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The Role of Silicon Technology in Organ-On-Chip: Current Status and Future Perspective

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Organ-on-chip (OoC) systems are microfluidic in vitro platforms constructed to expand the current understanding of organ-level physiology and response. This technology holds significant potential to transform drug discovery, precision medicine, and disease modeling while reducing animal model use. Recent developments in OoC technology have shown great promise, demonstrated using relatively simple microfluidic designs. Currently, the consensus in the OoC-related literature is that the future of OoC technology lies in the development of robust platforms that offer higher throughput, improved customization, and higher levels of integration of sensing and actuation modalities. The implementation of silicon micro-nanofabrication technologies can foster such a transition, but the application in the field remains limited. In this review, an overview of silicon micro-nanofabrication technologies is provided that have been or can be applied in the realization of compact OoC systems, with focus on integrated actuation and sensing modalities. Emerging technologies are highlighted for the heterogeneous integration of silicon-based and polymer-based components in OoC systems for the realization of compact and multimodal OoC platforms. Finally, the most promising avenues are outlined for silicon technology within the framework of OoC and the future of biomedical research and personalized medicine.

1. Introduction

Understanding human physiology requires insight into how living cells function in the complex organ-tissue microenvironment. In humans, multicellular tissues are linked together by an extracellular matrix (ECM) and organized in a 3D structure, continuously stimulated by chemical and physical factors critical for the regulation of cell differentiation and proliferation, function, and survival.[1] Traditional 2D cell models and animal models, however, fail to replicate these dynamic human conditions adequately. The integration of tissue engineering with micro-nanofabrication technology, notably organ-on-chip (OoC) systems, offers a promising alternative by replicating these complex environments more accurately.[2] Moreover, 3D organoids developed from patient-derived induced pluripotent stem cells can be cultured in these engineered microfluidic formats, positioning OoC and microphysiological systems (MPS) as transformative tools in personalized medicine.[3]

The development of OoC technology has shown great promise, exemplified by the development of complex systems such as lung-on-chip, blood-brain barrier, and multi OoC.[4–6] Motivated by the objectives of creating physiologically relevant systems while reducing reliance on animal testing, the OoC technology is progressing toward widespread commercialization, strongly supported by international regulatory communities and the pharmaceutical industry.[7] However, to enter the clinical practice and to further minimize the use of animal models, the next generation of OoC systems will require robust, integrated platforms with higher throughput and improved customization. This need has gained wide acknowledgment within the scientific community, as evidenced by numerous publications.[8–15] In many respects, these needs correspond closely to the well-established areas of silicon-based electronics and microelectromechanical systems (MEMS), indicating a complementary potential to meet the advancing needs of OoC technology.

Manufactured using similar microfabrication techniques as those that are used to create integrated circuits, silicon-based MEMS technology offers a pathway to the integration of mechanical and electrical microscale components on the same substrate. Through repeated sequences of thin film deposition, photolithography, and dry- or wet etching steps, the desired configuration of features is manufactured in a layer-by-layer fashion to realize thin film metal structures, interlayer connections, reservoirs, valves, membranes, or cavities.[16] This inherent versatility of microfabrication techniques allows for the design and manufacturing of multimodal systems, which can perform multiple functions within a single device platform. Thanks to the wafer-scale fabrication approach, MEMS technology facilitates the

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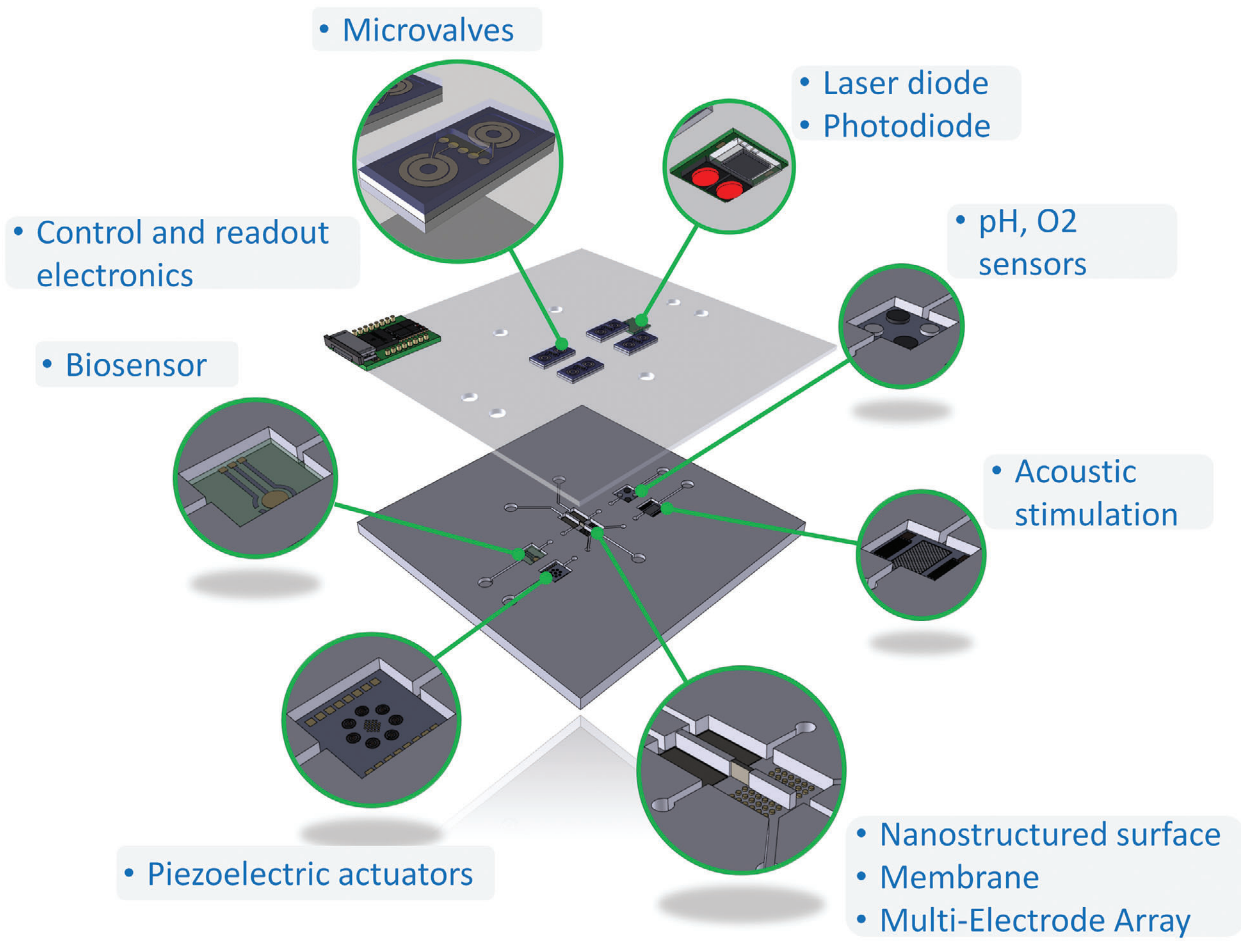

Figure 1. Silicon micro-nanofabrication technologies that have been or can be applied in the realization of compact OoC systems, with focus on integrated actuation, stimulation, and sensing modalities. The figure was originally created by the authors.

manufacturing of devices with high throughput and precision, and has the capability of manufacturing miniaturized structures with complex geometries and high aspect ratios.[16,17]

Through the incorporation of MEMS technology, OoC systems can benefit from having varied modalities in a compact form, offering new possibilities for advancement of the OoC field. Although examples of the use of silicon-based technologies in OoC can be found in literature, to date, the widespread adoption of silicon micro-nanofabrication and MEMS within the field of OoC research remains limited. To the best of our knowledge, no review comprehensively addresses the impact and potential of cutting-edge silicon-based devices or explores the future opportunities that MEMS integration could bring to OoC technologies.

This review aims to give an overview of the application of existing Si MEMS technologies in OoC, as well as to identify relevant Si MEMS technologies that have not yet been utilized in the field of OoC, but which hold potential for advancing the transition toward compact and multimodal OoC platforms. This review is not intended to provide detailed introductions to each technology; instead, it will direct readers to relevant, comprehensive reviews where necessary. First, to provide context for the development of silicon-based OoC systems, we briefly outline key milestones in the evolution of silicon technology, which drove advancements in microfabrication techniques that eventually found application in OoC devices. Next, we review the various *stimulation and actuation* methods used in OoC systems, highlight existing applications of silicon and MEMS, along with their potential for future innovations (**Figure 1**). Third, we then review *sensing* methodologies and devices, focusing on those particularly suitable for Si MEMS, including recent applications in OoC systems, and the outlook for improved sensing capabilities enabled by advanced MEMS. Fourth, we discuss established and emerging technologies for the *heterogeneous integration* of silicon MEMS and polymer materials commonly used in OoC, to achieve hybrid, highly functional devices. Finally, we will discuss some of the main barriers and limitations of silicon technology, and, lastly, we will discuss how the silicon-based MEMS technologies presented can pave the way for the development of compact, multifunctional OoC platforms for the future of biomedical research.

2. Brief Overview of the Evolution of Silicon Technology and its Application in OoC

The evolution of silicon technology has shaped the development of microfabrication techniques central to modern OoC systems. The foundation of silicon technology lies in the layer-by-layer

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deposition, patterning, and etching of thin films, combined with techniques for doping semiconductor layers and photolithography. These techniques were gradually developed from the 1950s, reaching a milestone in the mid-1960s with the advent of complementary metal-oxide-semiconductor (CMOS) technology, which employed arrays of MOS transistors to enable complex logic functions. The introduction of dynamic random-access memory (DRAM) in 1967 added another critical component, propelling the semiconductor industry forward. Together, CMOS and DRAM have driven significant advancements in silicon microfabrication, enabling precise microstructuring that underpins much of today's technology landscape.[18]

Silicon technology's compatibility with microfabrication techniques made it a natural platform for early microfluidics research in the 1970s. One of the first applications was the development of miniature gas chromatographs and micromachined inkjet nozzles, demonstrating the potential of silicon-based devices to handle microscale fluid flow.[19,20] Through the 1980s, researchers applied these methods to chemical and biological assays, ultimately leading to the introduction of the micro-total analysis system (μTAS) concept in 1990 by Manz and colleagues.[21] This silicon-based device was designed to integrate sample preparation, separation, and detection on a single chip, providing a compact, automated alternative to traditional macroscale laboratory analysis.

By the early 2000s, researchers began applying silicon-based microfabrication to create cell-culture environments, laying the groundwork for organ-on-chip (OoC) devices. Initial examples included for liver and kidney models, where microfabricated silicon structures supported fluidic transport and nutrient exchange for cell cultures.[22,23] These systems demonstrated the potential of silicon-based platforms to recreate physiological conditions and enable precise control of microenvironments to advance research in drug testing and disease modeling.

