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REVIEW

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Microfabricated sensors for non-invasive, real-time monitoring of organoids

Yoojeong Kim[1†], Erick C. Chica-Carrillo[1†] and Hyunjoo J. Lee[1*]

Abstract

Organoids are three-dimensional cell clusters derived from stem cells and closely resemble the physiological characteristics of human tissues. As the next-generation biological model, organoids provide new opportunities for drug discovery, disease modeling, and personalized medicine. To fully harness the potential of organoids, real-time monitoring of biological states and functional evaluation of organoids are crucial. This review highlights recent advances in real-time, in situ biosensing technologies, including microelectrode arrays for electrophysiological recordings, chemical sensors for biochemical detection, and strain sensors for monitoring mechanical properties. While the development of miniature sensors for non-invasive, long-term, and real-time monitoring of organoids is in the early stage, these sensors are an essential part of organoid technology which would provide new insights into human developmental biology, pathophysiology, and drug discovery. After reviewing the seminal works on the microfabricated sensors for organoids, we also provide an outlook of the field including a discussion on the remaining challenges and future directions with a focus on integration of multiple sensors to facilitate organoid research and applications.

Keywords Biosensor, Microelectrode Array (MEA), Strain Sensors, Organoid

Introduction

Organoids, three-dimensional (3D) cell clusters derived from stem cells, have emerged as promising in vitro models that overcome conventional biological models such as 2D cell cultures and animal models [1, 2]. Conventionally, 2D in vitro and animal models have been widely used in biomedical research including drug discovery and disease modeling [3]. While 2D cell models are capable of being generated with high throughput and high reproducibility at a low cost, challenges in replicating the microenvironment often result in inaccurate representations of human physiology [4]. In contrast, animal models better reflect the tissue-specific microenvironments and functions of organs. However, significant differences in physiology and pathophysiology between species have prevented animal models from accurately predicting toxicity and efficacy of new drugs leading to the high failure rate of clinical trials in drug development [5, 6]. Organoids overcome these limitations of in vivo and in vitro models, as their generation from either pluripotent stem cells (PSCs) or adult stem cells enables precise recapitulation of the architecture and physiology of human organs [7–9].

Organoid technology has the potential to be applied in various biomedical research areas, such as disease modeling, personalized medicine, and drug testing [10–13]. In disease modeling, organoids are able to replicate specific pathological conditions more accurately than traditional models, providing more comprehensive insights into disease mechanisms, progression, and cellular responses [14–16]. Organoids enable researchers to explore complex disease pathways and potential therapeutic targets that are otherwise difficult to investigate using 2D cell cultures and animal models [13, 17]. In personalized medicine, patient-derived organoids provide a way to predict the efficacy and prognosis of individualized

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treatment [13, 18]. Lastly, the pharmaceutical industry also benefits from this new model as organoids provide improved prediction of human responses to drugs, which reduces reliance on animal models and improves the efficiency of clinical trials [19]. Accurate toxicology assessments and dose–response studies would accelerate drug development and ensure better safety profiles for potential therapeutic candidates.

To fully exploit the potential of organoids in various applications, precise and comprehensive methods for monitoring growth, analyzing biological states, and evaluating the functionalities of organoids are required (Fig. 1). The most widely used analysis platforms are currently optical imaging and gene expression analysis [20–23]. Optical imaging provides direct visualization of organoid morphology and structural maturation while gene expression analysis provides critical information on the molecular pathways active within organoids, helping to reveal functional differentiation and disease-specific signatures [24–30]. However, these assays are end-point assays where continuous and in situ monitoring of organoids is challenging. In addition, these assays

