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Emerging Biofabrication Strategies for Tissue and Organ Constructs

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# Compelling standardized and high-throughput micro-/millifluidic plates for biomedical research: from laboratory to market

**Longjun Gu[a,b], Peidi Liu[a], Wen Zhao[a], Yuhang Fan[a], Yuwen Wang[a], Pu Chen[a,c,*]**

## Abstract

Microfluidics has demonstrated significant potential for advancing biomedical research. However, the widespread adoption of current microfluidic devices within the biomedical community is hindered by 2 major challenges: standardization and throughput. To address these issues, emerging micro-/millifluidic plates based on microtiter plate format have been proposed. On the one hand, the established standards for microtiter plates facilitate clear communication between microfluidic engineers and end-users, enabling untrained users to manipulate micro-/millifluidic plates directly without the need to be proficient in understanding the mechanisms behind the platform. On the other hand, micro-/millifluidic plates inherit the high-throughput capabilities of microtiter plates, enhancing their utility in applications such as organ-on-a-chip and point-of-care testing. This review is intended to provide a timely and insightful overview of micro-/millifluidic plates, covering their design strategies, liquid-driven systems, applications, and commercialization status. Additionally, the review discusses the challenges facing micro-/millifluidic plates and highlights emerging positive trends in this field. We believe that our unique perspective on micro-/millifluidic plates can facilitate innovation and accelerate academic transformation by appealing to the microfluidic community to establish a consistent chip development plan to match end-user expectations in the biomedical field.

**Keywords:** Commercialization, High throughput, Micro-/millifluidic plate, Organ-on-a-chip, Standardization

## 1. Introduction

Over the past 3 decades, despite microfluidic practitioners making great efforts to expand the impact of microfluidics on biomedical applications, this innovative technology has not yet been widely embraced by end-users in the biomedical community. From an engineering standpoint, one primary reason is that microfluidic engineers, who are often nonexperts in the biomedical field, tend to overlook the experimental practices and workflows of end-users such as biologists and clinicians during the development of microfluidic chips. As a result, these microfluidic novices usually have to spend considerable time troubleshooting and adapting to these new tools rather than focusing on scientific advancements.[1] Another challenge is the delicate balance that objectively exists between the functional complexity and the throughput of microfluidic chips.[2] Complex, highly functional designs, along with customized operational processes, inherently limit the throughput of these chips, which in turn slows down sample production and data acquisition. Consequently, most existing microfluidic chips are generally suitable for small-scale laboratory research but are not easily scalable to meet the demands of applications in pharmaceutical and clinical diagnosis.[3]

Compared with microfluidic chips, the microtiter plate is widely recognized as a standard device in biomedical research due to its user-friendly operation and high-throughput testing capabilities. Since the establishment of microtiter plate standards (Table 1),[4–12] microtiter plates of various specifications have been mass-produced in industry and have become essential tools in a range of biomedical applications, including cell manipulation,[13] drug screening,[14] and clinical diagnosis.[15,16] Especially in COVID-19 testing, the microtiter plate significantly contributes to detecting the causative virus by using the reverse transcription polymerase chain reaction (RT-PCR) technique.[17] Alongside microtiter plates, a variety of commercial instruments such as robotic liquid handlers, plate readers, and high-content screening instruments have been specifically developed and employed for sample handling and analysis in microtiter plates. These advancements have made microtiter plates viable for workflow automation with minimal human intervention, thereby enhancing reproducibility and robustness in biomedical research.[18]

Chip design based on microtiter plate format represents a promising strategy to promote standardization and enhance the throughput of current micro-/millifluidic devices (Figure 1).[19–21] The platform that integrates micro-/millifluidic technology into a standard microtiter plate is defined as a micro-/millifluidic plate. Specifically, a microfluidic plate features micrometer-scale channels and handles fluid volumes in the nanoliter to microliter

[a]*Department of Biomedical Engineering, Tissue Engineering and Organ Manufacturing (TEOM) Lab, Wuhan University TaiKang Medical School (School of Basic Medical Sciences), Wuhan, Hubei, China,* [b]*Department of Intelligent Systems Engineering, Indiana University, Bloomington, Indiana, USA,* [c]*TaiKang Center for Life and Medical Sciences, Wuhan University, Wuhan, Hubei, China.*

**Corresponding author: Address: Pu Chen, Department of Biomedical Engineering, Wuhan University, 115 Donghu Road, Room 305, #3 Building, Wuhan, Hubei 430071, China. E-mail address: puchen@whu.edu.cn (P. Chen).*

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**Table 1**

**Comparison of standards for microtiter plates.**

| Standard | Scope | Design guidelines | Biocompatibility and safety | Industry adoption | Reference |
|---|---|---|---|---|---|
| ANSI/SLAS 1-2004 (R2012) | Footprint dimensions | Footprint, corner radius | NA | High-throughput testing industry | [4] |
| ANSI/SLAS 2-2004 (R2012) | Height dimensions | Plate height, top surface | NA | High-throughput testing industry | [5] |
| ANSI/SLAS 3-2004 (R2012) | Bottom outside flange dimensions | Flange height, flange width, chamfers (corner notches) | NA | High-throughput testing industry | [6] |
| ANSI/SLAS 4-2004 (R2012) | Well position | Well layout, well column position, well row position, positional tolerance, well markings | NA | High-throughput testing industry | [7] |
| ANSI/SLAS 6-2012 | Well bottom elevation | Well bottom elevation, well bottom elevation variation, intra-well bottom elevation variation, well depth, bottom thickness, well bottom width | NA | High-throughput testing industry | [8] |
| ISO 7581 | Bactericidal activity of a nonporous antimicrobial surface | NA | Bactericidal activity (Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus hirae, Escherichia coli) | Medical and pharmaceutical device industry | [9] |
| ISO 10993-5:2009 | In vitro cytotoxicity | NA | Cell damage, cell growth, cellular metabolism | Medical and pharmaceutical device industry | [10] |
| ASTM D6400-23 | Labeling of plastics designed to be aerobically composted in municipal or industrial facilities | Materials must meet compostability criteria | NA | Medical and pharmaceutical device industry | [11] |
| USP <1031> | Biocompatibility | NA | Biological reactivity | Medical and pharmaceutical device industry | [12] |

NA, not applicable.

range, enabling precise fluid control, miniaturization, and integration of complex biological functions, making it well-suited for point-of-care testing (POCT). In contrast, a millifluidic plate has millimeter-scale channels and operates in the microliter to milliliter range, allowing for the culture and manipulation of larger biological models under controlled flow conditions, which is essential for organ-on-a-chip systems. On the one hand, the established international standards facilitate clear communication between microfluidic engineers and the end-users, enabling these inexperienced users to operate micro-/millifluidic plates directly without the need to be proficient in understanding the mechanisms behind the platform. Users are therefore allowed to conduct experiments using this emerging platform while maintaining their conventional practices. On the other hand, micro-/millifluidic plates inherit the benefits of microtiter plates in high-throughput testing and have a considerable capacity to fulfill the demands for the detection and analysis of multiple samples. Since the development of the microfluidic capillary electrophoresis array based on standardized microtiter plate footprint,[22,23] micro-/millifluidic plates have gained increasing attention and sustained fast development tendency in research laboratories (Table 2). Meanwhile, numerous start-up companies originating from academic laboratories are working to accelerate the translation of this proof-of-concept into practical applications, aiming to extend the influence of microfluidic technology within the biomedical field.