Advancements in microfabrication techniques have provided the tools necessary for the development of increasingly sophisticated methods for actuation, stimulation and sensing functionalities in OoC, which are explored in detail in Sections 3 and 4.

3. Actuation and Stimulation

This section explores various actuation methods tailored to emulate specific physiological conditions within microenvironments. Silicon-based platforms enable the creation of complex structures such as microfluidic channels, micropumps, and microvalves to mimic key physiological processes. Additionally, their compatibility with advanced manufacturing techniques enables the integration of active components including sensors, electrodes, and actuators, enhancing the range of functionalities of the OoC device and creating more realistic organ models by simulating physical and chemical conditions with greater accuracy. Optical stimulation harnesses light for biological and mechanical actuation, with recent developments integrating light delivery elements into microfabricated devices for applications like optogenetics. Acoustic stimulation, facilitated by piezoelectric and capacitive micromachined ultrasonic transducers, offers non-invasive and precise manipulation of biological samples. Electrical stimulation achieved through integrated electrodes can regulate cell behavior and simulate physiological environments, while mechanical actuation methods based on electrothermal, electrostatic, piezoelectric, and electromagnetic approaches can replicate dynamic mechanical forces experienced by organs in vivo. Moreover, silicon's thermal and chemical stability allows it to withstand chemical treatments, sterilization processes, and high temperatures, enabling sustained experiments that might degrade polymer-based platforms. The scalability and reproducibility of silicon-based microfabrication ensures consistent performance across devices, making it promising for widespread applications in research and industry. This section examines silicon-based actuation technologies and their applications, providing insights into their advantages and limitations for enhancing the functionality of OoC systems.

3.1. Optical Stimulation

Light can be used as a means of biological and mechanical actuation in OoC systems. Light can be used as part of the device operation, for example, to control the motion of small amounts of liquid in a microfluidic device to generate micro-droplets or promote the mixing and reaction of agents.[27] However, the possibility of delivering a stimulus to various types of biological models is perhaps where the greatest advantage of photo-stimulation and actuation lies. Light stimulation can be used to trigger cellular responses like migration, proliferation, and differentiation, among others.

Experiments requiring light stimulation have traditionally employed optical fibers coupled to external light sources, and it continues to be applied in recent works as a cost-effective method. Generally, incorporation of light sources in OoC has been used for sensing (see **Section 4.3**), for example to enable light-absorption measurements.[28] On the other hand, optical stimulation has also been implemented in OoC. For example, Dhall and co-workers have used photo biomodulation on a dental implant-on-chip with light generated from an external light-emitting diode (LED) source.[29] In the field of optogenetics, targeted light stimulation is widely used for modulation of neurons. Recent advances in this field have enabled the integration of light delivery elements into microfabricated devices, such as neural probes.[30–32] There are different approaches to integrate light delivery elements, including monolithic integration of LEDs (i.e., the LED is manufactured in the same fabrication process as the rest of the device), direct illumination using off-the-shelf micro-LEDs, and waveguides coupled to remote laser diodes or LEDs.

Waveguides can direct the light from on-chip or external sources to specific locations in the culture chamber or microfluidic channels. Integration of waveguides with MEMS technology dates back to the 1990′s and has been used in applications ranging from telecommunications, micro-spectrometers, and display arrays.[33] For microfabricated medical devices such as neural probes, the use of waveguides for light stimulation offers seamless integration into the microfabrication process as well as high spatial precision, design flexibility, size reduction, and the ability to enable several optical stimulation sites from a single light source. Monolithically integrated MEMS-based neural probes incorporating waveguides able to produce spiking activity in ontogenetically modified neurons have been demonstrated by various groups in the last decade, using silicon oxynitride and SU8 as core waveguide materials (**Figure** 2A-i).[34–36]

Monolithic integration of LEDs is possible but costly because they require non-silicon semiconductors to be incorporated into a silicon-based fabrication process. This can be achieved either by using non-silicon substrates (e.g., sapphire) or by growing epitaxial layers of such non-silicon materials on top of the silicon substrate. For example, Wu et al. fabricated very small LEDs (10 µm x 15 µm) monolithically with a probe using epitaxial InGaN on a Si substrate, providing high-resolution light delivery but low light output power due to the extra small LED footprint.[37] McAlinden et al. fabricated LEDs on a sapphire wafer with a GaN epitaxial layer, allowing for targeting single neurons but raising concerns regarding heating due to the sapphire wafer.[38] Other studies have reported on high-density µLED arrays, thin-film LEDs fabricated on GaN-on-sapphire wafers, and LEDs fabricated on GaN-on-Si wafers.[39–41] However, precise illumination of a small area is difficult due to the incoherent radiation of micro-LEDs. This issue can be addressed by fitting arrays of microlenses on the LED to redirect the emitted light. Microlenses made of glass or PDMS can be manufactured using photolithography and dry/wet etching, two-photon polymerization, self-assembly, or molding.[42]

Commercial LEDs can be beneficial for higher light output power requirements or to get around the low power limitations of tiny LEDs or light sources and waveguides. They can be bonded into probes (Figure 2A-ii), and can be used in conjunction with waveguides to control and deliver light to specific locations (Figure 2A-iii).[43–46]

3.2. Acoustic Stimulation

Acoustic stimulation can be used to interact with biological samples, cells, and tissues in OoC. The use of acoustic stimulation techniques offers non-invasive and precise alternatives to manipulate cellular microenvironments, mimic physiological mechanical cues, promote cell differentiation, among other applications. Sound or ultrasonic waves in miniaturized OoC systems can be produced using piezoelectric and capacitive micromachined ultrasonic transducers (PMUT and CMUT, respectively) by means of a vibrating membrane in the devices.

PMUTs comprise a piezoelectric membrane that deforms when subjected to an applied voltage, which can produce acoustic waves when operated at the right frequency range. An electric field applied to the piezoelectric material induces a strain in the direction normal to the piezoelectric film surface. If the strain is produced by AC signals in the correct frequency range, the piezoelectric membrane will vibrate, producing sound waves. CMUTs operate based on changes in capacitance between closely spaced conducting plates. Applied voltage between the conducting plates can modulate the gap between them, making them able to generate acoustic waves.[47]

Low-intensity ultrasound is an emerging modality for neuromodulation, i.e., activation or suppression of neural activity.[48,49] In OoC applications, the technique has been used to deliver stimuli to cells cultured on an ultrasound transducer surface to study the calcium signaling resulting from the stimuli. The cells were placed directly on the surface of a parylene-coated ultrasound transducer, and the calcium signaling response to a range of vibrational parameters was observed by confocal microscopy.[50] Lee et al. have used an array of 16 PMUTs to deliver targeted stimulation with high spatial resolution to neuron-astrocyte co-cultured samples (Figure 2B-i).[51] The PMUTs consisted of a silicon membrane and a lead-zirconate-titanate (PZT) layer on the membrane as a piezoelectric actuator.

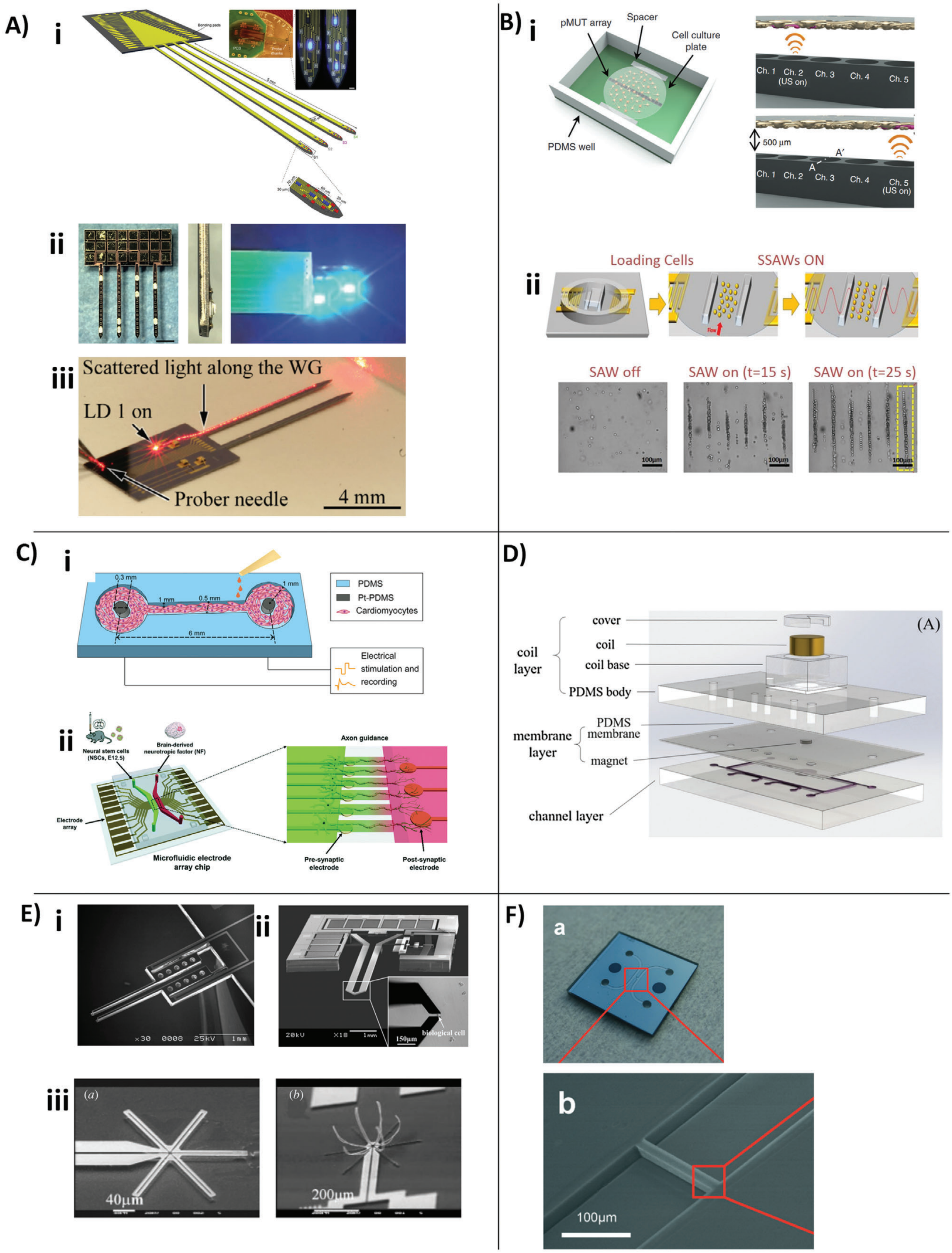
In addition to neuromodulation, micromanipulation of cells in their native environment can also be achieved with acoustic stimulation. Cohen et al. have used acoustic waves to organize neurons into clusters, driving the neurons to form connections and networks, thus bypassing the need for pre-patterned physical surfaces or chemical inputs (Figure 2B-ii).[52] While this work was carried out using acoustic waves generated with commercially available, large-scale PZT transducers, the authors envision that micron-scale cell patterning resolutions can be achieved using microfabricated arrays.