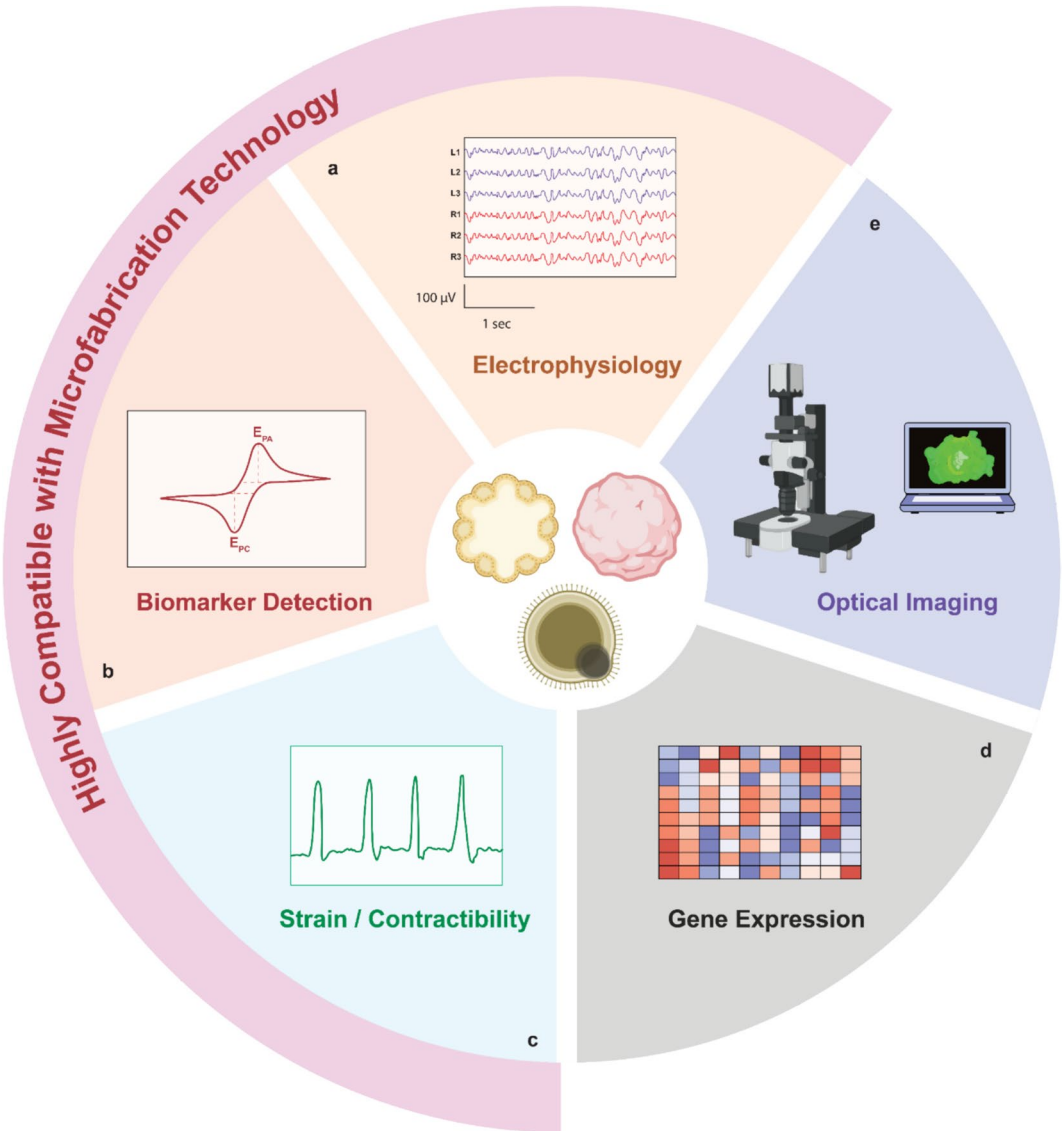

Fig. 1 Core techniques for organoid instrumentation. **a** Electrophysiology: captures electrical activity from electrogenic organoids. **b** Biosensing: detects biomarkers through various methods, with electrochemistry being the most compatible with miniaturization. **c** Strain: assesses mechanical properties of tissue, such as contractility and deformation. **d** Gene expression: evaluates transcriptional profiles. **e** Optical imaging: visualizes organoid structures and dynamics at high resolution. Icons created with https://www.BioRender.com

do not evaluate the functions of organoids such as the beat rate of cardiac organoids and electrophysiological firing of brain organoids, which could serve as an indicator for the efficacy of new drugs. To achieve long-term, continuous, and real-time monitoring of both biological and functional characteristics of organoids, it is essential to develop miniaturized sensors, such as chemical, physical, and electrical sensors that allow integration into cell culture platforms. Microfabricated miniature sensors for organoids are essential in creating non-invasive and stable systems capable of tracking dynamic organoid states over extended periods. These sensors offer a potential means to improve the uniformity of the organoid culture, facilitate accurate disease modeling, and provide abundant data for high-throughput drug screening.

In this review, we briefly discuss sensor technologies developed to monitor organoids, with a focus on microfabricated devices designed to record electrophysiological signals, detect specific biomarkers, and measure mechanical properties. Chemical sensing is crucial for monitoring metabolic activity and is often employed in drug testing and disease modeling to capture real-time biochemical changes [31, 32]. Electrophysiological recordings are also vital for evaluating the functional activities of electrogenic organoids, such as brain and heart organoids, which are closely linked to pathophysiology [10, 33–35]. Strain sensing helps evaluate the mechanical properties of organoids and monitor the responses of organoids to external stress [36–38]. After reviewing seminal works on microfabricated sensors for continuous evaluation of organoids, we briefly discuss current challenges and propose future directions for organoid sensors.

