeling of conduction heterogeneity.

Similarly, Feiner et al. developed a flexible cardiac patch that integrated a gold MEA within a porous nanofiber scaffold (48). The patch used SU-8 encapsulation and a polypyrrole-based drug delivery layer, enabling simultaneous signal recording and local pharmacological stimulation. When cultured with human cardiomyocytes, the platform maintained electrical fidelity under mechanical strain and delivered localized stimuli, demonstrating the value of multi-functional integration in dynamic cardiac environments. The device retained functionality under bending and provided stable signal acquisition while minimizing tissue disruption.

To improve electrode-tissue interfacing, Liu et al. engineered 3D micropillar electrodes from a conductive hydrogel composed of PEDOT:PSS and iridium oxide (49). Upon hydration, the micropillars swelled anisotropically, increasing surface contact and improving signal amplitude compared to their rigid counterparts. This approach demonstrated that conformal interface dynamics such as swelling could be harnessed to enhance both electrical sensitivity and mechanical compliance in soft tissue contexts.

To push the limits of softness and stretchability, Lee et al. engineered an ultrasoft nanomesh electrode composed of Au-coated electrospun polyurethane fibers (50). The mesh, conformally adhered to fibrin hydrogels seeded with hiPSC-derived cardiomyocytes, enabled stable recordings of cardiac electrical activity while accommodating tissue contraction. This spaghetti-like structure provided mechanical invisibility, thus preserving physiological behavior during signal acquisition.

Beyond passive sensing, nanomaterial-enhanced Field-Effect Transistors (FETs) offer another frontier in extracellular recording. Dai et al. proposed a stackable, 64 FET array integrated with silicon nanowires (51). This platform allowed real-time 3D mapping of cardiac action potentials within tissue volumes by folding into a multilayer format. The FET configuration offered higher spatial resolution and signal amplification, illustrating the potential of active electronics for capturing fast electrophysiological events in volumetric constructs.

While extracellular systems dominate practical applications, intracellular recording offers additional depth by directly accessing transmembrane potentials. Though often invasive, recent innovations such as nanopillar electrodes and volcano-shaped microelectrodes have enabled brief or passive intracellular access with significantly enhanced signal amplitude. These methods are not yet broadly adopted in HoC systems but offer insights into ion channel function and pharmacological response that complement extracellular approaches.

The electrical monitoring in HoC platforms has evolved from rigid MEAs to soft,

integrative electrode systems capable of stable, high-resolution recording under realistic physiological conditions. Future work should focus on unifying soft material design, active electronics, and 3D integration to capture spatiotemporal cardiac dynamics with both precision and durability.

4. Disease modeling and interpretation in HoC with flexible electronics

4.1 Disease modeling in HoC

HoC platforms utilize microfluidic channels, soft tissue engineering, and biomimetic stimulation to replicate key aspects of human cardiovascular physiology *in vitro*. In contrast to conventional static 2D cultures, these systems use dynamic mechanical strain, electrical pacing, and biochemical gradients, facilitating precise modeling of disease phenotypes and drug responses (52). This integration of environmental signals enhances the proliferation, alignment, and differentiation of human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), enabling applications that range from physiological disease modeling to personalized pharmacology (53, 54).

Genetically engineered hiPSC-CMs play a crucial role in modeling hereditary cardiac diseases, including Barth syndrome. Wang et al. developed a microengineered system cultured with patient-specific hiPSC-CMs that exhibit TAZ mutations (55). They noted phenotypes such as reduced contractility, disorganized sarcomeres, and diminished metabolic function, which closely resembled the clinical features of this mitochondrial cardiomyopathy.

Simultaneously, cardiac organoid models have emerged as an invaluable complement to tissue chips, presenting self-organizing, multicellular structures that mirror elements of early cardiogenesis. Hofbauer et al. developed hiPSC-derived organoids that demonstrated spontaneous morphogenesis and chamber-like structures with spatially organized myocardial and endothelial layers (56). These systems enable the exploration of morphogen gradients, cell-cell signaling, and cardiac morphogenesis in a scalable, self-patterned format.