3.3. Electrical Stimulation

Integration of electrodes in OoC systems is one of the most common adaptations to enable interaction with culture cells and tissues, either by monitoring their environment and behavior, or to deliver stimuli to produce a response. For example, electrical stimulation can be effective in regulating stem cells differentiation into neural, cardiac, vascular, osteoprogenitors, and other lineages, or to induce long-lasting alterations in synaptic connections between neurons.[53,54]

Polymer-based electrode pairs have been introduced in microfluidic platforms to provide alternating electric field therapy to cancer cells, to study the disruption of mitosis leading to tumor formation.[55] The electrodes consisted of a conductive PDMS-silver mixture. Similar polymer-based electrodes have been used for heart-on-chip applications by Zhang et al. (Figure 2C-i), where electrical stimulation was applied to activate cardiomyocytes. The electrodes were a polymer-based stack to form platinum electrodes on PDMS pillars.[56] Cardiomyocytes showed improved maturation and enhanced synchronous contractions as a result of electrical stimulation. The authors highlight that the ability to integrate multiple electrodes would enable cell-guiding capabilities in the heart-on-chip system. Indeed, although polymer-based electrodes may facilitate integration into microfluidic platforms for the OoC system and can also provide semi-transparent electrodes to enable optical inspection of the culture chambers, the preparation process can be laborious and device reproducibility can vary. Wafer-level microfabrication can address those limitations. Quirós-Solano et al. developed transparent, conductive polymer electrodes based on poly (3,4-ethylenedioxythiphene) polystyrene sulfonate (PEDOT:PSS) on stretchable PDMS membranes. Fabrication was carried out at wafer-level using conventional silicon processing techniques and subsequently releasing the membranes, which can then be incorporated into an OoC platform. Due to the silicon-based, wafer-level fabrication, it is also possible to scale up the design to produce stretchable microelectrode arrays (MEA).[57]

MEAs allow for electrical stimulation at cellular resolution. OoC systems incorporating MEAs have been successfully applied in neural models to mimic electrical signals occurring in the nervous system, for example, to mimic electrical cues to study


A)
i
ii
iii
Scattered light along the WG
LD 1 on
Prober needle
4 mm
B)
i
pMUT array
Spacer
Cell culture plate
PDMS well
Ch. 1
Ch. 2 (US on)
Ch. 3
Ch. 4
Ch. 5
500 µm
A
A′
Ch. 1
Ch. 2
Ch. 3
Ch. 4
Ch. 5 (US on)
ii
Loading Cells
SSAWs ON
SAW off
SAW on (t=15 s)
SAW on (t=25 s)
100µm
C)
i
0.3 mm
1 mm
0.5 mm
1 mm
6 mm
PDMS
Pt-PDMS
Cardiomyocytes
Electrical stimulation and recording
ii
Neural stem cells (NSCs, E12.5)
Brain-derived neurotropic factor (NF)
Axon guidance
Electrode array
Microfluidic electrode array chip
Pre-synaptic electrode
Post-synaptic electrode
D)
(A)
cover
coil
coil base
PDMS body
coil layer
PDMS membrane
magnet
membrane layer
channel layer
E)
i
ii
iii
×30 0008 25kV 1mm
20kV X18 1mm
150µm
biological cell
(a)
(b)
40µm
200µm
F)
a
b
100µm

synapse formation, development of neural circuits, and development of neuroprosthetics. Woon et al. integrated a MEA into a microfluidic platform to drive axonal growth (Figure 2C-ii).[58] Using electrical stimulation, neural stem cells were successfully differentiated into neural cells. The MEA consisted of Au/Cr electrodes fabricated on soda-lime wafers, which were subsequently integrated into a PDMS microfluidic platform. Silicon-based processing can enable highly integrated systems to control sensing and actuating tasks in OoC, such as complementary metal-oxide semiconductor (CMOS) technology, which is commonly used in integrated circuits and allows for the implementation of complex electronic systems with low power consumption and high reliability. Dragas et al. developed a high-density multimodal CMOS-based MEA system consisting of 59760 platinum electrodes for neural recordings of action potentials, local field potentials, impedance measurements, neurotransmitter detection, and electrical stimulation for neuron-on-chip applications.[59] The array covered an area just over 10 mm^2 and was divided into independently addressable sets of electrodes controlled by a switching matrix. Although a disadvantage of CMOS technologies is that silicon is an opaque substrate which hinders the ability to carry out optical inspection of the samples during experiments, solutions to produce transparent electrodes with silicon-compatible materials such as graphene can be explored. Following this idea, Shaik et al. developed a multimodal thin film transistor (TFT) array with transparent indium-tin-oxide (ITO) electrodes for sensing and stimulation of neuronal cell ensembles.[60] The array is controlled by a switch matrix, with the electrodes connected to the field effect transistor (FET) source terminal. For stimulation tasks, the gate electrode enables the transistor, and the drain line can provide the electrical stimulation.

3.4. Mechanical Actuation

The ability to mimic the dynamic mechanical forces experienced by organs in-vivo is crucial for accurately recapitulating physiological processes. Mechanical actuation methods enable the emulation of essential mechanical cues. The most widely used mechanical cues to regulate cell behavior in OoC systems are compression, stretching, and shear stress. A number of recent commercial OoC systems have incorporated forms of mechanical stimulation, as described in detail in a review by Thompson and co-workers.[61] For example, the introduction of shear stress and tensile strain actuation can simulate cardiac contractions and the stretching of blood vessels as a result of pulsatile blood flow in cardiovascular OoC models; cyclic tensile strain and stress are used to simulate the effect of air flow in the alveolar epithelium in respiratory OoC models; mechanical inputs can mimic the compressive and tensile strains in the intestinal epithelium during the waves of contractions caused by digestion in gut-on-chip models; and musculoskeletal models may require a range of biomechanical stimuli to replicate the effect of physical activity on articular cartilage, muscle cells and tendon OoC models.

Various mechanisms have been developed to induce these mechanical forces, each offering distinct advantages and limitations. Biomechanical inputs to alter cell culture behavior can be passive (e.g., substrate stiffness, geometric confinement, microstructured surfaces) or active (e.g., regulation of fluid shear stress, flow control, pressure, tensile and compressive strain).[62] This section explores some of the main mechanical actuation devices that can be employed in OoC systems. In general, devices for mechanical actuation are based on one of the following methods: electrothermal, electrostatic, piezoelectric, and electromagnetic. A comprehensive review by Chircov and Grumezescu provides a detailed review of technologies and the most representative MEMS biomedical systems with potential for OoC applications.[63]

Briefly, electrostatic actuation employs charged electrodes to generate electrostatic forces that enable mechanical motions such as bending or deflection. Common configurations include parallel-plate actuators and comb drives, offering simplicity of design and scalability. Piezoelectric devices have already been introduced as acoustic actuators. The deformation induced by applied electric fields can also enable controlled compression, stretching, or vibrations to mimic physiological motions in OoC systems. Electromagnetic technologies use electromagnetic fields to induce mechanical motion or fluid flow, enabling precise control for drug delivery in personalized medicine applications. Devices like micropumps and microvalves, which can provide controlled fluid displacement and transport, can be based on electrostatic, piezoelectric, and electromagnetic methods. Lastly, electrothermal actuators offer versatility by generating mechanical motions such as bending, stretching and twisting, with the advantage of low-voltage operation.[64,65] Microgrippers utilizing electrothermal actuation have potential for cell sorting and manipulation in OoC.

3.4.1. Micropumps and Microvalves

Micropumps provide the capability to facilitate the circulation of culture media, nutrients, and signaling molecules within OoC

Figure 2. A) i) 3D schematic and optical micrograph of a brain probe incorporating monolithic μLEDs: Reproduced with permission.[35] Copyright 2013, IOP Publishing Ltd. ii) Probe assembly with off-the-shelf micro-LEDs bonded on the probe shafts: Reproduced with permission.[46] Copyright 2022, Nature Research. iii) Two-shank optical electrode with laser diodes on the head and a waveguide integrated along the shanks: Reproduced with permission.[43] Copyright 2017, IOP Publishing Ltd. B) i) Schematic of a pMUT array for localized ultrasound neural stimulation: Reproduced with permission.[51] Copyright 2019, Nature Research. ii) Schematic of a standing surface acoustic wave (SAW) system used for cell arrangement. The micrographs show the formation of lines of cells when the SSAW is on: Reproduced with permission.[52] Copyright 2020, Nature Research. C) i) Schematic of a 3D pillar electrode for cardiac tissue: Reproduced with permission.[56] Copyright 2018, Elsevier. ii) Schematic of a microfluidic chip electrode array for axonal guidance: Reproduced with permission.[58] Copyright 2022, The Royal Society of Chemistry. D) Schematics of valveless electromagnetic micropump: Reproduced with permission.[69] Copyright 2020, Elsevier. E) i) SEM image of an SU-8 hot-and-cold-arm micro-gripper structure for cell manipulation: Reproduced with permission.[78] Copyright 2007, Elsevier. ii) SEM image of a Chevron type micro-gripper: Reproduced with permission.[80] Copyright 2008, IOP Publishing Ltd. iii) SEM images of a micro-cage structure in open (a) and closed position (b): Reproduced with permission.[81] Copyright 2005, IOP Publishing Ltd. F) Optical and SEM images of a microfabricated chip with a lateral porous membrane between two compartments: Reproduced with permission.[88] Copyright 2015, The Royal Society of Chemistry.

systems. Micropumps can generate controlled flow rates, pulsatile flow patterns, and adjustable flow directions within microfluidic channels, allowing for the delivery of nutrients, drugs, and biomolecules to specific regions of the OoC platform. The design and operation of MEMS-based micropumps and microvalves can based on several actuation methods, covered in the following reviews.[66,67]

In recent years, polymer-based micropumps and microvalves have gathered attention as an alternative to silicon-based devices due to their biocompatibility, low cost, and easy processing and prototyping.[63] Polymer-based micropumps using a wide variety of actuation principles have recently developed with an aim at OoC. Some exemplar developments include portably packaged electromagnetic PDMS membranes for liver and breast cancer cultures (Figure 2D), an electromagnetic bi-directional flow pump with straightforward prototyping for drug delivery and DNA hybridization, and a thermoplastic-based pneumatic microvalve and pump system which can be easily micromachined.[68–70] These are only a few examples among a large number of developments available in the literature, which showcases the maturity and variety of designs and manufacturing methods now available for polymer-based devices.