Microfabricated sensors for organoids

Microelectrode arrays for electrophysiology recording

Electrophysiological recording of organoids is crucial for assessing the functional maturity and activity of electrogenic organoids, reflecting real-time neural or cardiac responses. For brain organoids, these measurements provide insight into neuronal network development, synaptic connectivity, and spontaneous activity patterns. Similarly, for heart organoids, electrophysiology is vital for monitoring rhythmic contractions and the propagation of electrical signals, which are essential for evaluating cardiac functionality.

2D microelectrode arrays (MEAs), neural probes, and electrocorticography (ECoG) arrays are widely used neuro tools to measure electrophysiological signals from in vitro 2D culture cells and in vivo animal models [39–42]. MEAs, first introduced by researchers at Harvard University in 1972, have been widely utilized for extracellular signal recording. The microfabricated fine electrode patterns allowed for high spatial resolution and real-time electrophysiological signal measurements [43]. High-density MEAs have been developed and commercialized based on complementary metal-oxide semiconductor (CMOS) technology. Several organoid studies utilized 2D MEAs to measure and analyze electrophysiological signals from brain organoids (Fig. 2Ai–iii) [44–47]. In addition to the increase in density, MEAs have been improved in terms of microelectrode materials (*e.g.*, hydrogels) and shapes (*e.g.*, microneedle) to improve the contact between the microelectrodes and tissues, thus improving signal-to-noise ratio (SNR) (Fig. 2Aiv, v) [48, 49]. O. Phouphetlinthong et al. developed a cantilever structure integrated with a single channel per shank (similar to a microneedle) which spans vertically over 200 μm and demonstrated the recording of local field potentials from neurons deep inside the 3D organoids (Fig. 2Avi) [50]. However, the use of 2D MEAs for three-dimensional (3D) organoids is inherently limited because of the mismatch in shape. Organoids are free in shape in 3D through self-organization. Thus, without deformation of the organoids, 2D MEAs interfaced with 3D organoids tend to provide only limited electrophysiological information from a small contact area. To acquire high-density signals from 3D organoids on 2D MEAs, the organoids need to be deformed in shape to form a stable attachment to 2D MEAs, sacrificing the integrity of the organoids.

To address the limitations of 2D MEAs, several works adopted neural probes to measure electrophysiological signals from 3D organoids where shank-type MEAs were inserted into 3D organoids. D.A. Soscia et al. reported an array of out-of-plane MEAs fabricated on a flexible polyimide substrate, which could be actuated vertically, enabling 3D measurements of the inner regions of organoids (Fig. 2Bi) [51]. Similarly, H. Shin et al. reported 3D multifunctional multi-shank neural probes with a high-density microelectrode array, thin optical fibers, and microfluidic channels for precise modulation of neural networks within the organoids (Fig. 2Bii). This work demonstrated the measurement of synaptic latencies and transmission velocities within a compartmentalized 3D neural tissue, utilizing localized optical stimulation and drug delivery for detailed analysis of neural circuit dynamics [52]. While neural probes enable electrophysiological recording from the inner region of the organoids, the invasiveness nature of the recording may cause tissue damage and limit long-term continuous monitoring.

In response to these limitations, recent advancements focus on the development of flexible substrate-based MEAs, which gently wrap around the surface of the organoids, providing a non-invasive alternative for electrophysiological recordings while maintaining the structural integrity of the tissue over extended periods. C.