Acute cardiac pathologies, including ischemia, have been effectively modeled through the precise control of oxygen tension in microfluidic environments. For example, Liu et al. developed integrated platinum nanopillar electrodes along with hypoxia-controlled media flow to replicate ischemic injury (57). This platform enabled monitoring of electrophysiological changes such as narrowed action potentials linked to ATP-sensitive K^+ channel activation. Mechanical loading was employed to replicate chronic pressure overload on veins and trigger cardiac hypertrophy. In engineered tissue chambers, both static and cyclic stretch resulted in increased expression of hypertrophic markers such as ANP (Atrial Natriuretic Peptide), alongside morphological remodeling of cardiomyocytes (3, 55).

Inflammatory and vascular pathologies are simulated by integrating endothelial layers and implementing controlled shear stress in microfluidic co-culture systems. This approach has discovered endothelial barrier dysfunction, the expression of pro-inflammatory cytokines, and leukocyte adhesion in the context of disturbed flow, key

indicators of early atherosclerosis. The implementation of multi-organ co-culture formats allows for the simultaneous study of cardiac and vascular components, effectively mimicking the complex tissue-tissue interactions observed in systemic cardiovascular diseases (58). These examples collectively demonstrate the advancing potential of HoC platforms to replicate various cardiovascular disease states, reinforced by hiPSC-CM genetics, biomimetic microenvironments and organoid arrangement (59).

4.2 Drug screening and pharmacological profiling

The integration of flexible electronics has significantly expanded the pharmacological uses of HoC platforms, allowing for continuous measurement of drug-induced changes in electrophysiology and contractility. The transition from end-point assays to real-time monitoring significantly improves the identification of subtle or transient effects, especially those linked to proarrhythmia and cardiotoxicity.

Flexible microelectrode arrays (MEAs) and strain gauges have been utilized to assess the functional impact of ion channel modulators. For instance, Zhang et al. developed a platform with silicon-nanowire–integrated MEAs which recorded field potentials and beat rate across cardiac tissues (60). They demonstrated how E-4031 (a hERG blocker) and verapamil (an L-type calcium channel blocker) produced dose-dependent prolongation of field potential duration and reduced beat frequency, respectively. However, since both drugs ultimately prolong the QT interval, MEA readouts alone could not discern which ion channels are primarily affected.

To support higher throughput and multiplexing needs, Keung et al. developed a two-tiered monitoring platform using human ventricular-like cardiac tissue strips (hvCTS) and organoid chambers (hvCOC) (61). Twenty five cardiotropic compounds were screened and achieved 100 % sensitivity for negative inotropes, 86% for positive inotropes, and 80% for null inotropes in hvCTS, with hvCOC enhancing the detection of positive inotropy. This robust assay design enabled systematic, physiologically meaningful inotropic profiling. At a similar scale, Lind et al. introduced a 24-well platform using microgroove PDMS cantilevers equipped with flexible gold strain sensors (62). They performed dose–response studies for 12 cardiac drugs as well as performed duplicate endothelial barrier experiments. Their system successfully measured twitch stress and beat rate while simulating vascular barrier dynamics, showing delayed toxicity when drugs traversed an endothelial layer.

Despite these advancements of integrating electronics, most HoC platforms rely solely on electrical or mechanical sensing. This restricts interpretation, as changes in beat rate or contractility cannot be linked to specific cellular disturbances such as mitochondrial stress, oxidative injury, or calcium processing deficits. Various reviews highlight the significance of integrating biochemical sensors into HoC systems (63, 64). These could include electrochemical probes sensitive to Reactive Oxygen Species (ROS), aptamer sensors for monitoring ATP, or

indicators for metabolic flux. Combined with electrical and mechanical sensing, biochemical sensors could offer a more detailed understanding of how drugs influence cardiac physiology. Further improvements in multimodal and high-throughput HoC platforms that integrate flexible electronics will be essential for precise, automated, and physiologically meaningful cardiotoxicity screening in preclinical drug development.