Microvalves are used to regulate the passage of fluids, samples, and reagents within microfluidic systems, replicating the intricate flow control observed in living organisms. By selectively opening and closing fluidic channels, microvalves enable the simulation of physiological conditions and the creation of dynamic microenvironments. Precise control over fluid flow can facilitate controlled cell culture perfusion, drug delivery, and chemical stimulation to study organ functionality. Microvalves can be designed to have rapid response times, low power consumption, and compatibility with microfabrication techniques. Actuation mechanisms of microvalves include electrostatic, piezoelectric, electromagnetic, pneumatic, among others, as reviewed in depth in.[66,71]

Microvalves in OoC applications encompass a diverse range of innovations for specific demands. For instance, Sadeghi et al. have introduced electrostatic microhydraulic systems featuring microvalves and pistons with the capacity to exert significant levels of force and deflection, thus enhancing both sensing and actuation precision.[72] Patrascu et al. have incorporated biocompatible materials to produce static and dynamic mode microvalves for fluidic dynamics regulation in OoC systems.[73] Low leakage behavior was demonstrated by leveraging the tight sealing properties of parylene-C-coated diaphragms on both silicon and glass substrates.[74,75]

Advances in polymer-based micropumps and microvalves underscore the maturation of polymer technology; their seamless integration into intricate OoC systems marked by elevated complexity remains a challenge due to the devices complex structure.[71] Silicon technology still offers the advantage of providing a pathway for scalable production, thereby laying the groundwork for the potential commercialization of these advanced microfluidic devices. Indeed, recent efforts by Jin and co-workers show a refreshed interest on silicon-based systems by integrating a phase-change micropump based on CMOS-MEMS technology incorporating an on-chip control system and sensors.[76]

3.4.2. Microgrippers

Microgrippers serve as valuable tools for sample manipulation, sorting, redirection, and modification of the sample environment, particularly in pick-and-place tasks, enabling the manipulation and handling of biological samples such as cells or tissue constructs. The most established actuation mechanisms for microgrippers are electrothermal, electrostatic, shape memory alloys, and electromagnetic designs.[64]

Electrothermal actuators employed in the design of microgrippers can be classified into three main types: hot-and-cold arm, Chevron, and biomorph actuators. Hot-and-cold-arm type actuators consist of two or more arms with asymmetric thermal expansion, allowing for controlled bending (Figure 2E-i).[77,78] Chevron-type actuators, characterized by their V-shape structure, generate linear motion based on the total amount of thermal expansion in the V structure. Two opposite Chevron actuators can be combined to form a two-finger gripper. Chevron actuators have been utilized in the development of single-cell and blood vessel grippers, as well as for cell pick-and-place tasks (Figure 2E-ii).[79,80] Biomorph-type actuators comprise multiple layers of different materials with distinct thermal expansion coefficients, enabling out-of-plane deflection. This type of actuator finds utility in sample manipulation, mechanical stimulation, and modification of the surrounding environment. A notable example is a microcage structure fabricated on a silicon wafer and whose operation is based on the difference in thermal expansion coefficients between diamond-like carbon and nickel films to produce off-plane movement. The fabrication process is fully compatible with silicon technology. The microcage has been employed for cell and particle sorting applications (Figure 2E-iii).[81]

3.5. Geometrical Actuation

3.5.1. Cantilevers

Resembling the principle of operation of an atomic force microscope (AFM), cantilevers have found applications in measurements of mechanical properties and motion of cells and tissues. To date, cantilevers in OoC systems have mostly been used as motion-sensing devices. For instance, submillimeter size cantilevers have been used to asses diastolic and systolic stresses in heart-on-chip platforms.[25] The cantilevers in this work were fabricated on PDMS by laser cutting. However, silicon-based microfabrication approaches closer to the manufacture of AFM cantilevers can improve manufacture precision, miniaturization, and scalability, as well as the potential to monolithic integration with other sensors and actuators on the same chip. Oleaga et al. have integrated cantilever chips with customized multi-electrode arrays in a multi-OoC system incorporating co-cultures of hepatic and cardiac cells for toxicological investigations of hepatic metabolism and its impact on cardiac function.[82] Cantilevers fabricated on silicon-on-insulator (SOI) wafers were used to perform contractile force measurements of cardiac tissue via laser-based detection methods. The addition of actuation elements to such MEMS-based devices can enable mechanical actuation on cultures. Coln et al. demonstrated a piezoelectric cantilever to provide stimulation to mechanosensitive cells by applying electrical pulses to the piezoelectric film of the cantilever, inducing deflection.[83]

3.5.2. Membranes

OoC systems can incorporate membranes to apply controlled mechanical deformations to cells and molecules, or to control the culture environment by serving as barriers between compartments or to regulation of microfiltration and extraction. In most LoC systems, membranes are conventionally made of thin polymer films such as polycarbonate (PC) and PDMS. Membranes can be patterned such that liquid can pass through, or they can be non-porous that only allow gas diffusion.[84] Membranes are often used in gut-on-chip applications to allow filtration of nutrients from a separate compartment; and for ventilation control in lung-on-chip, and other models like blood-brain barrier, cardiac muscle fibres and liber sinusoids.[85]

The use of materials compatible with silicon processing can be advantageous to allow higher degrees of customisation OoC by enabling the monolithic incorporation of membranes. Silicon- and silicon dioxide-based membranes are used in OoC for compartmentalization and filtration.[86] In an early study by Pagonis and Dimitrios, free-standing membranes were formed by electrochemical anodization of patterned porous silicon.[87] This process was compatible with silicon processing techniques, allowing for batch fabrication. More recently, Leïchlé and Bourrier used silicon-on-insulator substrates to produce porous silicon membranes monolithically into planar microchannels by guiding the micropore formation by means of patterned electrodes on the silicon surface, achieving 10 µm thick membranes with 25 nm diameter pores (Figure 2F-i).[88]

By correct tuning of the silicon dioxide deposition parameters, mechanically robust and very thin (100-300 nm) membranes can be produced. These membranes are compatible with optical microscopy due to their transparency, and customized perforated patterns can enable diffusive transport.[86]

3.5.3. Micro- and Nanostructured Surfaces

The topography of surfaces can affect cell adhesion, proliferation, and differentiation in OoC applications. Control of nanotopographies, including nanopillars, nanowires, and nanodots, can be used to enhance cell adhesion and proliferation. In contrast, surfaces with nanopits and nanogrooves contribute to reduced cell adhesion while promoting cell alignment. Such nanostructured surfaces also be used to select, capture or separate specific cells or molecules. The influence of nanoscale features on cellular response and organization can be controlled by the nanoscale roughness of surfaces affecting the adsorption and interaction of proteins with cells. Moreover, the spatial organization of surface asperities has been identified as a driver for cell differentiation.[89] Biocompatible metals such as titanium, magnesium, steel, and alloys crucial for implants, can be nanostructured by techniques compatible with silicon fabrication using a variety of methods like electrochemical treatment, plasma etch and chemical etch. Carbon-based materials, including nanotubes and graphene, also relevant to tissue engineering applications, are microfabrication compatible. High-resolution patterning on these surfaces demonstrates precise control over biomolecule and cell adsorption. A detailed review of materials an processes for surface modification at the nanoscale and relevant applications in OoC devices is available.[90]

In a recent report, Pribyl and co-workers demonstrated the use of high aspect ratio needle arrays to investigate the bonding and proliferation of fibroblasts.[91] Notably, the nanostructured surface, essentially “black silicon”, a grass-like surface topography, is produced through reactive ion etching of silicon. The resulting nanostructured surface served as a master which could be subsequently replicated by nanoimprint lithography.

4. Sensing

The OoC systems are developed to recreate functional elements of the human organ precisely with the purpose of studying their reaction to change. Measurement of their state, as well as their response to various stimuli, at the system, organ and cell level is therefore an important task. Depending on the specific OoC application, different read-outs or sensing modes are needed to extract qualitative and quantitative information at timescales which may range from sub-second to days. Today, OoC technology is mostly dependent on manual off-chip analytical techniques which are known to be time-consuming, often require large sample volumes, and do not necessarily provide minute information about the OoC.[92] Therefore, there is an increasing interest in the integration of robust sensing modalities that can facilitate continuous monitoring of OoC systems and generate real-time analytical data over time. Reversible sensing setups would also be essential for long-term studies and repeated measurements, as they allow sensors to be reused or reset. The developed sensors must also reliably operate in a biological environment over extended periods without interfering with biological processes.

However, integrating sensing technologies for automated OoC sensing has yet to be accomplished for the most relevant physiochemical cues. One possible reason for the limited progress can be the need for highly flexible device fabrication processes to miniaturize the robust sensing elements to fit and integrate into the small areas of the OoC, which is challenging to achieve with the prevailing polymer-based fabrication processes.

In this section, we will present examples of silicon technology-based sensing methods that are currently applied in OoC. We also identify sensing modes which have the potential to be miniaturized and integrated using MEMS fabrication technology. The reader may also benefit from other recently published reviews that present the in-depth current state-of-the-art regarding various sensor technologies for OoC applications.[93–96]

4.1. Electrical Sensors

Perhaps the most established OoC sensing modality based on silicon fabrication technology is the integration of electrical measurements. Involving fabrication methodologies of relatively low complexity, microelectrodes are patterned on silicon or glass wafers using a combination of thin film metal deposition (such as

Pt, Au, or Ag), photolithography, etching, and surface passivation techniques. Based on this fabrication approach, various electrode patterns can be realized to facilitate different working principles and measurement capabilities of the developed sensors.