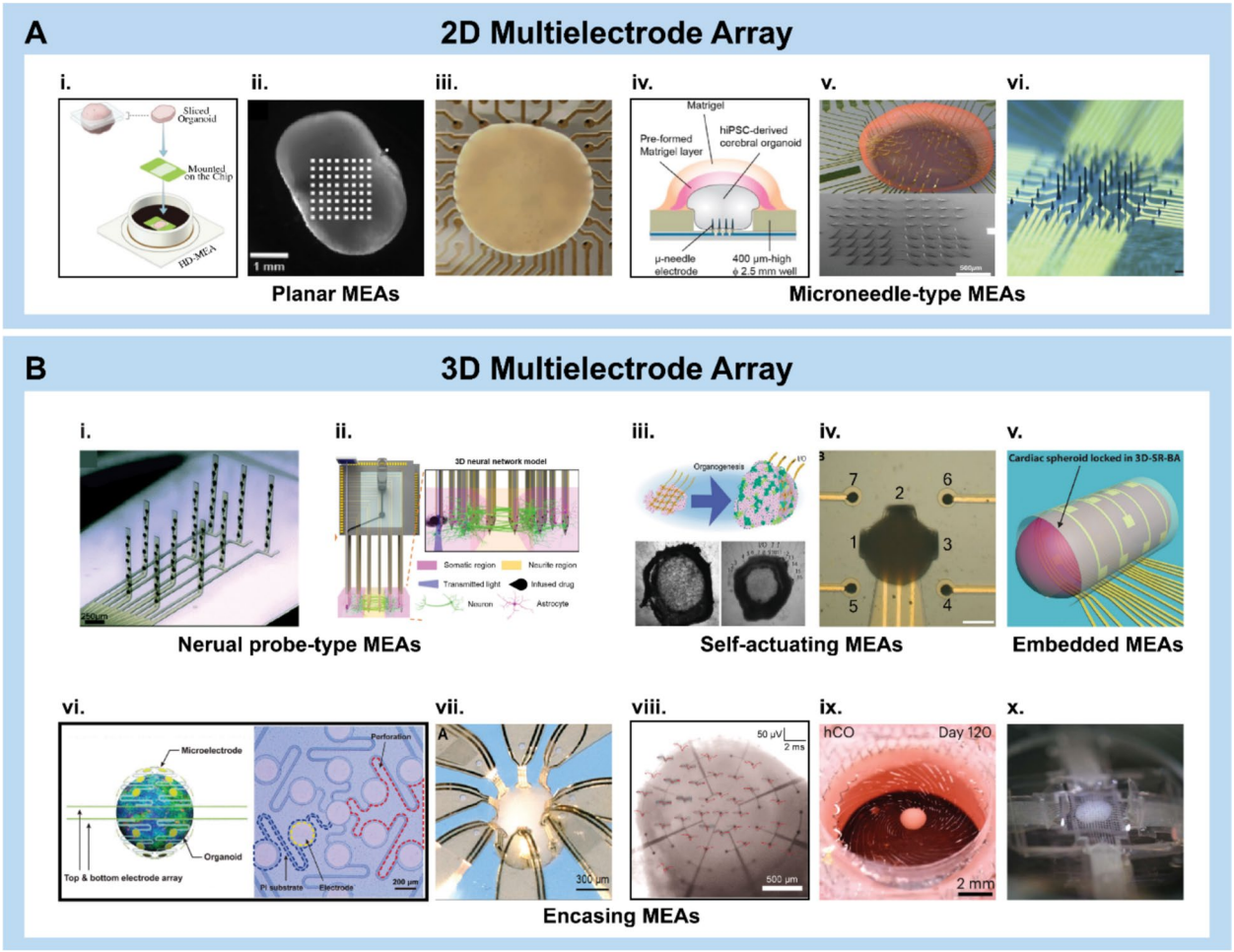

Fig. 2 Microfabricated sensors for electrophysiological recording. **A** 2D MEAs: i) schematic illustration of electrophysiological recording of sliced cerebral organoid on high density 2D MEA [44] © 2022 The Authors. All rights reserved, ii) Photograph of organoid plated on a 64-electrode plate [45] © 2021 Elsevier Inc. All rights reserved, iii) optical image of cerebral organoid plated on 64-channel MEA platform [46] © 2020 The Authors. All rights reserved, iv) schematic illustration of microneedle electrode array [48] © 2023 American Chemical Society, v) photograph of 3D liquid metal microneedles with different heights [49] © 2024 The Authors. All rights reserved, and vi) SEM image of cantilever MEA [50] © 2023 The Royal Society of Chemistry. All rights reserved. **B** 3D MEAs: i) Photograph of 3D MEA post-actuation [51] © 2022 The Royal Society of Chemistry. All rights reserved, ii) schematic illustration of multi-shank neural probe-based 3D MEAs [52] © 2021 The Authors. All rights reserved, iii) schematic illustration and optical image of embedded MEA [57] © 2019 American Chemical Society. All rights reserved, iv) schematic illustration of self-rollable MEA [59] © 2019 The American Association for the Advancement of Science. All rights reserved, v) optical image of self-foldable shell-type MEA [60] © 2022 The American Association for the Advancement of Science. All rights reserved, vi) schematic illustration and optical image of stretchable MEA for encasing of 3D organoids [39] © 2020 IEEE. All rights reserved, vii) optical image of 3D multifunctional device enclosing a spheroid [53] © 2021 The American Association for the Advancement of Science. All rights reserved, viii) optical image of mesh electrode array [54] © 2023 Elsevier B.V. All rights reserved, ix) photograph of kirigami stretching MEA for brain organoid recording [55] © 2024 The Author(s), under exclusive licence to Springer Nature America, Inc. All rights reserved, and x) photograph of liquid metal-polymer conductor-based mesh neuro-interface with a human hippocampal organoid [56] © 2024 The Authors. All rights reserved