The emerging micro-/millifluidic plate holds significant potential to revolutionize the use of traditional micro-/millifluidic chips in biomedical research, thereby building a substantial user base. However, an in-depth summary and analysis of this innovative micro-/millifluidic platform have been lacking. In this review, we aim to present a timely and insightful overview of micro-/millifluidic plates from laboratory to market. We summarize the design strategies, liquid-handling systems, applications, and commercialization efforts associated with micro-/millifluidic plates. Additionally, we discuss the challenges facing this technology as well as the positive trends that are driving its development. We believe that our unique perspective on micro-/millifluidic plates can foster innovation and accelerate the translation of academic research by encouraging the microfluidic community to establish a consistent chip development roadmap that aligns with end-user expectations in the biomedical field.

## 2. Design strategies for micro-/millifluidic plate

In the design of micro-/millifluidic plates, one of the primary objectives is to unify the standards of the platform that further provide simple, reliable, and validated testing protocols for biomedical research. Nonspecialist end-users merely need to follow the standard operating procedure to accomplish the device operation and data acquisition. Another key objective is to preserve innovative concepts in chip design to cater to the diverse demands of biomedical applications. Importantly, even though microfluidic engineers must abide by the microtiter plate footprint during the chip design, their creative ideas can still be transformed into specific micro-/millifluidic plates rather than being stifled. To date, 2 mainstream design strategies have been demonstrated according to the microwells are treated as individual or integrated units (Figure 2).

### *2.1 Micro-/millifluidic plate design based on individual microwell*

In micro-/millifluidic plates where microwells are treated as individual units, the microwells serve as containers that provide space for integrating functional inserts, including customized components,[24–26] modified transwells,[27–29] biomimetic substrates,[30–32] and biosensors.[33,34] Each microwell is thus

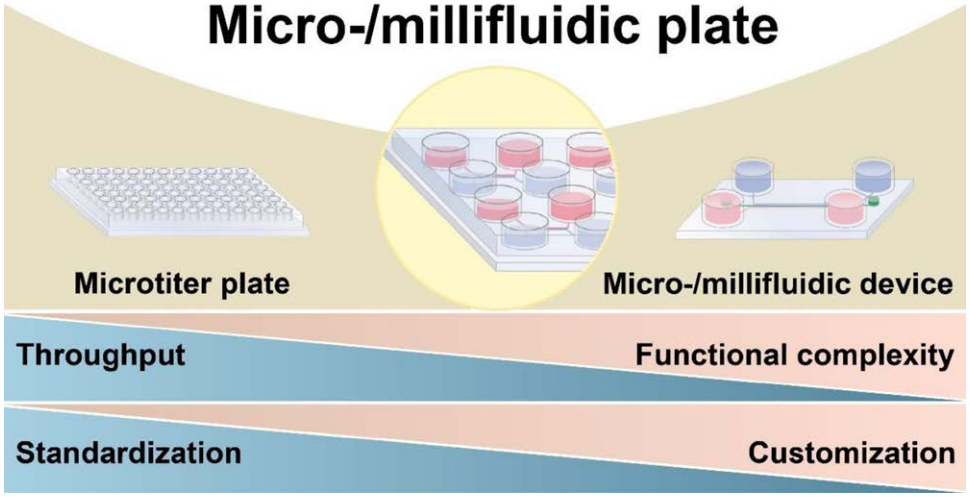


**Figure 1.** The micro-/millifluidic plate combines the advantages of microtiter plates and micro-/millifluidic devices, achieving an optimal balance between functional complexity, throughput, customization, and standardization. Specifically, the micro-/millifluidic plate integrates the high throughput and standardization of microtiter plates with the superior customization and functional complexity of micro-/millifluidic devices. This emerging platform balances scalability, adaptability, and functionality, making it suitable for diverse applications in biomedical research.

endowed with specific functions, allowing it to act as an independent micro-/millifluidic device for various biomedical applications. Typically, customized components divide the microwells into multiple horizontal regions for cell culture, such as left or right regions,[35,36] inner or outer regions,[37,38] and self-defined regions.[39] Different regions are either separated from each other or interconnected by microchannels,[40,41] micropillars,[42] and liquid rails.[43,44] A notable example is the microcavity array, a design that consists of hundreds of independently and regularly arranged microcavities within a single microwell.[45] It provides a promising strategy to overcome the limitations of the conventional organoid culture system based on the Matrigel dome, which lacks robustness in morphogenesis and compatibility with high-content analysis.[46] Both our group and Decembrini et al.[47] employed hydrogel-based microcavities as artificial niches, providing consistent physical and biological microenvironments to direct the generation of the liver,[48,49] retinal,[47] cerebral,[50] and colorectal cancer[51] organoids with uniform sizes and morphologies. In addition to the microcavity array, a 3D-printed inhibiting insert[52] and hanging drop dripper[53–55] integrated into the micro-/millifluidic plate have also been demonstrated to improve the cell spheroid and organoid homogeneity by unifying the spatial location and cell concentration. However, both inserts are limited by the throughput capacity predetermined by the microtiter plate format. In contrast to the microcavity array, the component with connected regions aims to construct histotypic and organotypic models with spatially-defined heterocellular architectures such as neurovascular units,[56] neuromuscular junctions,[57] and vascularized tumor tissues.[58,59] In this kind of customized component, heterogeneous cells are precisely positioned in different regions with connecting microstructures promoting cell–cell interactions and guiding some special physiological processes like angiogenesis,[60] axon elongation,[57] and immune cell directional migration.[61]

Transwell is another type of insert that provides 2 distinct vertical regions for cell culture[62] and it can be modified to perform a wider range of tasks in reconstituting the microenvironment in vivo, such as dynamic culture[63,64] and chemical gradient generation.[27,65,66] Compared with customized components, the porous membranes on transwells provide a more adequate exchange of nutrients and gas, minimize hypoxia injury, and improve the maturity of models.[67–71] However, the limited optical transparency of these membranes is a potential stumbling block for in situ observation. Moreover, transwells restrict microwell organization to up-down regions, limiting the potential for more complex cell arrangements.

Unlike customized components and modified transwells, which prefer to compartmentalize the microwells using physical boundaries to achieve the differential arrangement of heterogeneous cells, the micropatterned substrates employ invisible boundaries to construct heterocellular architectures with micron-level resolution analogous to that found in native tissues and organs. Different types of cells are precisely localized using removable micropatterned stencils[72] and further coating the substrates with extracellular matrix to provide selective binding sites for specific cells.[73–75] In addition to chemical modification of the substrate to accomplish the heterocellular arrangement, substrates can also be granted topographical cues that are crucial for regulating cell fate.[76–78] For instance, integrating biomimetic polydimethylsiloxane (PDMS) substrate that mimicked the curvature of glomerular capillaries improved podocyte differentiation efficiency.[79]

The final category, biosensor, represents a versatile class of inserts capable of monitoring multiple physiologically relevant tissue properties in a real-time, continuous, and noninvasive manner.[80,81] Currently, the main transduction principles applied to micro-/millifluidic plates are based on electrical and mechanical signal propagation.[82–84] The microelectrode array (MEA) is a common biosensor that is widely used for recording electrical activities in tissues, such as neural and cardiac tissues.[85–87] Traditional MEAs are often based on opaque printed circuit board (PCB) substrates, which pose significant challenges for microscopic observation. To address this challenge, transparent glass or thermoplastic-based substrates are used as alternatives that offer additional assay flexibility, including bright-field imaging and immunofluorescence.[88] However, these MEAs still face other limitations, such as reduced capability to monitor 3D tissues,[89] and the metal electrodes often have short operational lifespans due to saturation or degradation.[81] Except for electrical activity, mechanical forces generated by tissues such as cardiac and skeletal muscle are also essential to their function.[90,91] Mechanical biosensors, such as microcantilevers or microwires,