Direct measurement of cellular electrical characteristics such as transepithelial/endothelial electrical resistance (TEER) is widely applied and also implemented for high-throughput OoC applications.[97,98] By placing two electrodes on both sides of a cellular monolayer growing on a semipermeable membrane, current or voltage is dispatched to estimate the monolayer's integrity as a sum of paracellular and transcellular resistance. The measurement indicates the tightness of the cell junctions and, consequently, the integrity of the cellular barrier to the OoC, permitting studies such as the blood–retinal barrier and liver toxicity.[99,100]

The MEAs consisting of grid of multiple small-scale electrodes may also be applied for sensing (see Section 3.3 for actuation). The surface containing MEAs is typically integrated as the base of the OoC system and seeded with cells, thus providing both external or internal sensing capabilities.[101] MEAs provide a noninvasive means of recording electrical signals and are typically applied to monitor the electrophysiological activities of neurons or cardiomyocyte action potentials. In a study by Liu et al., heart ischemia on a chip was modeled by monitoring the electrophysiological action potentials upon low oxygen exposure by extracellular or intracellular bioelectronics.[102] The device consisted of 16 probes, with 30 µm-diameter Pt-black-coated Au electrodes fabricated for external measurement to the cells (**Figure 3**A-i). For internal measurement, high-aspect-ratio Pt nanoelectrode pillars (150–200 nm diameter, 1.5–2.0 µm height) were fabricated in groups of 5 per Au pad by milling holes through the Au insulation layer using focused ion beam (FIB) followed by Pt deposition. A simple PDMS channel was bonded on the bioelectronic device to house the cardiomyocytes and induce hypoxia. With the device, they could perform multiplexed and accurate recordings of ischemia continuously for 5 h. Looking ahead, larger or denser arrays of >1000 nanoelectrodes can be implemented, currently only shown in off-chip studies of neural and retinal recordings.[103,104] In addition, improvements in nanofabrication techniques could give probes with nanoscale concavities, or smaller diameters.[105–107] Also, as the in vitro structures are becoming 3D, the fabrication of 3D MEAs could give greater insight into the complex multidimensional spheroid and organoid environment.[101]

The shared fabrication processes related to electrical sensors enable the possibility of integrating multifunctional sensing capabilities on the same substrate area for the simultaneous assessment of multiple cellular responses. Integrating MEAs and interdigitated electrodes (IDEs) has been demonstrated for recording cardiac electrophysiology and contractility (Figure 3A-ii), and Maoz et al. combined TEER with MEAs for a heart-on-chip to study both the integrity of the endothelium and the electrical activity of heart cardiomyocytes simultaneously (Figure 3A-iii).[108,109]

4.2. Electrochemical Sensors

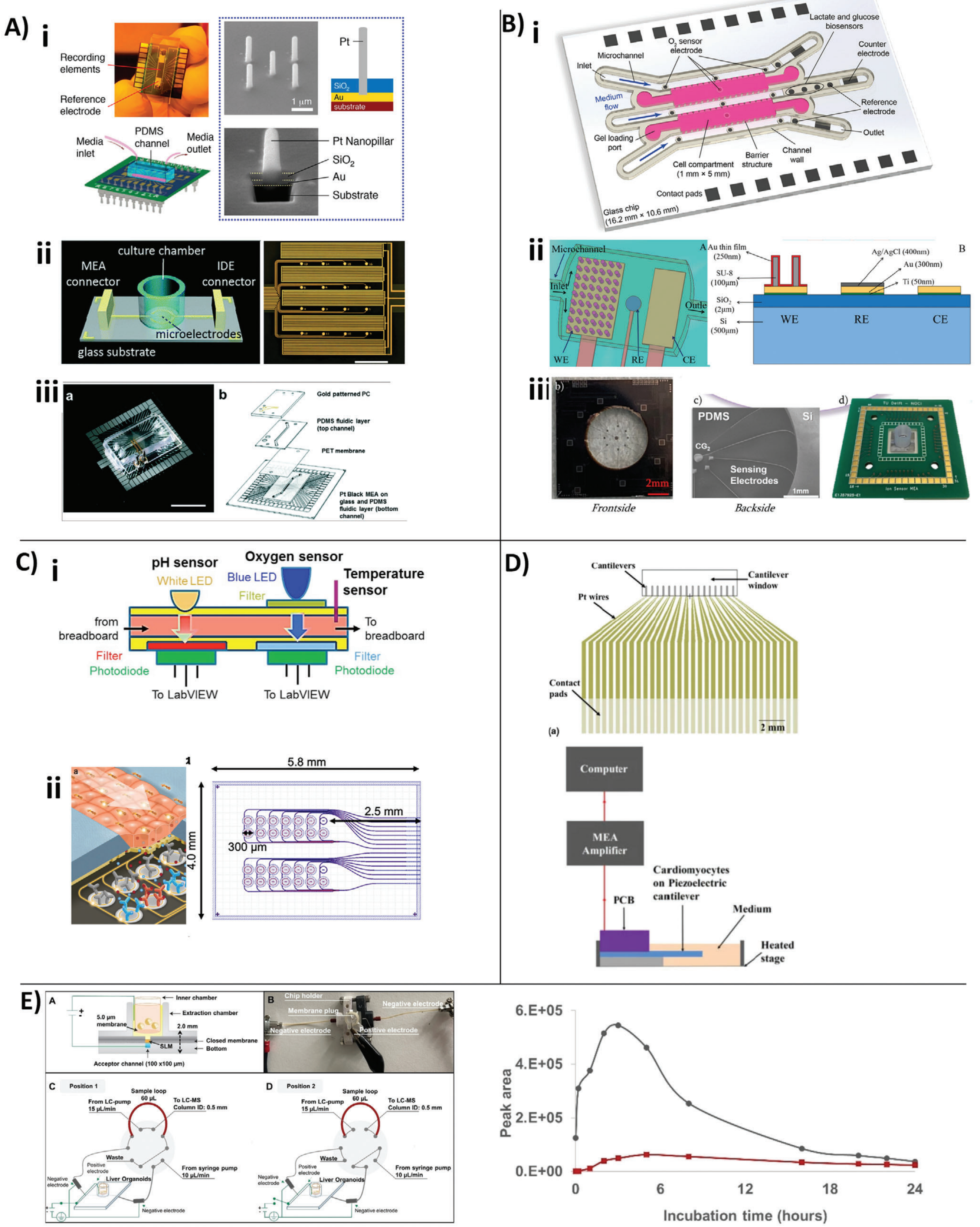
Another sensing modality that has emerged for OoC systems is the transduction of a selective biochemical interaction into an electric signal, namely electrochemical (EC) sensors for potentiometric, amperometric, and impedimetric measurements, for monitoring, e.g., metabolic activity (O_2, pH, glucose, lactate) and secreted biomarkers of an OoC system.[110] For amperometric biosensors the readout reaction is often irreversible and, consequently, the sensing area is typically placed separately to the cells and often in modular systems coupled fluidically to the OoC. Low-cost and optically clear glass wafers have commonly been used as electrode substrates, enabling multiplexed measurements by amperometry of protein biomarkers, as demonstrated for liver-on-chip, muscle-on-chip, and body-on-chip.[111–114] To increase the device compactness, Dornhof et al. embedded the sensing area downstream to the cells and on the same chip.[115] They measured the oxygen level, lactate, and glucose concentration to assess the energy metabolism of breast cancer cells on the chip, all implemented on a 16 mm × 10 mm chip area (Figure 3B-i). The miniaturized 200 µm-diameter working electrodes were placed outside the cell culture area so that the occurring biochemical reactions did not influence the cells but were close enough for an undiluted, low-volume medium to be measured. With the current setup, they were able to continuously monitor the cell culture conditions for 6 days.

Another example of increasing the compactness of the sensor without compromising on the surface area is the fabrication of working electrode micropillars for measuring lead in tap water, as demonstrated by Hu et al.[116] The electrode micropillars were fabricated by sputtering gold on the surface of SU-8 negative photoresist pillars, realizing 432 micropillars that were 40 µm in diameter and 100 µm in height (Figure 3B-ii). By expanding the electrode's surface area and thus its contact with the target molecule, the method enhances the response current. This resulted in high-sensitivity measurements, achieving a detection sensitivity for the lead ions of 0.15 ppb.

Miniaturized alternatives to the planar EC sensors are the FET sensors, which operate by modulating the conductivity between its two main terminals, called the drain and the source, by varying the voltage on a third terminal, called the gate (see also **Section 3.3** for actuation).[117] The measurements are based on changes in the electric field at the gate due to a binding event. As the detection mechanism in FETs is inherently based on the field effect, the FET does not require an absolute reference electrode potential as required for EC measurements. Aydogmus et al. presented a study on a compact FET-based EC sensor for in situ real-time measuring of pH, demonstrated by monitoring the growth of stem cell-derived cortical neurons (Figure 3B-iii).[118,119] The fabrication approach was tailored to be OoC-friendly, as the device was fabricated on a hybrid silicon/polymer substrate, where the silicon-based part included the electronics such as the source and drain terminals of the transistor and pads of the gates. With PDMS spin-coated on top of the electronics and substrate, silicon was etched from the back (with SiO_2 stop), a well was formed and PDMS was exposed to contact the extended electrodes.

4.3. Optical Sensors

By detecting shifts in refractive index or changes in luminescence and absorption properties, optical sensors present a sophisticated alternative to traditional electrode integration for sensing in OoC


A) i
Recording elements
Reference electrode
PDMS channel
Media inlet
Media outlet
Pt
1 μm
Pt Nanopillar
Au
Substrate
ii
culture chamber
MEA connector
IDE connector
microelectrodes
glass substrate
iii
a
b
Gold patterned PC
PDMS fluidic layer (top channel)
PET membrane
Pt Black MEA on glass and PDMS fluidic layer (bottom channel)
B) i
Lactate and glucose biosensors
Microchannel
Inlet
Medium flow
Counter electrode
Reference electrode
Outlet
Gel loading port
Cell compartment (1 mm × 5 mm)
Barrier structure
Channel wall
Contact pads
Glass chip (16.2 mm × 10.6 mm)
ii
Microchannel
Inlet
WE
RE
CE
Au thin film (250nm)
SU-8 (100μm)
Si (500μm)
Ag/AgCl (400nm)
Au (300nm)
Ti (50nm)
iii
PDMS
Si
Sensing Electrodes
2mm
1mm
Frontside
Backside
C) i
pH sensor
Oxygen sensor
White LED
Blue LED
Filter
Temperature sensor
from breadboard
To breadboard
Filter
Photodiode
To LabVIEW
ii
5.8 mm
2.5 mm
300 μm
4.0 mm
D)
Cantilevers
Cantilever window
Pt wires
Contact pads
(a)
2 mm
Computer
MEA Amplifier
Cardiomyocytes on Piezoelectric cantilever
PCB
Medium
Heated stage
E)
A
Inner chamber
Extraction chamber
Closed membrane
Bottom
SLM
Acceptor channel (100 x100 μm)
B
Chip holder
Membrane plug
Negative electrode
Positive electrode
C
Position 1
D
Position 2
Sample loop 60 μL
From LC-pump 15 μL/min
To LC-MS Column ID: 0.5 mm
Waste
Liver Organoids
From syringe pump 10 μL/min
Negative electrode
Peak area
6.E+05
4.E+05
2.E+05
0.E+00
0
6
12
18
24
Incubation time (hours)

systems. As optical sensing can be achieved without the need for physical contact between the instrument and the sensing surface, optical sensors pose minimally invasive monitoring while still ensuring cellular environment integrity, making these sensors ideal for dynamically studying cellular responses with minimal perturbation.[120] Owing to these advantages, numerous optical sensors have been developed for OoC studies.