Shim, et al. reported stretchable MEA for the first time (Fig. 2Bvi) [39]. By patterning the PI substrate with serpentine patterns, the MEAs were designed to be highly stretchable which conformally encapsulated free-form 3D neuronal tissue without causing damage. By designing a perforated electrode pocket, stretchable MEAs also allowed for continuous media exchange. Similarly, Y. Park et al. developed a pocket-type mesoscale bending framework suitable for 3D tissue which enveloped the surface of the organoids for effective measurements (Fig. 2Bvii) [53]. Also, M. McDonald et al. reported a mesh microelectrode array designed to suspend neural organoids in a hammock-like structure, allowing unimpeded growth while supporting long-term electrophysiology

(Fig. 2Bviii) [54]. Recently, X. Yang et al. introduced kirigami electronics, an ultrathin electrical recording platform that integrated seamlessly with neural organoids and assembloids in suspension, enabling long-term recording without disrupting the 3D self-organization (Fig. 2Bix) [55]. The KiriE system successfully monitored spontaneous neural activity in human cortical organoids, detected phenotypes linked to genetic disorders, and captured activities in corticostriatal assembloids. Liquid metal-polymer conductors (MPC)-base stretchable mesh electronics were reported by Y. Wu et al. (Fig. 2Bx) [56]. They developed a 128-channel flexible neural-interface that integrates with human hippocampal organoids (hHOs).

In a different approach, flexible mesh MEAs were completely embedded in the organoids from the initial culture stage, allowing the electrodes to be fully integrated within the organoid for long-term measurements (Fig. 2Biii) [57, 58]. Self-actuating flexible MEAs which could envelop organoids with reliable contacts have also been proposed. A. Kalmykov et al. developed a self-rolled biosensor array capable of encasing cardiac spheroids to investigate the three-dimensional propagation of signals (Fig. 2Biv) [59]. Similarly, Q. Huang et al. suggested a self-foldable 3D shell MEA for brain organoids, using differentially cross-linked SU-8 bilayers (Fig. 2Bv) [60]. Both approaches employ residual stress to facilitate actuation during the release process, actively capturing the organoids. These flexible 3D MEAs enable long-term electrophysiological recording by adapting dynamically to the complex 3D architecture of the organoids.

Biochemical sensors for organoids

Organoids allow for a more efficient and rapid evaluation of physiological responses, enabling better insights into several experimental conditions and outcomes. To fully maximize the use of organoids as effective biological models, it is essential to accurately capture and transduce changes in specific biomarkers pertaining to individual organoids into signals through biosensors. While electrophysiological signals offer valuable insights into a wide range of responses and diseases, most microelectrode platforms primarily focus on detecting these signals without considering their sensitivity to specific biomarkers [61]. Thus, recent advances in biomarker sensing have expanded beyond electrophysiology to include the detection of critical biomarkers (Fig. 3Ai–iii).

An example of such a biomarker in brain organoids is dopamine (DA), as it plays a crucial role in motor function and reward pathways. Dysregulation of DA is often linked to conditions such as Parkinson's disease, one of the most common neurodegenerative diseases characterized by impaired movement. Therefore, accurate measuring of DA secretion from organoid disease models in response to drug treatment is crucial, as this serves as a marker for the effectiveness of potential therapies [61]. An et al. developed a mesoporous gold (Au) nanodot-patterned 3D concave electrode (Fig. 3Ai) to assess the electrochemical response of dopamine to drug-based treatment on brain organoids [61]. In another study, Zanetti et al. developed a redox-cycling method combined with the modification of a self-assembled monolayer of 3-mercaptopropionic acid (Fig. 3Aii) to assess dopamine release differences between isogenic pairs in extended cultivation periods of up to 5 weeks [62]. These studies demonstrated that surface modification is an efficient strategy to quantify dopamine electrochemically. Another known cause of Parkinson's disease is the increase and subsequent aggregation of the α-synuclein (SNCA) gene that leads to neurotoxicity. Lee et al. developed peptide-imprinted poly(hydroxymethyl 3,4-ethylenedioxythiophene) nanotubes (Fig. 3Aiii) for the electrochemical detection of SNCA. In specific, molecularly imprinted polymers in Poly(EDOT-OH) with an SNCA peptide were developed to form nanotubular structures that enabled continuous SNCA monitoring [63].