**Table 2**

**Comparison of micro-/millifluidic plates, micro-/millifluidic devices, and microtiter plates.**

| Feature | Micro-/millifluidic plates | Micro-/millifluidic devices | Microtiter plates |
|---|---|---|---|
| Definition | Hybrid platform combining micro-/millifluidic channels with the standardized format of microtiter plates | Miniaturized devices with precisely engineered channels for fluid manipulation | Standard well plates (eg, 48-, 96-, 384-well) used for liquid-based assays |
| Standardization | Partially standardized (ANSI/SLAS, ISO, and ASTM standards applied but still evolving) | Highly customized, lacks universal standards | Fully standardized with well-established formats |
| Throughput | High throughput, compatible with automation and parallel experiments | Low-to-medium throughput | High throughput, optimized for large-scale screening |
| Functional complexity | - Integrates microfluidic functionalities with high-throughput<br>- Suitable for complex assays like cell culture, drug screening, and diagnostics<br>- Supports automation and real-time monitoring | - Provides precise fluid control and microenvironment management<br>- Suitable for organ-on-chip and lab-on-a-chip applications<br>- Complex designs enabling multistep assays | - Basic fluid handling for static assays<br>- Primarily used in drug screening, ELISA, and biochemical tests<br>- Limited control over fluid dynamics and real-time monitoring |
| Customization | Highly customizable—designs can be tailored for specific applications | Highly customizable—chip designs can be tailored for specific applications | Minimal customization—fixed well sizes and layouts |
| Advantages | - Flexible for a wide range of applications<br>- Compatible with high-throughput automation systems<br>- Well-defined plate format for easy integration | - Highly customizable for specialized applications<br>- Ideal for complex, multistep assays<br>- Excellent fluidic control for precise experiments | - Economical and mass-produced<br>- Universal compatibility with many laboratory instruments<br>- Well-established for high-throughput screening |
| Disadvantages | - Partial standardization limits adoption<br>- Scalability challenges in mass production | - Lack of standardization hinders broader adoption<br>- Limited throughput<br>- Requires sophisticated design and fabrication techniques | - Limited fluid control<br>- Inflexible design<br>- Not suitable for complex assays or real-time analysis |

are commonly used in this context. These sensors bend in response to tissue contraction, and the resulting contraction forces can be measured by electronically or optically detecting the deflection of the sensors.[92–94]

In general, the advantage of individual microwell-based micro-/millifluidic plates is that they can inherit and even increase the throughput of the original microtiter plate. The functional inserts can be designed independently from the microwells, allowing them to be easily installed in users' standardized microtiter plates and detached for subsequent analysis. However, the fluid flow, which serves as a key hallmark in microfluidic devices, has not been widely demonstrated in this kind of micro-/millifluidic plate, probably due to lacking sufficient integration space and unified design for the fluid control system. In most cases, the fluid is driven manually, either by connecting to a syringe pump[63] or employing an orbital shaker,[66] which potentially reduces the compatibility and usability of the micro-/millifluidic plate.

### *2.2 Micro-/millifluidic plate design based on integrated microwell*

For micro-/millifluidic plates where microwells are defined as integrated units, the microwells are regularly connected by microchannels, forming multiple parallel microfluidic chips, and the final micro-/millifluidic plates.[95,96] Microwells serve diverse purposes, including liquid handling,[97,98] cell culture,[99] biochemical reaction,[100,101] and sample detection.[102,103] In most cases, the original microwell format is preserved, with microchannels integrated among or within the microwells. For example, a typical micro-/millifluidic plate may feature each chip containing 3 microwells, with up to 128 independent chips formed within a 384-well micro-/millifluidic plate. The microwells at either end function work as inlets and outlets for culture medium perfusion, while the middle microwells serve as the core, embedded with scaffolds designed to mimic native tissues.[104–107] Specifically, a perfusable tubular scaffold termed "AngioTube" was suspended across the tissue culture microwell and connected to both inlet and outlet.[108] It provides mechanical stability for a vessel lumen and supports the self-assembly of various parenchymal tissues, such as the liver,[109] cardiac,[108] kidney,[110] lung,[111] and solid tumors.[112] The scaffold's walls featured nanopores and microholes to enhance cell–cell interactions and improve biomolecular exchange between endothelial and parenchymal cells.[113] Moreover, microcantilevers were strategically integrated into the scaffold to noninvasively probe the contraction of the tissues. PREDICT-96 micro-/millifluidic plate is another example that adapts and extends organ-on-a-chip (OoC) systems to a 384-well plate format.[114] Unlike the AngioTube, PREDICT-96 utilizes bilayer chips with 2 overlapping microchannels positioned between 2 sets of inlets and outlets. Different cell types were cultured on opposing sides of a basement membrane, while the micropores on the membrane promoted cell–cell interactions. Furthermore, a recirculatory flow has been demonstrated by employing a programmable pneumatic pump positioned in the plate lid that was fluidically coupled to the micro-/millifluidic plate via a set of vertical tubes that extend into the microwells.[115–117]

In addition to retaining the original microwells, they also can be removed or redefined to accommodate specific design requirements for microfluidic chips with well-defined configurations, such as double-T junction,[23] Christmas tree-shaped network,[118] parallel microwell array,[119–121] and culture chamber with three assembly ridges.[122] Essentially, this kind of micro-/millifluidic plate can be regarded as an array of conventional microfluidic chips. However, optimizing the number and arrangement of these chips is crucial to ensure compatibility with standard microtiter plates. For instance, in a micro-/millifluidic plate, 96 microwells were replaced by filtration devices of the same number, while each device was positioned at a 45-degree angle to accommodate a long filtration channel. Cell suspensions were loaded into the upper right inlets and driven through the micropillar arrays using air pressure. Cells that were poorly deformable could not pass through the micropillar gaps, resulting in the occlusion of these gaps. The micropillar arrays were strategically placed in the positions of the original microwells,