For non-light-absorbing analytes, analyte-specific sensing dyes are often utilized, particularly for monitoring physical parameters such as pH, O_2, and CO_2.[121] These sensors have found applications in OoC systems for studying the pH of gut microbiome, investigating the effects of electrical stimulation in heart-on-chip systems, and have also been implemented into high-throughput formats.[98,122,123] This sensing methodology traditionally relies on bulky optical fibers, which can limit the compactness of the system. Addressing this limitation, Zhang et al. developed an integrated module for measuring pH and O_2 within their multisensor OoC platform (Figure 3C-i).[112] The O_2-sensing involved embedding the O_2 quenchable luminescent dye ruthenium in PDMS and deposited at the chamber's bottom. This dye was excited by a high-power blue LED above the microfluidic channel, with a band-pass excitation filter positioned between them. Below the detection channel, two silicon-based photodiodes, shielded by a long-pass filter, captured the signal. In contrast, the pH measurements were based on the change in absorption due to the color shift of phenol red upon acidification. The setup included a broadband LED as the light source above the channel, with a photodiode equipped with a long-pass optical filter located beneath the fluidic channel to detect the optical signal. The current setup allowed for continuous monitoring of the physical parameters over a period of 5 days. Similar setups for pH measurements have later also been applied for other OoC applications.[99,124]

Surface plasmon resonance (SPR) is a well-established technology that enables the detection of a wide range of molecular biomarkers. In SPR, polarized light is directed onto the transducing surface, typically a thin film metal, triggering a plasmon effect. This effect then alters the refractive index of the surface material, which in turn affects the resonance angle of the reflected light. These changes can be precisely detected allowing the accurate identification of biomolecules binding.[125] Localized SPR (LSPR), involving localized plasmons in discrete nanoparticles or nanorod surfaces, have been used for studying the secretion of insulin from pancreas-on-chip.[126] However, the angle of light incidence and detection needs to be controlled and varied with high precision, requiring sophisticated mechanical and optical components (such as lasers, prisms, or gratings, and detectors). Hence limiting the compactness of the measuring setup.

Surface nano-structuring in an OoC can also be used to enable surface-enhanced Raman spectroscopy (SERS), an analysis technique that enhances Raman scattering signals—inelastic scattering of photons by molecules, providing information about molecular vibrations and structure.[127] SERS leverages LSPR to amplify these signals. SERS is often achieved using metal nanoparticles like gold, and it can also be optimized with nanolithography-based surface structuring in a silicon-based microfabrication process. This technique has been successfully incorporated into microfluidic platforms for the sensitive detection of pesticides in water, bacteria, DNA, and mRNA.[128–130] Further, due to its highly sensitive and specific molecular identification capabilities, SERS is a powerful tool with great potential for future cancer diagnostics in 3D cell models.[131]

Nanophotonics, i.e., manipulation of light by physical structures on the order of magnitude of the wavelength of light, is a rapidly evolving field within silicon micro- and nanofabrication and represents an attractive avenue for integrating sensing in OoC systems. Although a wide variety of photonic structures exist (interferometers, photonic crystals, ring resonators, etc.), they share a common general operating principle: they detect the change in the local refractive index caused by the presence of an analyte. To achieve specificity, the nanophotonic component is decorated by an analyte-specific material such as a selective membrane or an antibody. One example of a nanophotonic sensor is the ring resonator. Ring resonators function by transferring light from a bus waveguide into adjacent rings, creating resonances at specific wavelengths according to the geometry of the ring and the effective refractive index of the surrounding medium. The resonant wavelength is affected by the refractive index of materials near the waveguide, thus the binding of high-refractive index materials (e.g., proteins) to antibody-functionalized ring resonators will result in a shift of the resonant wavelength that can be quantified. The first application of a resonance-based photonic sensor for OoC has been introduced in a study by Cognetti et al. for measuring cytokines in a lung-on-chip (Figure 3C-ii).[132] The photonic chip was compactly incorporated at the base of the bottom channel of the chip, with analyte diffusion from the cell through 100 nm thick nanoporous silicon nitride membranes. The overall biosensor chip footprint was 5.8 mm × 4.0 mm, with antibody functionalized silicon nitride ring resonators in a 7 × 2 ring array with a 350 μm pitch in both directions. With this setup, they were able to measure the cytokine secretion upon bacteria exposure for 150 min.

Figure 3. A) Integration of various electrical sensors for OoC. i) MEAs device for measuring action potentials in heart-on-a-chip: Reproduced with permission.[102] Copyright 2020, American Chemical Society. ii) Combining MEAs and IDEs for recording cardiac electrophysiology and contractility: Reproduced with permission.[109] Copyright 2017, The Royal Society of Chemistry. iii) Combined TEER with MEAs for heart-on-a-chip: Reproduced with permission.[108] Copyright 2017, The Royal Society of Chemistry. B) Integration of electrochemical sensors for OoC. i) A breast cancer-on-a-chip and sensing platform that includes the integration of lactate, and glucose sensing capabilities: Reproduced with permission.[115] Copyright 2022, The Royal Society of Chemistry. ii) Integration of working electrode micropillars for sensitive analyses of lead in tap water: Reproduced with permission.[116] Copyright 2019, IOP Publishing Ltd. iii) Compact FET-based EC sensor for in situ real-time measuring of pH: Reproduced with permission.[119] Copyright 2023, Nature Research. C) Integration of optical sensors for OoC. i) A heart-liver-on-chip sensing modular platform that includes the integration of pH and O_2 sensing capabilities: Reproduced with permission.[112] Copyright 2017, National Academy of Sciences. ii) A photonic ring resonator biosensor-integrated chip for sensing lung epithelial inflammatory cytokines: Reproduced with permission.[132] Copyright 2023, The Royal Society of Chemistry. D) A piezoelectric cantilever for measuring muscle tissue contraction: Reproduced with permission.[83] Copyright 2019, Springer Link. E) Automated sample preparation using electromembrane extraction directly coupled to LC-MS for drug analysis of liver organoids: Reproduced with permission.[143] Copyright 2022, Wiley.

For insight on how to further integrate optical components such as LEDs, waveguides and photodiodes using CMOS technology, see Section 3.1.

4.4. Mechanical- and Electromechanical Sensors

Mechanical and electromechanical sensors can transduce a change in force, mass or stress into an electrical signal, either by detecting it directly (measurement of deflection) or by detecting a shift in resonance frequency (e.g., of a vibrating membrane or beam). These sensors are based on piezoresistive and/or piezoelectric materials, both of which are well established ingredients of MEMS fabrication technology, with several emerging materials with novel or improved properties in development. In the context of OoC, piezoelectric cantilever sensors have been applied for label-free measurement of muscle contraction of cardiomyocyte cells, shown in a study by Coln and co-workers (Figure 3D).[83] The device incorporated the piezoelectric sensing thin film AlN on top of the cantilever sandwiched between two Pt electrodes. Cardiomyocyte cells were incubated on top of the cantilever, with the force of the beating cardiomyocytes causing the cantilevers to bend, producing a mechanical stress that in turn generated an electric potential difference across the two electrodes.

Different sensing principles based on surface acoustic waves (SAW), i.e., acoustic waves that travel along the surface of a piezoelectric substrate, and film bulk acoustic resonators (FBAR), which operate using the bulk modes of vibration, can be applied to measure binding of an analyte to a substrate. Contrary to EC biosensors, these sensors do not rely on a redox reaction for detection and are thus nondestructive to the biological system. Their miniaturized design, high sensitivity and simple operation are highly suitable for integrating with OoC systems. However, few reports exist on the integration of such sensors with microfluidics, mostly due to the influence of the liquid flow on the mass loading on the sensor surface, which in turn interferes with the frequency response measurement.[133,134] Achieving high mass sensitivity has nevertheless proven to be possible in a microfluidic format, demonstrated by Zheng et al. who applied shear mode AlN film-based FBAR in a microfluidic channel to detect carcinoembryonic antigens.[135]

4.5. Automated Sampling and Sample Preparation for Off-Chip Analysis

While integrating on-chip sensors within the OoC device is appealing, not all analytical needs can be addressed by integrated miniaturized sensors. Consequently, it is often necessary and preferable to extract a sample from the OoC for off-chip analytical procedures. In the foreseeable future there will be a need to collect samples and analyze them off-chip using well-established off-line analytical tools such as ELISA, mass spectrometry, polymerase chain reaction, and flow cytometry.[92,136] However, several steps of the off-chip analytical procedures, including sampling, sample preparation, and detection, can benefit from automation, enhancing the precision and efficiency of real-time OoC assays. MEMS fabrication technology has long been established for various microfluidic applications involving sample preparation, such as mixing liquids and reagents, reaction, separation, sorting, and cell lysis.[137]

As the in vitro model protocols and OoC-device technology continue to improve, it is of increasing interest to be able to sample the same population over a prolonged period. With regards to off-chip analysis, longitudinal sampling of the OoC constituents, i.e., periodic sampling, would have to be performed with high repeatability and without affecting the biological equilibrium. We therefore expect that the sample volumes available will be in the sub 10 µL-range. Here, time-controlled sampling for off-chip analysis can be performed with high repeatability by integrating microvalves and micropumps into the OoC setup (see Section 3.4.1), a technology originally used to develop precise and miniaturized drug delivery systems.[138]

Low sample volumes, low analyte concentration, and complex sample matrices (high salt and protein content and hydrogel that can interfere with the analysis) generate a strong need for miniaturized systems for clean-up and pre-concentration of the extracted sample, i.e., miniaturization of sample preparation procedures.[139] One example of a sample preparation technology that has shown potential for OoC is electromembrane extraction (EME).[140] By applying an electrical field, analytes are selectively migrated from the OoC medium across an oil-immobilized membrane to a clean aqueous solution for downstream analysis. The non-polar fashion of the oil-immobilized membrane makes the EME technology favorable for extracting small hydrophobic drugs, e.g., pharmacokinetic (PK) or pharmacodynamic (PD) studies during drug development, which is a current commercial focus of OoC systems.[141,142] A proof-of-concept system has been presented by Skottvoll et al., where they studied the PK of methadone by combining liver organoid incubation, EME, and mass spectrometry analysis in an automated fashion (Figure 3E).[143] The device was mainly fabricated using thiol-ene polymers and equipped with an organoid incubation chamber, fully separated from the extraction zone constituting the oil-immobilized porous polypropylene membrane. With this setup, methadone and metabolites were extracted and channeled to the downstream analysis using a switching valve, continuously monitoring the PK of methadone for 24 h. With electrodes placed external to the device and challenges with robust operation, EME is an example of a possible sample preparation candidate that could benefit from technical improvements made possible by silicon-based MEMS technology for integrated sample clean-up from the OoC system.