Animal models are considered to be the gold standard in determining drug tolerability and effectiveness prior to clinical trials. However, significant shortcomings exist regarding the transferability of results, largely due to critical anatomical and physiological differences between animal models and humans. To address this gap, organoids also serve as useful tools due to their human-derived origin and ability to more accurately mimic pharmacokinetics. To this end, electrochemical sensors capable of capturing secreted biomarkers following drug treatments represent a useful tool to further advance drug discovery (Fig. 3Bi, ii). Shin et al. developed aptamer-based microfluidic electrochemical biosensors (Fig. 3Bi) that are specific to the creatine kinase (CK)-MB biomarker to measure small amounts of the marker released by cardiac organoids in response to drug treatments [64]. Lastly, field effect transistors have also been proposed as in situ detection platforms to evaluate organoid condition in drug screening. Tian et al. proposed a non-destructive and real-time field effect transistor (NDRS-FET) biosensor (Fig. 3Bii) to monitor responses of liver organoids to drug screening by quantifying levels of secreted albumin [65].

To use organoids for high-throughput drug screening, it is essential to culture a highly uniform set of organoids in a large quantity. To achieve such uniformity, culture conditions must be closely and precisely monitored. The microenvironment plays a critical role in organoid development, and microfluidic systems are frequently employed to maintain control over such conditions [66]