4.3 Challenges in signal interpretation

The integration of flexible electronics into HoC platforms has achieved outstanding spatiotemporal resolution in the monitoring of cardiac electrophysiology and biomechanics. The ability to detect beat rate, field potential duration, conduction velocity, and strain dynamics in real-time has proven essential for evaluating tissue function and drug response. Nonetheless, a significant challenge persists such as identifying the biological sources of comparable readouts across various pathological or pharmacological conditions.

A decrease in contractile amplitude could be linked to mitochondrial dysfunction, impaired calcium handling, oxidative stress, or changes in β-adrenergic signaling. Similarly, changes in the AP waveform may indicate hERG inhibition, activation of K^+ channels due to ischemia, or conduction block associated with fibrosis (65, 66). Flexible electronics commonly indicate downstream phenotypes, meaning their signals lack inherent specificity to particular cellular pathways.

The integration of multiplexed sensors has initiated progress in bridging this gap. Liu et al. integrated intracellular nanopillar electrodes with extracellular MEAs in hypoxic conditions, noting a correlation between action potential narrowing and ATP activation (57). Nonetheless, numerous studies still rely on electrical or mechanical readouts without simultaneous biochemical or metabolic markers.

Li et al. emphasized that while beat rate and force amplitude are accurate measurements, they are often considered as broad indicators of viability or maturity (67). The absence of integrated ROS, calcium, or ATP sensors restricts interpretation to surface-level observations. Furthermore, the sensing data often average across heterogeneous tissue regions, potentially masking focal defects. To address this challenge, it is essential to utilize high-density, spatially resolved electronics, particularly those that incorporate both intra- and extracellular sensing, to detect microregional dysfunction.

Computational modeling has the potential to enhance experimental systems by modeling how cellular disruptions translate into signals at the tissue level. However, these models demand multimodal datasets to ensure proper validation. Currently, few platforms offer the biochemical-electrophysiological integration needed for model training, hindering interpretive development (68). In addition, it does not yet seem to have been realized that Machine Language supervised learning models can be utilized to decipher dysfunction at the organelle level, using only a multitude of mechano-electrical signals without the necessity of onerous biochemical sensor integration.

4.4 Perspectives in signal-based disease analysis

To enable precise, mechanism-specific analysis of cardiac function, the next generation of HoC platforms must transition beyond descriptive sensing and toward integrative, multimodal diagnostics. Recent studies have demonstrated innovative proof-of-concept devices that integrate electrical, mechanical, and biochemical readouts into a single chip. Zhang et al. presented a multisensor-integrated chip capable of real-time monitoring of tissue function, biochemical release, and electrophysiological changes across various organs (69). This multi-sensor platform established a foundation for cutting-edge cardiotoxicity screening and system-level interaction research.

Multiparametric sensing platforms, like those suggested by Li et al. (67) and Liu et al. (57), provide continuous readouts of action potential dynamics and mechanical force, while also holding the promise of integrating biochemical probes aimed at ROS, calcium, or ATP. These hybrid systems have the potential to determine whether extended field potential duration is due to metabolic inhibition, ion channel dysfunction, or the accumulation of ROS.

Moreover, inverse modeling provides a method for discovering upstream biological conditions from downstream outcomes. Utilizing validated datasets, these models can assist in pinpointing the potential origin of a signal deviation, for example, determining if reduced contractility is indicative of cytoskeletal disruption or calcium dysregulation (68).