5. Integration and Chip-To-World Interfacing

The usefulness of silicon technology for OoC applications relies not only on the ability to realize a specific sensing or actuation modality. Equally important is the capability for hybrid integration, which involves the effective incorporation of the silicon component into the OoC setup.[144] Depending on the device type and functionality, different levels of integration complexity are required. For example, MEAs for neuron stimulation and sensing (see Section 3.3 and Section 4.1) need to be in direct contact with the nerve cells and must therefore be an embedded part of the OoC device. In contrast, a sensor monitoring the pressure inside an incubation chamber can be remote, simply connected to the OoC device via microfluidic tubing to ensure fluid

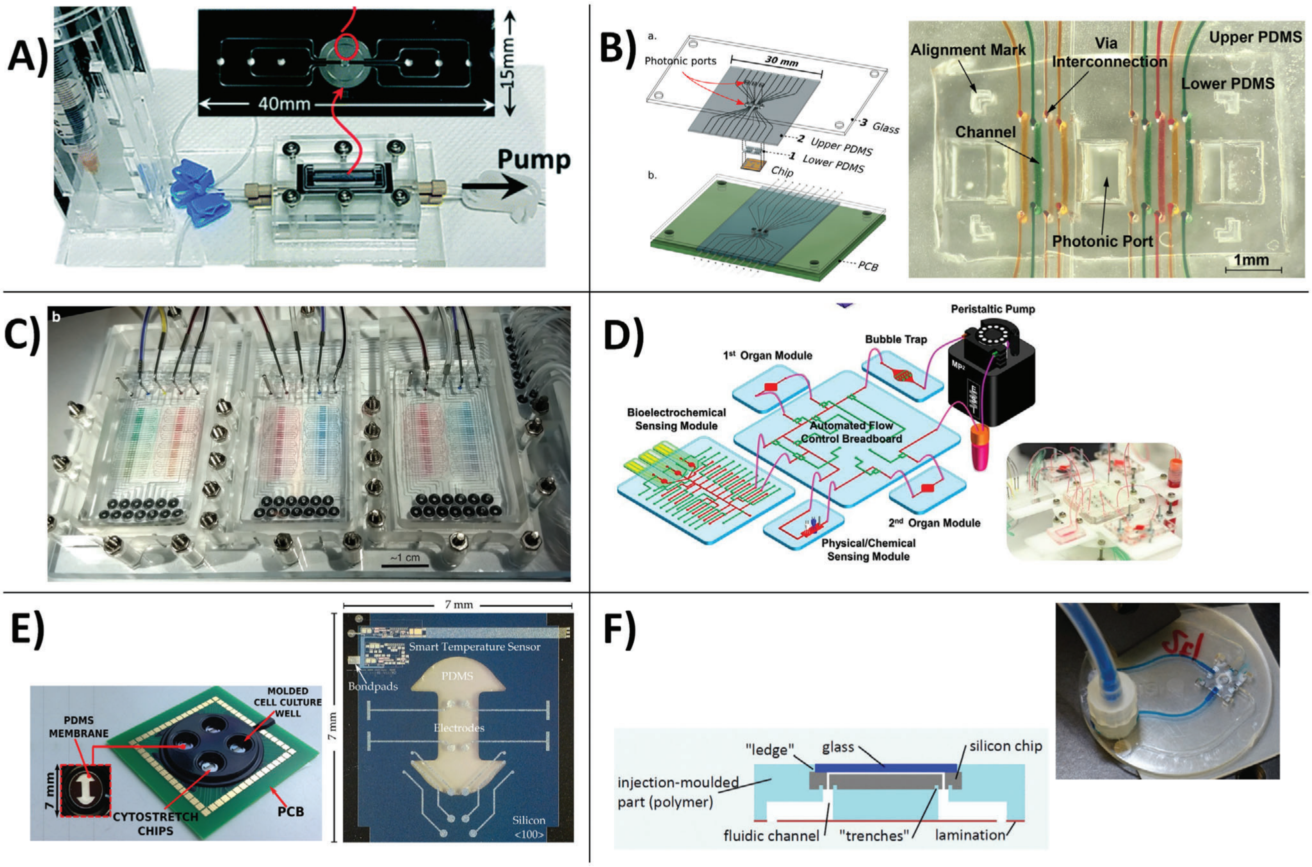


Figure 4. A) Clamping of a microfliudic chip: Reproduced with permission.[147] Copyright 2019, The Royal Society of Chemistry. B) PDMS microfluidics bonded to silicon substrate: Reproduced with permission.[150] Copyright 2020, MDPI. C) Microfludic breadboard: Reproduced with permission.[155] Copyright 2020, Nature Research. D) System integration by tubing: Reproduced with permission.[112] Copyright 2017, National Academy of Sciences. E) Monolithic integration: Reproduced with permission.[157] Copyright 2021, Elsevier. F) Heterogeneous integration of silicon chip in thermoplastic by injection molding: Reproduced with permission.[159] Copyright 2014, IEEE.

communication between the sensor and the sensed environment. In general, the necessary level of integration is typically higher for devices which perform stimulation than for devices which perform sensing. In this section we briefly summarize and categorize different integration approaches, highlight representative examples from literature, discuss criteria for selection of integration technology for a particular application and look into future developments. It is important to note, however, that this discussion will focus on the technical aspects of integrating silicon/glass-based devices with OoC systems and will not cover the hybrid integration of biological components into these systems.

5.1. Microfluidic Integration

In many cases, the silicon (or glass) component is essentially a flat substrate with a pattern of low, often sub-micron, topography (e.g., electrode array, waveguide pattern, nanostructured surface, electrochemical sensor) which needs to be integrated as part of the top or bottom microfluidic chambers, typically as the bottom, in a polymer-based microfluidic OoC device.

As a first approach, *mechanical clamping* of the silicon substrate with the microfluidic structure may be applied to generate a leak-tight assembly.[145] In most cases a dedicated holder or housing capable of generating sufficient, evenly distributed clamping pressure is required, as is a gasket between the substrates. However, when the microfluidic device is manufactured in an elastomer with a tacky surface, sufficient seal may be achieved even without clamping. Often the elastomer will spontaneously form a seal upon contact with silicon/glass which is sufficiently leak-tight for many low-pressure applications. This is the case with the well-known PDMS, and partly the reason for its popularity, in addition to its soft lithography properties.

In general, alignment accuracy ≈100 µm is achievable in mechanical clamping systems but can be pushed to the sub-100 µm level with careful implementation. The study by Wang et al. is an early example of integration of a glass substrate containing a MEAs with PDMS microfluidics for neuronal recordings.[146] More recently, Yunxiao et al. fabricated a silicon-structured adipose-on-a-chip with anodically bonded glass cover, interfacing the chip and connected tubing by clamping (**Figure** 4A).[147] One important advantage of clamped systems is the possibility to open and re-seal the device multiple times, which may be a desirable trait to gain direct access to the cells or organoids during an experiment.

Adhesive bonding is suitable in cases where the microfluidic device is manufactured in a rigid material, e.g., thermoplastics such as polymethyl methacrylate (PMMA), cyclic olefin (co)polymer (COP, COC), polyethylene (PE), and polycarbonate (PC), because these polymers do not have surface termination which readily permits molecular bonding to silicon or glass. A wide range of liquid adhesives are available, although their use can be challenging and often require special jigs to ensure proper alignment and bond accuracy. An attractive alternative to liquid adhesives are pressure sensitive adhesives (PSAs), which are polymer films, typically transparent, coated on both sides with an adhesive layer.[148] PSA can be purchased in different thicknesses, starting at ≈70 µm, and may be cut into the desired shape manually or by using laser cutters or knife plotters, and provides instantaneous attachment without the need for specific chemical, thermal or mechanical fabrication steps. However, the simplicity in use comes at a cost in terms of generally poor alignment accuracy and low resolution of the bond geometry. Bonding with PSA can be reversible in certain cases to permit repeated opening and re-sealing of the device.

In some cases, appropriate surface chemistry is available and direct *chemical bonding* of a polymer-based microfluidic layer to silicon or glass can be performed. Examples of this include plasma-activated bonding of PDMS via siloxane bonds formed from hydroxyl groups (Figure 4B), as well as covalent bonding of off-stoichiometry thiol-ene (OSTE+).[149–151] The latter is a two-component elastomer whose physical properties can be tailored by adjusting the mass ratio of its two constituents, and the elastomer can achieve rigid characteristics similar to those of a thermoplastic. Chemical bonding using OSTE+ has also been demonstrated for its biocompatible bonding abilities, i.e., bonding at low temperature without adversely affecting, e.g., biomolecules.[152] The biocompatible bonding abilities makes it possible to, e.g., complete any necessary biofunctionalization protocols prior to assembling and bonding the device.

5.2. System Integration

Another integration need arises when the silicon-based component is a stand-alone microfluidic chip, with its own inlets and outlets, which needs to be integrated into a system with other silicon or non-silicon microfluidic devices.

A straight-forward and perhaps obvious integration approach is to connect the independent chips via microfluidic tubing. Although technologically simple, the method is very efficient as it provides a fast and affordable manner to realize a sequentially connected fluidic network, which allows for fluid communication between different modules and permits relatively easy reconfiguration if needed.

One of the primary drawbacks of this modular integration approach is the spatial separation of the cell-containing chamber and the different operational modules, leading to a temporal disconnect as well. This separation eliminates the possibility to integrate most stimulation modes (apart from chemical), and, due to sample dispersion during flow and relatively large dead-volume between the chips, severely limits temporal resolution during sensing and analysis of short timescale events. To alleviate some of the limitations, several variants of modular microfluidic designs have been introduced over the years.[153] The common denominator of these approaches is to use pre-defined interfaces to connect different microfluidic chips into one system, typically by non-permanent connectors (e.g., clamping or press-fit) – either directly chip-to-chip or via an intermediate frame (the microfluidic equivalent of an electronic breadboard). This method permits elimination of microfluidic tubing, reduction of dead volume, and it introduces a certain degree of re-configurability. Notable examples from archival literature include “fluidic circuit boards”, modular systems consisting of discrete fluidic elements and Lego-type microfluidic building blocks (Figure 4C).[154–156] More advanced implementations include the multi-component network for continual in situ monitoring of organoids demonstrated by Zhang et al., which incorporates microbioreactors, several sensing units, medium reservoir, flow switching manifold and bubble traps (Figure 4D).[112] In this integration approach, each component in the system is in principle a stand-alone device with its own chip-to-world interface.

Several of the commercial microfluidic chip providers also have their own systems for modular microfluidic integration (e.g., Microfluidic ChipShop, Dolomite). In any case, the use of these systems requires that the chips are designed and manufactured with compatible interconnects. Despite efforts toward introducing industry standards, no standardized system for microfluidic interconnects exists today.