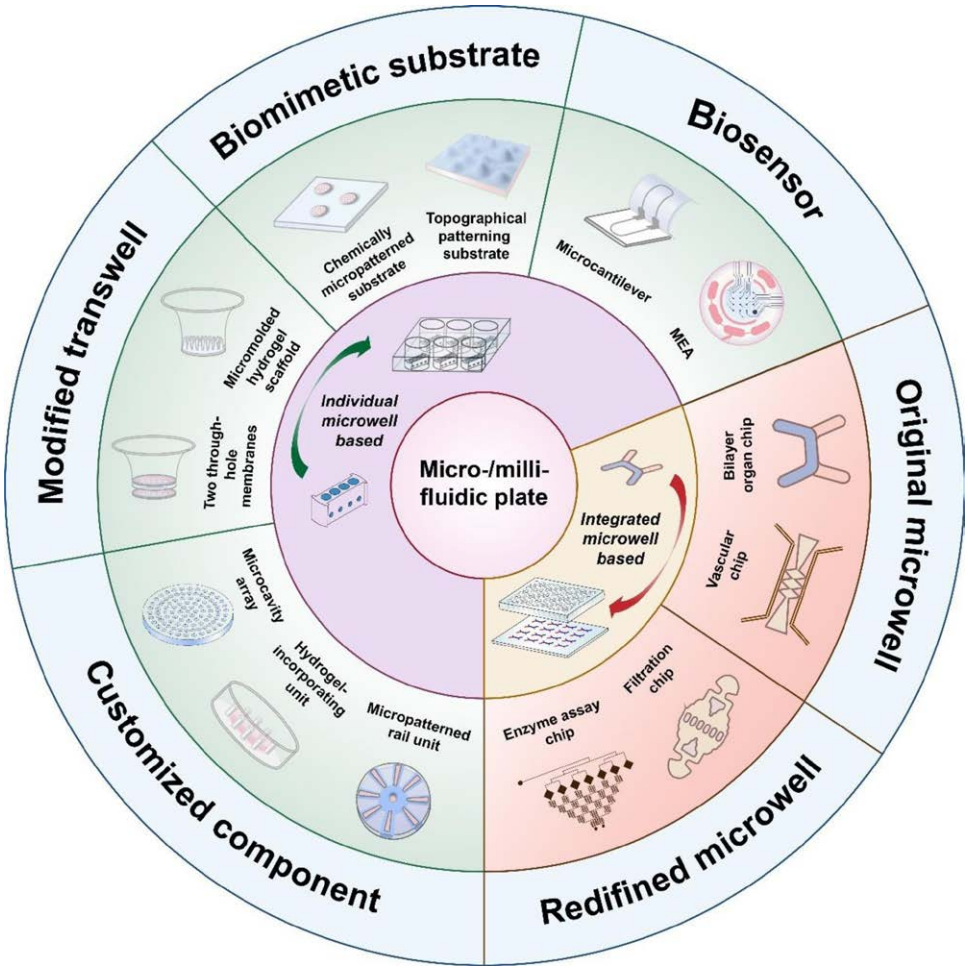


**Figure 2.** Two mainstream strategies for micro-/millifluidic plate design according to microwells are regarded as individual or integrated units. Specifically, in micro-/millifluidic plates where microwells are treated as individual units, the microwells serve as containers that provide space for integrating functional inserts, including customized components, modified transwells, biomimetic substrates, and biosensors. In micro-/millifluidic plates where microwells are defined as integrated units, the microwells are regularly connected by microchannels, forming multiple parallel microfluidic chips, and the final micro-/millifluidic plates. In this type of micro-/millifluidic plate, the original microwell format can be preserved or redefined.

allowing for high-throughput cellular imaging and quantification of the occluded gap percentage.[123]

In summary, this kind of micro-/millifluidic plates possess the ability to perform complex tasks. On the one hand, the available space for chip design extends beyond the microwells to encompass the entire plate, allowing for the integration of more functional structures into the chip. On the other hand, each microwell within the chip serves a unique function, and together, they collaborate to perform complex tasks. Despite these significant advantages, these derivative micro-/millifluidic plates still face challenges in fully achieving both functional complexity and multiplexing simultaneously due to the fixed dimensions of the microwell plate prototype. Depending on the application, an arbitrary number of chips (ranging from 4 to 192) are arranged in parallel on a single micro-/millifluidic plate.[118,124] Looking forward, multilayer structure design may offer a promising solution to balance the throughput and the functional complexity of these micro-/millifluidic plates.[125]

## 3. Liquid-driven systems for micro-/millifluidic plate

Liquid perfusion is a hallmark of microfluidic chips. In POCT systems, for example, precise fluid control is critical for sample loading, separation, and reaction processes.[126] In OoC systems, medium perfusion mimics the circulatory system, ensuring the transport of nutrients and oxygen while facilitating waste removal. Furthermore, mechanical force, like fluid shear stress, is proved to be a fundamental regulator of cellular behaviors.[127,128] To drive liquid perfusion, a variety of pumps have been adapted for use with micro-/millifluidic plates. The pumps can be categorized into 2 types: active pumps and passive pumps, based on whether they require external power sources to move the liquid (Figure 3 and Table 3).[129]

### 3.1 Active pump

Conventional syringe pumps,[130–133] peristaltic pumps,[134,135] pneumatic pumps,[136] and vacuum pumps[137,138] are all active pumps with prominent advantages in accurate fluid control in micro-/millifluidic plates.[129,139] These active pumps are also amenable to generating complex flow patterns, such as pulsatile and recirculatory flow.[140,141] For instance, Satoh et al.[142] developed an OoC system using a pneumatic pump to control medium circulation across multiple culture chambers in a unidirectional manner. This medium circulation mechanism relied on the synergistic effects of the pneumatic pump, the elevated inlet, and the Laplace valve. Among them, the pneumatic pump was

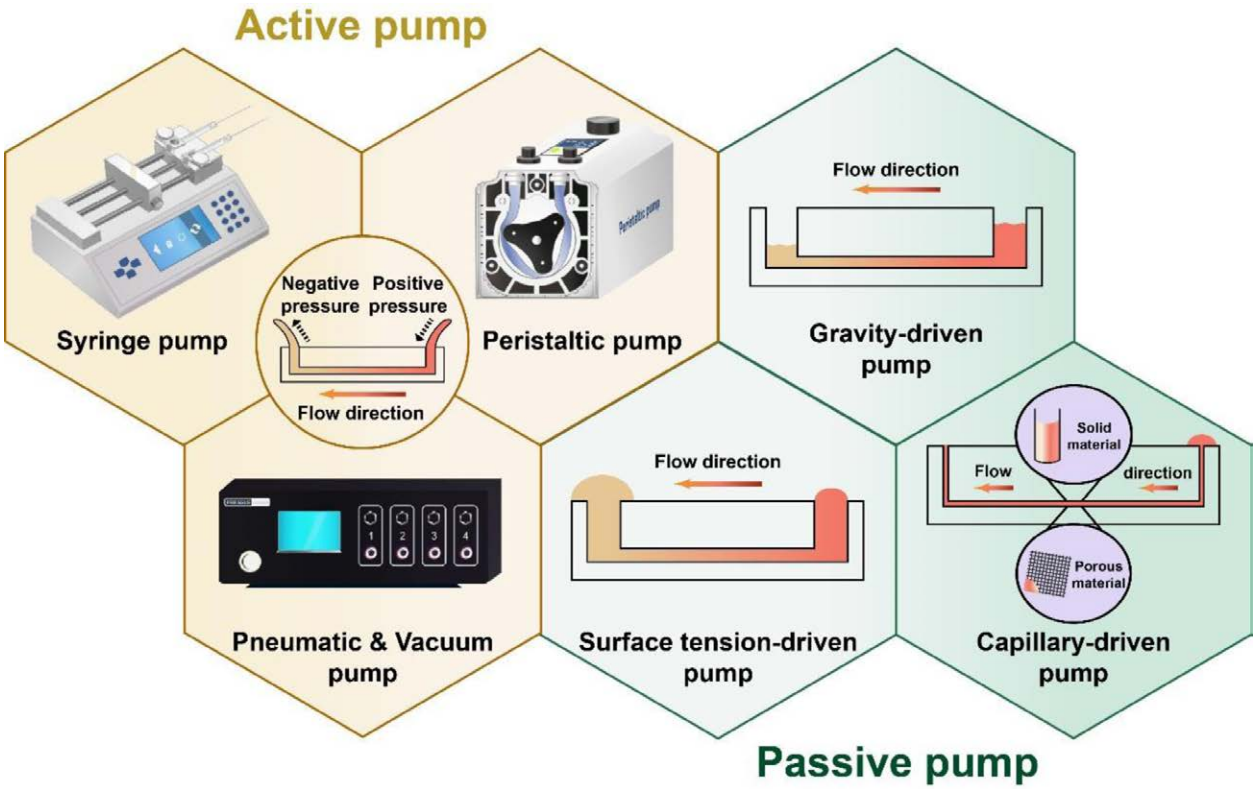


**Figure 3.** Two kinds of liquid-driven systems are used for micro-/millifluidic plates including active pumps (syringe pump, peristaltic pump, pneumatic pump, and vacuum pump) and passive pumps (gravity-driven pump, surface tension-driven pump, and capillary-driven pump).