Finally, efforts must be made to develop disease-specific benchmark libraries and patient-derived models. Machine learning classifiers trained on large, annotated datasets from multimodal platforms may soon be able to decode signal signatures with diagnostic resolution. Flexible electronics have revolutionized the ability of HoC systems to obtain extensive physiological data. The future is in integrating this ability with biochemical sensing, spatial mapping, and/or computational modeling to interpret these signals in ways that are biologically and pharmacologically significant. With advancements in integration, these platforms are poised to transform into predictive and personalized diagnostic instruments for cardiovascular disease and therapeutic evaluation. Particularly tantalizing is the possibility of using stand-alone electro-mechanical sensing – without input from biochemical sensors – to diagnose dysfunction, with cellular organelle or signaling pathway precision, using deep learning ML algorithms.

5. Conclusion

HoC platforms are rapidly advancing as next-generation *in vitro* systems for modeling human cardiac physiology and evaluating drug-induced cardiotoxicity. Yet, their full potential depends on the seamless integration of real-time, multimodal sensing technologies that can accurately capture both mechanical contractility and electrophysiological activity. The incorporation of flexible and stretchable electronics into HoC systems signifies the turning point for conformal, biocompatible, and durable interfaces that overcome the limitations of conventional rigid electronics.

This review emphasizes significant

advancements in the design of materials and devices that facilitate high-quality tissue-electronic biointerfaces. Soft substrates and engineered design strategies, including serpentine, mesh, and 3D coil structures, have demonstrated impressive stretchability and stability under physiological strain. Simultaneously, developments in device engineering, such as transfer printing, have facilitated conformal contact with dynamic cardiac surfaces.

Soft electronic systems can be applied to monitor cardiac function, focusing on strain-based sensors for assessing contractility and soft electrode arrays for mapping extracellular potentials. Innovations such as hydrogel micropillar electrodes, nanomesh conductors, and nanowire-integrated FETs demonstrate increasing modifications of sensor design for 3D cardiac constructs and tissue motion. Intracellular recordings offer improved resolution; however, their invasive nature and complexity hinder their practical use in soft platforms. Extracellular modalities are the most practical and scalable options for achieving integrated, long-term cardiac readouts.

However, obstacles still exist. In particular, section 4 emphasized the growing importance of interpreting the complex signals recorded by these platforms. While flexible electronics have enabled real-time tracking of beat rate, force amplitude, and electrical propagation, the biological specificity of these readouts remains undeciphered and represents a major challenge. Identical signal patterns can arise from diverse physiological disturbances, ranging from calcium dysregulation and mitochondrial stress to fibrotic remodeling and ROS accumulation. Without complementary biochemical or molecular readouts, attributing sensor outputs to specific disease mechanisms remains limited.

Nevertheless, recent studies show promising directions. Multiparametric platforms that combine electrical, mechanical, and biochemical sensing along with computational modeling and spatially high-density electronics are beginning to reveal more nuanced insight into cardiac dysfunction. Additionally, machine learning approaches trained on multimodal datasets offer new pathways; and may possess significant potential; to decode complex signal patterns and identify drug-specific or disease-specific signatures. Supervised neural networks and genetic algorithms represent but a subset of Artificial Intelligence that has not yet been utilized to associate simultaneous patterns of electrical and mechanical readouts – without incorporating biochemical sensors - to uniquely specific cellular organelle dysfunctional processes. Research along this suggestion is strongly recommended.

Looking ahead, the development of fully integrated systems that co-engineer soft tissue scaffolds with high-density, multimodal sensors will be essential to support long-term monitoring in 3D, vascularized, and organoid-like environments while maintaining tissue viability and function. Incorporating patient-derived hiPSC models alongside standardized signal libraries will further enhance the translational relevance of HoC platforms. Ultimately, the convergence of flexible electronics, advanced tissue engineering, and computational Machine

Language tools may cause a paradigm shift of HoC systems from descriptive assays toward predictive diagnostic technologies, with the potential to revolutionize precision cardiology, safety pharmacology, and personalized medicine.

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