5.3. Advanced Integration Methods: Monolithic- and Heterogeneous Integration

The modular-based integration approaches described above inherently involve the spatial separation of various components. This introduces limitations with respect to functionality, accuracy, reliability, and compactness. In addition, these approaches often necessitate extensive manual handling by highly skilled personnel, presenting a significant obstacle particularly for commercial applications. To address these challenges, two primary strategies exist: *monolithic-* and *heterogeneous integration*.

Monolithic integration refers to the incorporation of several functionalities on-chip as a result of one fabrication process or technology, in contrast with the addition of functionality post-fabrication, or the combination of several prefabricated functionalities as is the case in system integration. In the case of silicon microfabrication, one example is to include temperature sensing and pressure measurement inside the same microfluidic cavity, where the cavity and the piezoresistive circuits for the pressure and for temperature sensors are realized “simultaneously” during one fabrication process flow, and constitute monolithic parts of the device, recently demonstrated by Ponte et al. for OoC purposes (Figure 4E).[157]

Monolithic integration enables exploitation of the highest levels of available geometrical resolution, alignment precision, material and material stack properties, micro- and nanoscale sensing and manipulation modalities which silicon technology has to offer. On the other hand, it requires advanced design capabilities and thorough understanding of the principles of the sensing or stimulation methods to be integrated, as well as access to clean-room and fabrication infrastructure and expertise in the fabrication process itself. For these reasons, the use of monolithic integration in OoC device development is typically only possible through close interdisciplinary collaboration between scientists specializing in cell/organoid research and technology researchers from specialized micro- and nanofabrication environments.

In many cases, it is not possible to achieve all the desired device properties or functions by employing one single fabrication technology, but it still is desirable to realize a compact and precisely aligned device. *Heterogeneous integration* refers to such a combination of devices or sub-components fabricated by different technologies into one compact and accurately assembled device. Heterogeneous integration can involve various post processing steps using materials which are not readily available for, e.g., microfabrication, and/or various assembly and bonding methods (e.g., adhesive, thermal, compressive) performed using specialized precision alignment tools (Figure 4F).[158,159]

Emerging OoC applications which require ever more functional systems, comprising cellular constructs embedded in microfluidic architectures equipped with multimodal stimulation and sensing capabilities, cannot be realized using a single material or fabrication technology. Despite the obvious advantages and needs for efficient heterogeneous integration approaches in OoC, and consensus in the literature that the technological path forward for OoC devices leads toward higher levels of functionality and integration, there is to date little focus on development of new methodologies in the scientific communities. In analogy to microelectronics, we expect an increased focus on heterogeneous integration as an enabling technology for microphysiological systems, accompanied by both research and technological developments in specialized packaging technologies with biocompatibility and low dead-volume fluidic connections being the main drivers.

6. Challenges and Limitations

As stated in the introduction and evidenced by the preceding sections, a wide range of examples of the use of silicon-based technologies in OoC can be found in the literature; however, the widespread adoption of silicon micro-nanofabrication and MEMS within the field of OoC research still remains relatively limited. It is interesting to look into the challenges and barriers associated with silicon technology which may be responsible for this limited uptake.

Technology access: a major barrier to widespread uptake of silicon technology in OoC is its relatively low accessibility to the broad Life Science community. Silicon technology requires heavy infrastructure consisting of cleanroom laboratory facilities and advanced equipment, as well as highly specialized personnel. This represents high cost and, due to its high complexity, a significant competence gap between the scientists who can design and fabricate the silicon-based devices, and those who need them. A critical aspect in this regard is cross-disciplinarity and the establishment of convergent technology environments, where experts from biotechnology and Life Science can co-exist in close collaboration with those from physics and micro- and nanofabrication. Several notable ecosystems of this kind exist, but outside of those, the access to silicon technology is severely limited.

Biocompatibility, or more specifically, the suitability to host a biological environment, is another important aspect. Silicon (and silicon dioxide which is spontaneously formed on the surface upon contact with air) has properties that are very similar to glass in this regard. It is inert and non-toxic and may readily be biofunctionalized via hydroxyl functional groups.[144] Furthermore, silicon dioxide is hydrophilic and therefore has naturally low non-specific adsorption of molecules to its surface. However, it is also rigid, inorganic and non-permeable to gases, and does not intuitively represent a biologically hospitable environment. Gas exchange may be an issue which needs specific attention to ensure sufficient gas transport to (and from) living cells. Direct contact with cells and organoids may be undesirable depending on the cell type; however, the broad possibilities to deposit different (biocompatible) surface layers, both organic and inorganic, and to add biomolecule functionalization also make silicon a very versatile substrate (see Section 3.5.3). Its suitability for a particular application must be considered on a case-to-case basis.

Finally, *sample access*, both optical and physical, is a complicating factor when it comes to the use of silicon in OoC (as well as other Life Science applications). Since silicon is non-transparent to visible light, it is incompatible with optical microscopy which is perhaps the most important observation mode in biological research. If glass is bonded to the silicon chip as top cover, which is commonly the case, incident illumination microscopy (including fluorescence) is available for sample observation. There are methods to circumvent this issue, e.g. by integrating a glass window in the chip to permit local transmission illumination, but such an approach greatly complicates device fabrication. If physical access to the organoid or inner surfaces of the OoC is required, silicon or silicon/glass based devices may pose a challenge because the standard fabrication processes are not designed for easy disassembly. This contrasts with PDMS-based devices, which can be easily opened, cut, or punctured to access the inside of the chip. In the case of silicon, access must be planned ahead and solved already in the design phase, by integrating dedicated means for access. Alternatively, as discussed in Section 5, heterogeneous integration with materials which permit easier access may present a viable opportunity.

7. Conclusion and Perspective

While OoC technology is projected to change the future of biomedical research, achieving its full promise is still a distant goal, and will require overcoming numerous technical and biological challenges.

This review has explored the current state-of-the-art and future opportunities for silicon technologies and their potential role within compact, standardized, multimodal OoC systems. Examples of optical (or photonic), acoustic, electrical, and mechanical actuation and stimulation as well as sensing methods based on silicon technology have been reviewed. In many cases, each device has a single function, although some inspiring examples of multi-modality, i.e., the integration of several individual functions into one single device, already exist.

As evidenced by the broad range of examples found in literature, many stimulation and sensing modes can be realized using silicon technology, and many have already been implemented in micro physiological systems. Looking ahead, the interesting question is: what are the most promising avenues for silicon technology within the framework of OoC?

To answer this question, we briefly summarize the key attributes of silicon-based fabrication technologies and devices:

- *Resolution, feature size and miniaturization*: One obvious advantage of silicon-based fabrication technologies is resolution. Routinely reaching the sub-micron level, it translates to feature sizes which are at the sub-cellular scale. This means that complex, multilayered structures can be realized with the resolution to address individual cells, and sensors can be miniaturized to fit within fluidic compartments containing organoids.
- *Aspect ratio*: Plasma etching techniques permit the realization of mechanically robust structures with very high aspect ratios (≈10 and beyond), permitting the creation of highly 3D architectures.
- *Active elements*: the (semiconductor) properties of silicon itself, as well as standardized methodologies for integration of active material layers (ceramics, dielectrics, and metals) provide means for unique stimulation and sensing modalities such as piezoresistive (force and pressure measurements), piezoelectric (movement/deformation, acoustics, resonators), diodes (e.g., emission and measurement of light), and nanophotonic components (waveguides, photonic crystals, etc.).
- *Fabrication versatility* permits monolithic integration of active elements with geometrical features such as membranes, pillars, cavities, channels, springs and pistons in one single device.
- *Reliability, reproducibility and technological maturity* is very high, as evidenced by the omnipresence of silicon-based microchips in modern society. Although developmental costs are relatively high and require access to specialized infrastructure, the cost per device is relatively low in high-volume production.

With the above key features in mind, several attractive paths for silicon technology emerge:

- First, all applications that require high resolution, either in sensing, stimulation, or geometrical features (e.g., nanometer-scale membranes, high aspect ratio pillars), can benefit and, in some cases, depend on the implementation of silicon technology. One prominent example of such application is neuron/brain-on-chip where there is a need to both stimulate and read out cells at a resolution of the single cell level, another is the real-time readout of electrical signals caused by cell interaction.
- Second, applications that require highly integrated multi-modality of different sensing and/or stimulation modes, such as electrical stimulation combined with, e.g., nearby temperature measurements (i.e., within a few 10′s or 100′s of micrometers). Realization of this type of functionality can strongly benefit from the monolithic integration capabilities offered by silicon technology.
- Third, applications which require specific functions which are best achieved using silicon technologies, such as electromechanical actuation based on piezoelectric thin films, a wide range of nanophotonic applications, or sensing of pressure by a piezoresistive membrane.

In summary, silicon technology offers most value to those OoC applications which need increasingly high functional complexity while at the same time requiring high resolution. On the other hand, OoC devices that benefit from larger chambers, flow channels, and functional elements that are well suited for, e.g., polymer fabrication do not need silicon. However, the future of OoC technology is not a question about which technology to choose – rather, it is about how to combine them. High degree of functionality and multi-modality will no doubt require efficient fusion of different technologies into one single device.

A key enabler to fusing several modalities and materials on the same OoC platform is integration. We have reviewed various methods for integrating silicon or glass substrates with (polymer) microfluidics, and although we find excellent examples of advanced heterogeneous as well as monolithic integration, the vast majority of devices presented in the literature are, to date, based on relatively simple integration methods. We therefore expect an increased focus on heterogeneous integration as an enabling technology for OoC systems, accompanied by both research and technological developments in specialized packaging technologies.

Finally, silicon-based microchips are well established in the commercial domain. We foresee that silicon technology will take a prominent space for commercialization applications where standardization, high volume fabrication and robust OoC systems are required, such as products for the pharmaceutical industry or contract research organizations (CROs).

The introduction of silicon technology into the OoC domain does not come without its challenges. Perhaps the biggest one is related to technology access; heavy infrastructure consisting of cleanroom facilities and advanced equipment, specialized personnel, and relatively high development costs require large interdisciplinary projects and collaborations. In addition, more practical issues such as optical and physical access to the samples may pose limitations, especially in the development phase.

In conclusion, the journey toward fully realizing the potential of OoC systems is, no doubt, going to be a multilayered challenge. Joint multidisciplinary efforts of engineers, biologists, and clinicians will be crucial in realizing the full capabilities of OoC technology, paving the way for the future of miniaturized, robust, multimodal OoC platforms for biomedical research and personalized medicine. Silicon technology will, most likely, be an important part of that journey.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

F.S.S. contributed to the paper's concept, Sections 1 and 4. E.E.-C. contributed to the paper's concept, Sections 1, 2, and 3. M.M.M. contributed to the paper's concept, Sections 1, 5, 6, and 7. Original figures: E.E.-C.

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