**Table 3**

**Comparison of active and passive pumps in micro-/millifluidic plates.**

| Parameter | Active pump | Passive pump |
|---|---|---|
| Velocity range | 1 nL $min^{-1}$–1 mL $min^{-1}$ | 100 nL $min^{-1}$–100 μL $min^{-1}$ |
| Sustaining perfusion time | Hours to weeks | Minutes to hours |
| Liquid storage volume | A few milliliters to tens of milliliters | 10 μL–1 mL |
| Potential for external equipment integration | Syringe pump, peristaltic pump, pneumatic pump, vacuum pump | Perfusion rocker |

programmed to periodically apply pressure to tandem culture chambers for medium actuation. The elevated inlet and the Laplace valve were designed to prevent the medium from traveling back to the upstream chamber and stop the introduction of the gas into the microchannel, respectively. Although active pumps are still used as mainstream liquid-driven systems in micro-/millifluidic plates, these pumps are bulky and difficult to massively scale up.[143] Moreover, active pumps typically contain multiple auxiliary components, such as power sources, fluid connections, and tubing, which require fluid handling expertise. These cumbersome components may ultimately hinder the widespread adoption of such systems by biomedical end-users.[18] Therefore, enhancing usability should be a key consideration in the design of liquid-driven systems for micro-/millifluidic plates.

### 3.2 Passive pump

As an alternative to active pumps, passive pumps provide a solution for the limitations mentioned. Based on their advantages, including high level of integration, simplicity of operation, and portability, passive pumps have been widely adopted and applied to a large extent in biomedical applications.[144] In current micro-/millifluidic plates, passive pumping methods such as gravity,[99,145–148] surface tension,[149,150] and capillary force[151–153] have been successfully demonstrated for fluid actuation.

Gravity-driven pumps typically employ reservoirs filled with liquid at different heights to achieve fluid actuation. During the working process, the fluid flows continuously from the higher inlet to the lower outlet until the liquid levels in the reservoirs equalize. A continuous flow can be maintained over long experimental periods by regularly refilling the open inlet or placing the micro-/millifluidic plate on a perfusion rocker to create a hydraulic head difference between the inlet and outlet.[154] However, as the hydraulic head difference decreases, the flow rate gradually diminishes.[129] To maintain a constant flow rate, autonomous droplet dispensers are ingeniously integrated into the inlets to balance the volumes of the replenished and drained fluid.[154,155] The prominent advantages of gravity-driven pumps include simplified system design, the elimination of complex auxiliary components, and improved usability. Additionally, air bubbles are easily removed in micro-/millifluidic plates with open microwell configurations.[156] Despite these benefits, the drawbacks of gravity-driven pumps include a limited range of flow rates and the inability to generate pulsatile flow.

The surface tension effect is another strategy utilized for fluid actuation, which is generated by the internal pressure difference between 2 liquid drops with unequal volume. According to the Young–Laplace equation, smaller liquid drops have higher internal pressure than larger ones, and this pressure difference drives the fluid and dictates the flow direction.[157] Similar to gravity-driven pumps, surface tension-driven pumps require only simple components (an inlet, an outlet, and a connection

microchannel) for system operation, rendering them easy to integrate into micro-/millifluidic plates with a high degree of parallelism. Surface tension-driven pumps also function as an open system with standardized interfaces, allowing automatic liquid filling at the inlet via robotic liquid handlers. Surface tension-driven pumps have already been used to support dynamic cell cultures in micro-/millifluidic plates for applications such as drug screening and disease diagnosis.[158–160] While they allow for the refilling of liquid to maintain continuous flow, surface tension-driven pumps are not suitable for long-term perfusion culture due to the limited volume of the liquid drops, which is typically in the microliter range.[161,162]

A capillary-driven pump operates on the principle of capillary action that allows fluid to move through narrow channels or porous materials. Based on the substrate material, capillary-driven pumps based on solid material and porous material have been widely used in micro-/millifluidic plates.[163] The capillary-driven pump was initially proposed in the context of a Si microfluidic chip.[164] In microfluidic systems, the spontaneous liquid transport through microchannels is governed by capillary forces arising from the interaction between liquid surface tension and solid interface geometry. Flow cessation occurs upon complete channel filling.[165] To address this limitation, absorbent matrices have been strategically implemented at channel termini to sustain continuous flow cycles. For example, when liquid is introduced into microwells of 96-well ELISA-optimized micro-/millifluidic plates, it propagates through spiral microchannels via capillarity. The terminal absorbent pads, exhibiting enhanced capillary potential compared with the microchannel network, continuously extract liquid from the system. This configuration enables sequential introduction of samples and reagents through the microchannels, thereby completing the analytical workflow.[166] In addition to solid materials, capillary-driven pumps have also been closely associated with the use of porous materials. Paper is a common-used porous material on which hydrophobic boundaries can be created by using techniques such as photolithography[167] and wax printing,[168–170] guiding fluid through patterned hydrophilic regions.[171] Except for paper, functionalized powders have also been demonstrated as ideal materials to form porous microzones on hydrophobic polymer plates.[172] The porous capillary-driven pump eliminates the need for narrow channels and prevents bubble entrapment.[165] However, it primarily relies on stochastic capillary flow within pore spaces, indicating that the inherent properties of porous materials, such as the porosity, will determine the fluid behaviors and cannot be regulated once the pumps are fabricated.[163,173]

Simplifying fluid handling challenges in micro-/millifluidic plate design through passive pumping strategies is an inevitable trend that will accelerate adoption. Advances in passive pumps will eliminate the need for auxiliary components and improve the integration of micro-/millifluidic plates. Passive pumps effectively lower the barrier to entry for the end-users, as they only require an automated liquid handler to operate. A prime example is the paper micro-/millifluidic plate used in POCT, where the liquid-driven mechanism is hidden, allowing users to focus solely on interpreting test results.[174,175] Another advantage of passive pump-based micro-/millifluidic plate is that they are easy to integrate, which helps establish standards for plate design, manufacturing, and testing within the industrial supply chain. This ultimately reduces costs and makes micro-/millifluidic plates more accessible.[1,176] While current active pumps offer superior fluid control and the ability to generate complex flow patterns, passive pumps gradually match these capabilities through the introduction of functional microstructures. For instance, continuous unidirectional perfusion with recirculation has been achieved in a gravity-driven flow system by incorporating supporting microchannels and passive valves.[177,178]

## 4. Applications for micro-/millifluidic plate

The development of standardized and high-throughput microfluidic devices aimed at enhancing the capabilities of end-users in biomedical research has always been a core goal for microfluidic engineers. The emerging micro-/millifluidic plate is highly compatible with these criteria, laying a foundation for its wide adoption throughout the biomedical community. Meanwhile, finding killer applications is equally important to trigger the broad adoption of these micro-/millifluidic plates. By definition, a killer application describes a product that has higher desirable properties than its predecessor and thus becomes indispensable.[179,180] In this perspective, micro-/millifluidic plates used in OoC and POCT may become the killer applications that propel microfluidics into the biomedical field (Figure 4).[18,181,182]

### *4.1 OoC*

A preclinical study is a necessary stage in the drug development pipeline, where the primary goal is to evaluate the efficacy and safety of drug candidates to eliminate ineffective and highly toxic candidates as soon as possible. To do so, the drug candidates undergo a series of stringent tests in 2D static cell cultures and animal models.[183] However, more than 80% of drug candidates fail to demonstrate efficacy and safety in clinical trials,[184] indicating the current models often cannot faithfully predict human responses to these drug candidates.[185] The limitations of these models have prompted the urgent need to develop models with better predictive ability. To meet this need, OoC systems were hatched through the convergence of microtechnology and biology.[186–188] On the one hand, the OoC systems recapitulate key tissue- and organ-level functions by mimicking physiologically relevant microenvironments in microfluidic devices. On the other hand, the species difference can be eliminated by using cells of human origin in OoC systems. OoC is a promising in vitro model bridging the gap between traditional 2D cell cultures and animal models. Despite their promise, most OoC systems currently operate at very low throughput, allowing only a limited number of replicates at a time.[189] Consequently, it is difficult to meet the requirements of practical pharmaceutical applications that need to screen thousands of drug candidates in a short time.[190] Developing novel OoC systems based on microtiter plate format can effectively increase the number of replicates per plate, promote the faster transition from personalized to standardized design, and enhance the repeatability and reproducibility of the system.