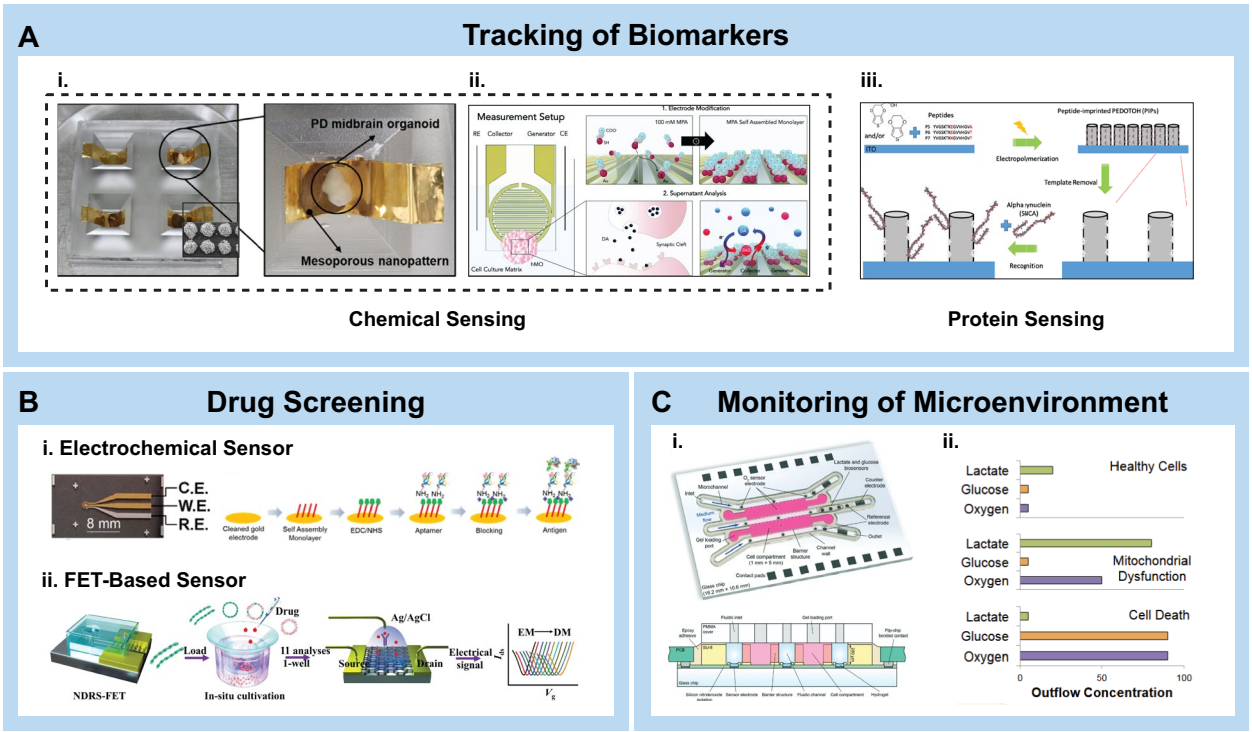

Fig. 3 Applications of miniaturized biosensors for organoids. **A** Instrumentation for biomarker sensing: i) optical image of a 3D concave electrode patterned with a mesoporous Au nanodot for dopamine detection [61]. © 2024 American Chemical Society. All rights reserved, ii) schematic illustration of modification process of two interdigitated electrodes for electrochemical dopamine detection [62] © 2021 Royal Society of Chemistry. All rights reserved, and iii) schematic illustration of preparation of peptide-imprinted poly(hydroxy 3,4-ethylenedioxythiopene)-coated electrodes and their sensing of SNCA [63]. © 2020 American Chemical Society All rights reserved. **B** Electrochemical analysis for drug screening: i) optical image of the device and schematic illustration of preparation method of a three-electrode system functionalized with aptamers to detect cell-secreted biomarkers upon drug treatment [64]. © 2016 American Chemical Society. All rights reserved, and ii) schematic illustration of a field-effect transistor (FET)-based platform used to monitor liver organoid response to candidate drug compounds [65] © 2024 Elsevier B.V. All rights reserved. **C** Integrated sensors for monitoring of microenvironment: i) schematic illustration of a microfluidic chip integrated with electrochemical biochemical sensor arrays for acquisition of relevant parameters in real-time [67] © Royal Society of Chemistry. All rights reserved. and ii) schematic of biomarker variation effects on cell states [68] © 2016 The Proceedings of the National Academy of Sciences. All rights reserved

(Fig. 3Ci, ii). As a result, real-time monitoring of key metabolic parameters is crucial to ensure optimal growth and functionality of the organoids. Dornhof et al. developed a microfluidic platform for matrix-based 3D cultures (Fig. 3Ci). Electrochemical and biosensor arrays for oxygen, lactate, and glucose were integrated into the microfluidic platform, and long-term sensor performance over more than a week on tumor organoids was demonstrated [67]. Similarly, Bavli et al. presented a microfluidic platform that integrated medical-grade electrochemical sensors inside the chip (Fig. 3Cii) to monitor glucose and lactate in a liver organoid [68]. Each of these studies highlights the capabilities of the integration of multiple sensors with a microfluidic chip to obtain relevant data in organoid condition monitoring. Zhang et al. demonstrated a more advanced platform [69]. An automated modular design platform which was integrated with multiple organoid models and multiple sensors was proposed. This platform enabled both monitoring of the microenvironment parameters, such as pH and temperature, and sensing of soluble biomarkers on liver and heart organoids using a microfluidic-controlling breadboard. This study proposed new uses of modular platforms such as in situ monitoring of various parameters in drug screening.

Physical sensors to monitor mechanical properties

Monitoring strain and contractility in organoids is essential for evaluating their mechanical properties and functionalities, which directly reflects tissue-level physiological responses. In particular, for cardiac organoids, measuring contractility provides insight into the ability of the heart to generate rhythmic contractions and propagate mechanical signals, which are key indicators of cardiac maturation, and disease states. Similarly, in muscle and other mechanically active tissues, strain monitoring enables the assessment of tissue stiffness, elasticity, and responses to external stimuli, which are critical for

understanding disease progression, such as fibrosis and muscular dystrophy. Strain and contractility measurements also enable non-invasive, real-time tracking of tissue development, offering a powerful tool for studying how mechanical forces drive cellular organization and function during organoid maturation.

While miniaturized devices have been widely developed to measure contractility in 2D cardiac and muscle cells, only a few studies have reported similar measurements in 3D tissues. S. Watanabe et al. proposed a quartz crystal resonator (QCR)-based force sensor probe capable of measuring stiffness across a wide range of biological and synthetic samples, successfully evaluating Young's modulus of organoids with high resolution and accuracy [70]. Similarly, Q. Lyu et al. reported an all-soft and ultrasensitive organoid force-sensing system, featuring an elastic force-sensing diaphragm based on nanocracked platinum film (Fig. 4i) [71]. This system enabled reliable, sensitive, and instantaneous probing of cardiac organoid contractility within a soft cell culture well, even allowing for wireless remote monitoring via smartphone. J. Yin et al. developed a contractility sensor specifically designed for 3D tissues, overcoming the limitations of traditional 2D systems [72]. Their device enabled real-time measurement of mechanical forces within cardiac organoids, offering critical insights into how contractions propagate through the tissue in three dimensions. Meanwhile, D. E. Fullenkamp et al. developed a flexible, three-dimensional electronic framework for real-time, spatiotemporal analysis of electrophysiological and mechanical signals in engineered heart tissues (EHTs), which could be fully integrated into a cell culturing platform without any additional stages (Fig. 4ii) [73]. It enabled dynamic, non-invasive, and long-term assessments under physiological conditions, supporting multisite measurements across the tissue. Their strain sensor was successfully used to track responses to pharmacological agents and capture electrophysiological characteristics of reentrant arrhythmias. These physical sensors are a set of valuable tools for advanced organoid research.