Up to now, micro-/millifluidic plates have been utilized in the development of both single-organ and multiorgan systems, depending on the target applications.[191–193] Single-organ micro-/millifluidic plates are commonly used to study specific tissue and organ functions without involving the complexity of other organ systems. For example, the liver is the largest internal organ in the human body. It performs various essential biological functions, such as the synthesis of proteins and lipids, secretion of bile, and metabolism of drugs.[194] However, hepatocytes cultured as monolayers typically exhibit nonpolarized and rapidly lose their liver-specific functions.[195] The PhysioMimix micro-/millifluidic plate integrates 12 chips in parallel, enabling the

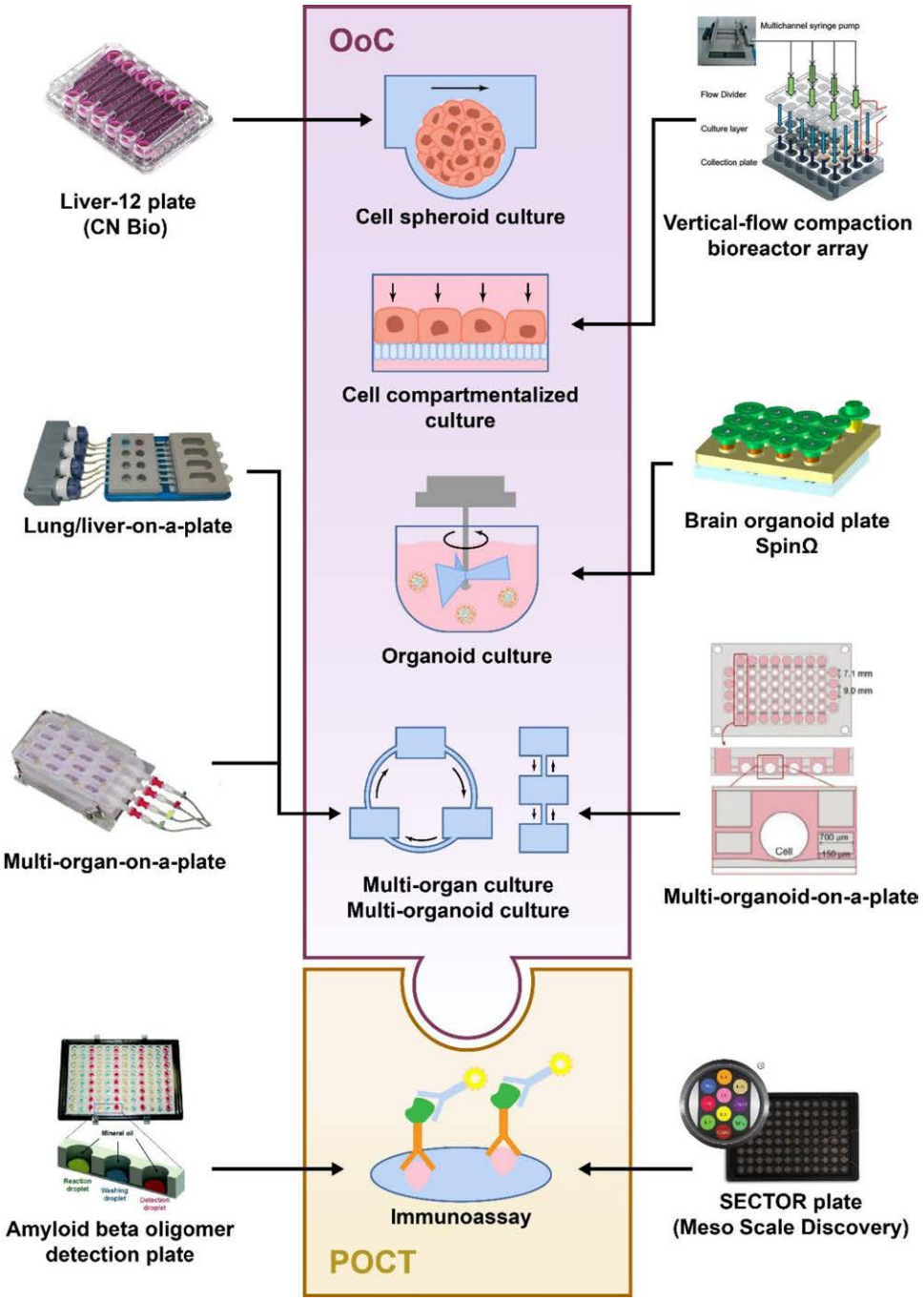


**Figure 4.** Typical applications of micro-/millifluidic plates for biomedical research including OoC and POCT.

dynamic culture of hepatocytes to maintain their phenotypes and functions by providing continuous oxygen and nutrients as well as biomechanical stimuli through the fluid shear stress.[196] Additionally, by replacing the laminar flow with vertical flow, the high flow resistance of porous membranes will induce pressure inside culture chambers, which exerts compaction forces on hepatocytes. This mechanical compaction simulates the pressure experienced by hepatocytes inside the abdominal cavity. As a result, the hepatocytes exhibit accelerated repolarization, in vivo-like cuboidal morphology, and better liver metabolic and synthetic functions.[197] Moreover, biophysical cues like arterial strain waveform[198] and oxygen tension[199] have also been proven to play an important role in regulating the phenotypes and functions of vascular smooth muscle cells and alveolar basal epithelial cells, respectively. Except for biochemical and biophysical cues, the spatial arrangement of the cellular structure also has a significant impact on regulating the microenvironment of the embedded cells.[200,201] By converging OoC and dielectrophoretic bioassembly, cells can be spatially arranged to form liver lobules and then transferred and cultured in 96-well micro-/millifluidic plates.[202] Similarly, advanced extrusion-based bioprinting[203,204] and acoustic bioassembly[205–207] techniques have also been demonstrated to construct functional tissues with predetermined cellular structures in micro-/millifluidic plates, such as cerebral cortex, liver lobule, cardiac, and tumor.

Different from single-organ micro-/millifluidic plates, multiorgan micro-/millifluidic plates are suitable for investigating the interactions between different tissues and organs.[208] To investigate the potential toxicity linked to metabolism by the liver, at least one other OoC is connected to the liver-on-a-chip. For example, a lung–liver micro-/millifluidic plate has been developed to assess both acute and chronic toxicity of pathogens, where lung tissues are cocultured with liver tissues. The micro-/millifluidic plate had 4 multiorgan chips, and each chip comprised 2 adjacent compartments to house the lung and liver tissues. Peristaltic pumps were employed to drive the culture medium in a circulatory manner. The liver's detoxification ability was validated using aflatoxin B1 (AFB1), demonstrating that cocultured liver tissues reduced the AFB1 toxicity in lung tissues, indicating liver-mediated detoxification decreased lung tissue cytotoxicity[209] In addition to toxicity screening, liver-target organ micro-/millifluidic plate also opens possibilities for testing prodrugs that only become biologically active after liver metabolism. The bioactivation process for prodrugs named capecitabine and cyclophosphamide targeting colorectal cancer has been recapitulated in liver-colorectal cancer micro-/millifluidic plates.[41,110] In these 2 micro-/millifluidic plates, capecitabine and cyclophosphamide were transformed into metabolites 5-fluorouracil and 4-hydroxycyclophosphamide respectively, and then acted on colorectal cancer located at the compartments downstream.

Different from OoC, organoid follows intrinsic developmental programs and forms by self-organization and differentiation of stem cells.[210–212] Organoids represent a complementary yet distinct approach to achieving the same goal as OoCs: replicating key aspects of native organ structures and functions in vitro.[213–215] The convergence of OoC in organoid is leading to technological advances that allow proper biochemical and biophysical microenvironments and consequently overcome the limitations of this nascent technology such as lack of reproducibility, significant heterogeneity, and limited level of maturity and function.[216,217] As a striking example, 3D-printed miniaturized spinning bioreactors, called SpinΩ, were developed to fit standard 12-well microtiter plates and used for generating forebrain organoids with high reproducibility as well as minimized heterogeneity and variability.[218] Above the cover, a single electric motor drove 12 spinning shafts through a set of interconnected gears. The parameters of spinning shafts and leaves were systematically optimized to dynamically culture organoids in the suspension medium while preventing their aggregation at the center of each microwell. The forebrain organoids recapitulated critical features of human cortical development, including progenitor zone organization, neurogenesis, and especially a distinct human-specific outer radial glia cell layer. These organoids could also present pathologic features of microcephaly when infected with Zika virus. Together, SpinΩ provided a versatile system for modeling human brain development and disease and for drug screening. Furthermore, OoC also provides opportunities to mimic biological interactions at higher levels of organization, which remains a critical challenge in current organoids. In practice, liver, intestinal, and stomach organoids were cultured in 3 adjacent compartments connected via microchannels. Gravity-driven flow was generated by employing a perfusion rocker and further allows communication between different organoids. Bile acid homeostasis regulated by the interactions between liver organoid and intestine organoid is proved in such a multiorganoid micro-/millifluidic plate.[219]

### 4.2 POCT

POCT plays a vital role in the improvement of clinical outcomes in medical healthcare management.[220] In 2022, the global market of POCT has reached US$43.2 billion, with projections to grow to US$72.0 billion by 2027. Lab-on-a-chip (LOC) is considered one of the important technological drivers to transform the POCT industry. Especially the micro-/millifluidic plate with high throughput and sensitivity is now paving the way for the next generation of POCT platforms.[221] For example, an ELISA micro-/millifluidic plate based on a 96-well format has been developed for immunological detection of Staphylococcal Enterotoxin B at concentrations as low as 0.1 ng $mL^{-1}$.[222–224] The plate contained 3 layers of functional structures for sample loading, detection, and removal, and thus could provide a sample-to-answer process for immunological assays. Similarly, a droplet-based magnetic bead immunoassay was proposed to simplify washing steps and reduce sample or reagent consumption during the ELISA testing process. The immune reaction occurred within a small droplet in the reaction microwell and the antibody-conjugated magnetic beads were driven and manipulated by an XY-motorized magnet array stage to accomplish the following washing and detection step in the other 2 connected microwells, respectively. By using such a micro-/millifluidic plate, less than 5 pg/mL synthetic amyloid beta oligomers were detected as a model analyte for the early diagnosis of Alzheimer disease.[102] To further increase the detection throughput of the device, Meso Scale Discovery launched a multiplexed electrochemiluminescent micro-/millifluidic plate that enabled to simultaneously measure up to 10 analytes in the same 96-well. The plate also enabled highly sensitive wash-free sandwich immunoassays in complex sample matrices by using SULFO-TAG labels on the antibody, which emitted light when electrochemically stimulated at the carbon electrode surface.[225]

### 4.3 Other applications

In addition to the mainstream applications aforementioned, some micro-/millifluidic plates are also applied in cell biology for purposes such as cell transfection,[226] cell proliferation,[134] and cell agglomeration.[227] Cell transfection involves the deliberate introduction of exogenous molecules into living eukaryotic cells.[228] Compared with classical chemical transfection strategies, electroporation offers a nontoxic, cost-effective, and efficient alternative. Despite its advantages, traditional electroporation systems are not well-suited for high-throughput experiments due to their cumbersome manual operations. To meet this challenge, a standard 96-well suspended-drop electroporation device was developed in which biomolecules were able to be introduced into difficult-to-transfect cell types, such as primary neurons and differentiated neutrophils.[229] This device contained 2 machined gold-coated copper pieces and each of them had 96 electrodes. Vertical electrode pairs created by these plates function as suspended electroporation chambers, allowing for rapid and high-throughput cell transfection. However, the electroporation parameters for each chamber were not customizable. This issue could be mitigated by integrating a PCB into the suspended-drop electroporation system.[226] The PCB incorporates 8-row electrodes and 12-column electrodes mounted on its top and bottom surfaces, which are connected to 2 electrodes within each electroporation chamber. This modification provides individually addressable capabilities, enabling the transfection of various cell types with a wide range of biomolecules.

## 5. Commercialization for micro-/millifluidic plate

The degree of innovation and adoptability are both crucial for the commercial success of a technology.[230] Although innovative microfluidics has offered several solutions for biomedical research, few products have achieved widespread adoption and commercial success.[231] One major aspect that hinders the growth of microfluidics is the lack of standards necessary for harmonizing microfluidic engineers and end-users. Micro-/millifluidic plates offer a promising tool to surmount the barriers to commercialization. The chip design based on the microtiter plate format not only follows the original commercial standards but also attracts massive loyal users of this classic device. Moreover, the micro-/millifluidic plates target niche markets where other existing technologies cannot meet the needs of the users and thus create a foundation for successful commercialization.

Numerous companies have now participated in market competitions (Table 4). Among them, MIMETAS, founded in 2013, is one of the representative companies, which occupies the commercial space through its unique technological advantages. MIMETAS successfully raised US$21.0 million in a Series B funding round in 2018. Currently, the company has launched 4 OrganoPlate platforms (OrganoPlate 2-lane 96,[232–235] OrganoPlate 3-lane 40,[236,237] OrganoPlate 3-lane 64, and OrganoPlate Graft[238]), supporting up to 96 tissue and organ models on a single micro-/millifluidic plate. The standardized microtiter plate format makes the OrganoPlate compatible with robotic liquid handlers and broad imaging and testing equipment. In all types of micro-/millifluidic plates, the phaseguides are the unique core microstructures that enable precise and barrier-free definition of hydrogels and cells in spatial based on meniscus pinning effect,[239,240] and consequently improve the ability of the platform in studying cell–cell interactions,[241] migration,[242,243] invasion,[244] transport,[245] and angiogenesis.[236,246] Moreover, gravity-driven pumps are employed and a commercial perfusion rocker, OrganoFlow, is used together to provide continuous medium flow with minimal settings required. Based on these advantages, the OrganoPlate enables the construction of perfused tubules (eg, intestinal epithelium tube,[247–249] renal tubule,[250] and blood vessel[251]) and barrier tissues (eg, blood–brain barrier,[252] glomerular filtration barrier,[253] and blood–retinal barrier[254]) without artificial membranes. These advanced models will further be used in investigating drug adsorption, the loss of barrier function caused by drug toxicity, and the permeability of compounds.