Outlook

In this review, we have discussed the emergence of organoids as an attractive and promising biological model to streamline biomedical research and therapeutic development. By mimicking key structural and functional aspects of human tissues, organoids provide a more physiologically relevant model to study disease mechanisms, drug responses and biomarker dynamics. The integration of miniaturized sensors into these systems has further expanded their utility, by enabling precise, real-time monitoring of biochemical and physiological processes within the organoid and its microenvironment. These sensors facilitate the detection of essential biomarkers, such as neurotransmitters, proteins, ions, and metabolites, which provide insights into cellular behavior under various controlled conditions.

However, despite such advancements, several other key challenges remain. First, the development of additional sensing methods for a wider range of organoids and their respective biomarkers is needed to overcome conventional sensing limits, better understand drug treatments, and more accurately determine the effect of the microenvironment on various components of organoid-media interactions, such as signaling molecules, expressed biomarkers, ion concentrations, and pH levels. Further refinement of the physical interface between the organoid and sensor is also needed to ensure consistent, high-quality recording of electrophysiological data, yet this aspect remains underexplored in current works. Lastly, there is a clear need for more contractility and strain sensors, particularly for cardiac organoids. These sensors are essential for

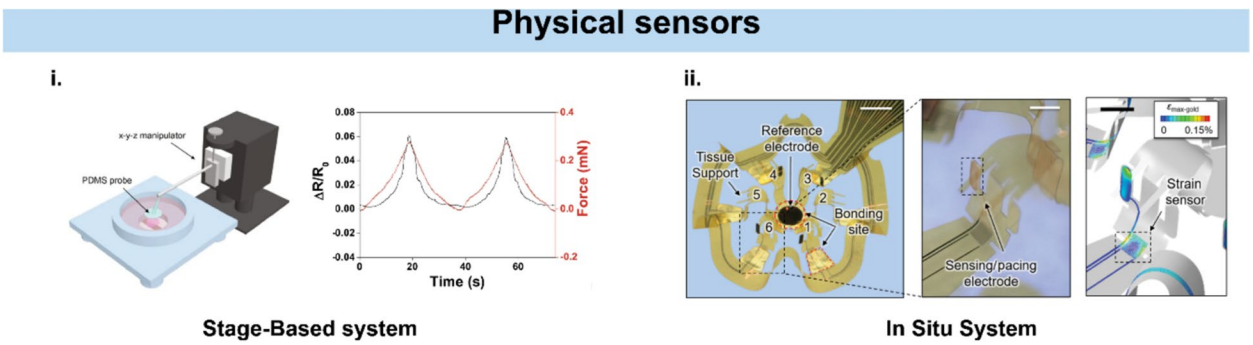

Fig. 4 Physical sensors for organoids. **i** Schematic illustration of diaphragm-based force sensor and measured changes in dynamic resistance [71] © 2022 The Authors. All rights reserved. **ii** Optical images and schematic illustration of flexible 3D multifunctional sensors [73] © 2024, The American Association for the Advancement of Science. All rights reserved

assessing the biomechanical properties of tissues, which also play a critical role in the accurate replication of the organ in vivo.

Looking forward, the integration of multiple sensors, possibly through platforms such as microfluidics, will be key for robust and comprehensive monitoring of the overall organoid condition. Such integrated systems have the potential to provide real-time feedback on organoid health, environmental conditions, and response to treatments in a much more detailed manner than what is currently possible. Moreover, the integration of these sensors with AI-driven data analysis could significantly enhance the precision and interpretation of measurements allowing for adaptive responses based on tissue dynamics. Furthermore, AI may assist in identifying subtle patterns and anomalies in the obtained data, further improving fidelity of organoid models. This direction promises to enhance reliability of the organoid models in research and translational medicine.

Abbreviations

AI	Artificial intelligence
CK	Creatine kinase
CMOS	Complementary metal-oxide semiconductor
DA	Dopamine
ECoG	Electrocorticography
EHT	Engineered heart tissue
hHO	Human hippocampal organoids
MEA	Microelectrode array
MPC	Metal-polymer conductors
NDRS-FET	Non-destructive and real-time field effect transistor
PSC	Pluripotent stem cell
QCR	Quartz crystal resonator
SNCA	α-Synuclein
SNR	Signal-to-noise ratio

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Author contributions
Yoojeong Kim and Erick C. Chica-Carrillo wrote the review and designed the figures (contributed equally). Hyunjoo J. Lee reviewed and edited the manuscript and figure design.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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