Except for MIMETAS, companies like 4Design Biosciences, Draper, and CN Bio have also developed their micro-/millifluidic plates with prominent advantages. The 4Design Biosciences Vascularized Micro-Organ Platform supports 16 parallel chips with 3 tissue models in series as replicates. The chip allows clear localization and visualization of cell interactions, such as the vascularization of tumors and the perfusion of the medium through the microvascular network.[255,256] Draper's PREDICT96 employs 192 integrated pumps that allow for exquisite control of upper and lower microchannel flow conditions

**Table 4**

**Summary of micro-/millifluidic plate start-ups and their core products.**

| Company | Selected products | Applications |
|---|---|---|
| MIMETAS | OrganoPlate 2-lane 96<br>OrganoPlate 3-lane 40<br>OrganoPlate 3-lane 64<br>OrganoPlate Graft<br>OrganoReady products (latest trade name) | OoC |
| CN Bio | Liver-12 & -48 plates (MPS-LC12 & MPS-LC48)<br>Barrier Plate (MPS-T12)<br>Dual-Organ Plate (MPS-TL6) | OoC |
| Draper | PREDICT96 | OoC |
| 4Design Biosciences | Vascularized Micro-Organ Platform | OoC |
| CellAsic | CellASIC ONIX Micro-/millifluidic plates | OoC |
| AMSBIO | Reinnervate Perfusion Plate<br>Alvetex Scaffold Wellplates | OoC |
| InSphero | Akura 96 or 384 Plate | OoC |
| 3D Biomatrix | Perfecta3D Hanging Drop Plates | OoC |
| DAXIANG | IBAC (Integrated Biomimetic Array Chip) M<br>IBAC (Integrated Biomimetic Array Chip) 0<br>IBAC (Integrated Biomimetic Array Chip) S1 | OoC |
| CytoNiche | 3D FloTrix microSPIN | OoC |
| Neurosetta | RosetteArray | OoC |
| MyCartis | MyCartis Evalution | POCT |
| QuantaMatrix | QMAC-dRAST Panel<br>QMAC-DST PLUS Panel | POCT |
| Meso Scale Discovery | SECTOR Plates<br>QuickPlex Plates | POCT |
| Microfluidic ChipShop | Fluidic 102<br>Fluidic 600<br>Fluidic 627 | Cell-based assays, hybridization assays, chemical synthesis |
| Unchained Labs | Lunatic<br>Stunner | Protein and nucleic acid quantification, gene therapy |
| Anatrace | High-Throughput Crystal Former Plate (CF-HT2) | Crystal growth |
| m2p-labs | Microfluidic FlowerPlate<br>Microfluidic Round Well Plate | Synthetic biology, clone screening, media optimization, bioprocess development, anaerobic fermentations |

for each organ model. Sensors and probes in the plates enable real-time monitoring of tissue functions and evaluating the response to drug exposures.[257,258] PhysioMimix multichip plates developed by CN Bio support up to 48 tissue scaffolds as single-tissue replicates[259] or interconnected in multitissue circuits as demonstrated with tissue scaffolds and Transwell inserts.[260] These micro-/millifluidic plates are versatile platforms with immense potential to enhance the capability in disease modeling, drug safety evaluation, and pharmacokinetics study. Especially a lung-on-a-chip based on PREDICT96 has been successfully demonstrated in investigating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and replication, and further evaluating the antiviral efficacy of 3 drugs named Paxlovid, Molnupiravir, and Remdesivir in COVID-19 treatment.[261,262]

## 6. Challenges and perspectives

According to Emergen Research, the global microfluidics market reached US$20.14 billion in 2021 and is projected to grow at a compound annual growth rate of 16.1% through 2030. By 2030, the market size is expected to reach US$77.28 billion, with the biomedical field being a key driver of this growth. Micro-/millifluidic plates are emerging as powerful tools for biomedical research, combining the high throughput and standardized format of microtiter plates with the advanced functionalities of micro-/millifluidic devices. However, several challenges need to be addressed to fully unlock their potential and facilitate broader adoption.

### 6.1 Standardization of micro-/millifluidic plates

Existing standards, such as ANSI/SLAS, ISO, and ASTM standards, are loosely applied to micro-/millifluidic plates. These standards primarily address plate designs and general laboratory practices but do not fully address the unique challenges of micro-/millifluidic systems, such as fluid dynamics, surface chemistry, and integration with external systems. As a result, micro-/millifluidic plates are still in the early stages of standardization. Future efforts should focus on refining existing standards and developing new, comprehensive guidelines that cover the entire lifecycle of micro-/millifluidic plates.[263] Establishing consistent performance evaluation criteria and quality control standards will be crucial to ensure the reproducibility, reliability, and scalability of microfluidic systems. A collaborative effort between researchers, industry leaders, and standardization bodies is necessary to address these needs.

### 6.2Materials and manufacturing strategies

The materials and manufacturing strategies for micro-/millifluidic plates have not been standardized. During the research phase, efficiency and ease of fabrication are prioritized to facilitate rapid prototyping and experimentation. However, transitioning to large-scale production requires considerations such as market demand, cost efficiency, and manufacturing scalability. These differing priorities often result in discrepancies in material selection and fabrication techniques, making it challenging to bridge the gap between laboratory development and commercial viability.

Silicone rubber, particularly PDMS, is widely used in the fabrication of micro- and millifluidic plates due to its optical transparency, gas permeability, and biocompatibility[264]. However, the tendency of PDMS to absorb small molecules can affect the temporal and spatial concentrations of chemicals, compromising the reliability of experimental results, particularly in clinical diagnosis and drug testing.[265–267] Furthermore, the existing fabrication techniques for PDMS-based plates are unsuitable for large-scale production due to challenges in scaling-up manufacturing process.[143]

Thermoplastics like polystyrene (PS) and cyclic olefin copolymer are promising alternatives for both laboratory experiments and commercial production. Fabrication techniques such as hot embossing,[268] laser engraving,[269] and micromilling[270] can optimize microstructures during the laboratory stage. Once the final design is determined, injection molding can enable rapid prototyping for industrial-scale production.[271] However, injection molding is unsuitable for plates with complex microstructures or functional features due to limitations in material flexibility and filling narrow, deep cavities.[272] Advances in 3D printing technology offer solutions to these challenges by enabling the rapid and cost-effective fabrication of intricate structures, enhancing design flexibility, and accelerating prototyping.[273,274] Future innovations in high-resolution printing and multimaterial integration will be key to bridging the gap between research prototypes and commercial products.

### 6.3 User accessibility and integration

The interaction between end-users and micro-/millifluidic platforms is critical for their adoption.[275] Many current plates rely on multiple external devices, such as liquid-driven pumps, microscopes, and computers, which require professional skills and experience to operate. This reliance complicates automation and scalability.[276] Future efforts should focus on integrating micro-/millifluidic plates with automated experimental platforms and intelligent analysis systems. By incorporating advanced sensors and real-time data analysis, these systems can continuously acquire, process, and interpret complex data, enabling intelligent adjustments during experiments without human intervention.[277,278] Artificial intelligence (AI) can optimize data collection, analysis, and decision-making, significantly enhancing automation, accelerating workflows, and improving accuracy.[279–282] For instance, Tebon et al. and Al Shihabi et al.[283,284] developed a high-throughput drug screening platform combining bioprinting, high-speed live cell interferometry (HSLCI) imaging, and machine learning. This platform continuously monitors bioprinted tumor organoids via HSLCI imaging, while AI-driven segmentation and tracking enable precise, label-free mass measurements and automated analysis.[283,284] Future AI-driven micro-/millifluidic plates will benefit from more intuitive tools and standardized algorithm selection guidelines. Advances in explainable AI and automated model training will further enhance AI's reliability and accelerate its adoption in high-throughput screening and precision analysis.[285] Additionally, replacing multiple external devices with smaller, integrated components within the micro-/millifluidic platform will streamline workflows, reduce the need for specialized skills, and make the technology more scalable and accessible.

### 6.4 Future directions

Significant progress remains to be made before micro-/millifluidic plates can be fully integrated into the biomedical research pipeline. Microfluidic engineers have already made strides in design strategies, materials, fabrication techniques, and liquid-driven systems, which are essential for expanding the adoption

of this technology. These efforts aim to build a broad user base and facilitate academic advancements. Moreover, micro-/millifluidic plates have advanced beyond the proof-of-concept stage and are now positioned to demonstrate their value in key biomedical applications, such as drug development and clinical diagnostics.

## Conflicts of interests

The authors declare that they have no conflicts of interest.

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## Author contributions

Longjun Gu: Conceptualization, writing—original draft, writing—review & editing, visualization. Peidi Liu: Visualization, writing—review & editing. Wen Zhao and Yuhang Fan: Writing—review & editing. Yuwen Wang: Visualization. Pu Chen: Conceptualization, funding acquisition, supervision, writing—review & editing.

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