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Assembly of Multi-Compartment Cell Mimics by Droplet-Based Microfluidics

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In recent years, there has been a growing interest in multi-compartment systems as a means of developing materials that mimic the structure and function of biological cells. These hierarchical systems, including artificial cells and cell-like reactors, can efficiently perform biochemical tasks by exploiting compartmentalization inspired by biological systems. However, the bottom-up design of cell mimics presents significant challenges due to the need for precise and efficient assembly of components. This short review examines recent advances in droplet-based microfluidics (DBM), which has emerged as a powerful technique for creating cell-like systems with multi-compartment architectures, precise composition, and biomimetic functionality. DBM has proven to be a reliable method for generating populations of cell-mimics with a compartment-in-compartment structure, some of which have adaptable properties that resemble the dynamic properties of natural cells. Notable examples will be discussed to illustrate how droplet-based microfluidics provides a versatile approach to create, manipulate, and study cell-mimics.

1. Introduction

Cell-mimics are multi-compartment systems that reproduce the structure and function of natural cells. They represent an important step toward the development of intelligent, autonomous, and modular life-like systems.[1] Cell-mimics can be tailored to efficiently perform diverse biochemical tasks and can be designed to interface with natural cells, bridging the gap between materials science and biology.[2] A basic cell-mimic design consists of a primary compartment, such as a polymer or lipid vesicle, that encloses various structural and functional components, including subcompartments, cytoskeletons, nucleic acids, proteins, and enzymes. However, as the complexity of components increases, a major obstacle becomes the ability to replicate the multicompartmental characteristics found in eukaryotic cells while maintaining precise control over the internal composition. Even the simplest compartment-in-compartment architecture, such as a liposome-in-liposome, poses significant assembly challenges, and the method of assembly becomes critical as it directly influences the level of complexity that can be achieved in a cell-mimic. Existing methods such as electroformation,[3] film hydration[4] and emulsion transfer[5] can generate multi-compartment structures, but often suffer from drawbacks such as low reproducibility, reduced production yield and limited control over the composition of these structures. On the other hand, droplet-based microfluidics (DBM) provides a powerful and versatile method for constructing cell-mimics. This method involves the precise formation of droplets by manipulating different flows within micro-sized polydimethylsiloxane (PDMS) or glass channels, allowing the precise assembly of droplets and vesicles.[6] The development of microfluidic devices using PDMS chip technology and glass capillaries has facilitated the rapid production of droplets at high rates (kHz) while ensuring precise size control and monodispersity. These advantages have positioned DBM as a robust technique for engineering hierarchical systems with intricate and precise compartment-in-compartment architectures.[7–9]

DBM not only facilitates the assembly of cell mimics, but also enables their manipulation and analysis within the controlled environments provided by lab-on-a-chip devices. For example, cell-mimics generated in an assembly chip can be seamlessly transferred to a test chip, where their performance and properties can be directly evaluated without the need for manual transfer to separate vessels.[10] This integration of assembly, manipulation, and analysis within a single microfluidic platform streamlines the workflow and increases the efficiency of studying artificial cells.[11,12] In general, droplet-based microfluidics (DBM) enables precise manipulation of experimental variables in the creation of cell-mimics. It provides precise control over factors such as internal composition and

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architecture.[13,14] This control extends to post-formation stages by allowing adjustment of the composition of the external medium in which the cell-mimics are studied. In general, DBM allows researchers to fine-tune and study the characteristics of cell-mimics with a high degree of accuracy.

This brief review is focused on representative examples of cell-like structures that were constructed using DBM methodologies. The post-assembly architecture and functionality of these cell-mimics are discussed, with particular attention paid to the role of hierarchical organization in the regulation of biocatalysis and adaptive internal structure. Although hierarchical structures can be achieved with different materials, we will focus on vesicle-based systems in which the main compartment is a polymer or lipid vesicle.

2. Cell-mimics incorporating membrane-based sub-compartments

Cell-mimics can be designed to mimic the multi-compartment architecture observed in eukaryotic cells. These designs typically involve the inclusion of subcompartments (<1 μm) as organelle-like modules within a larger main compartment (>1 μm), as shown in Figure 1. In addition to serving as reservoirs for active molecules such as enzymes, the properties of these compartments themselves play a critical role in defining the functionality of the cell mimic. Compartments that possess adaptable properties, such as stimuli-responsive self-assembly, contribute to the inherent adaptability of the cell-mimic. Throughout this review, we will use the terms "static" or "dynamic" to emphasize the characteristics of each type of cell-mimic (Figure 1b). Thus, cell mimics with adaptable or responsive structures will be referred to as dynamic, while those with unresponsive architectures will be referred to as static. The efficient and reproducible encapsulation of compartments using DBM greatly facilitates the creation of cell-mimics with varying degrees of structural adaptability.

Figure 1a illustrates a commonly used PDMS chip design capable of producing polymer and lipid vesicles, which are typically used as the main compartments of cell-mimics. The process involves dissolving or dispersing the cargo in an aqueous phase (W1). This phase is then emulsified with an organic phase (OP) carrying the main compartment components. The obtained water-in-oil emulsion is subsequently dispersed in another aqueous phase (W2), leading to the formation of water-in-oil-in-water droplets that encapsulate the cargo. Removal of the oil phase leads to the formation of vesicles, completing the formation of cell-mimics.[15] One notable advantage of DBM is that the cargo within the droplets can also be another compartment, allowing for the creation of multi-compartment architectures. This method was used by researchers in the Weitz group who used a microfluidic capillary device to create cell-mimics with a polymersome-in-polymersome architecture (Figure 2).[16] The number of subcompartments was controlled by adjusting the flow rate of the innermost phase and the inner diameter of the collection capillary. This multi-compartment architecture facilitated the sequential release of encapsulated materials by controlling the rupture of the compartments in various ways, such as using an alcoholic solution, applying mechanical stress, or inducing osmotic shock.

A recent example from the Robinson group describes the development of static cell-mimics for biocatalysis with a liposome-in-liposome architecture (Figure 3).[17] In their work,

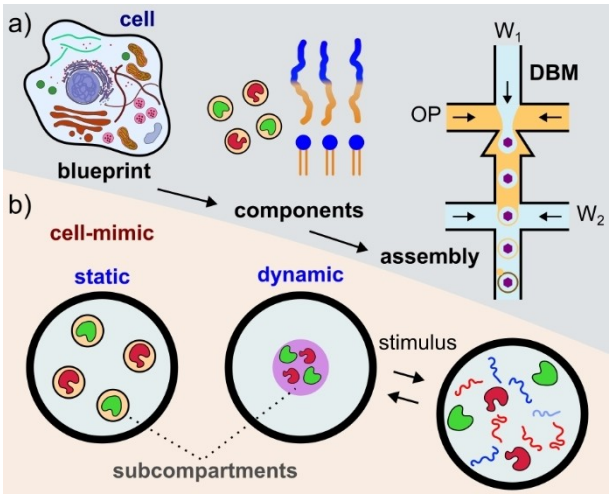

Figure 1. Formation of multicompartmentalized systems through droplet-based microfluidics (DBM). (a) Bio-inspired bottom-up assembly of cell-mimics by DBM. The schematic of the assembly step shows a typical PDMS chip design for the production of double emulsion droplets. (b) Cell-mimics with static and dynamic hierarchical organization. Static: the number and composition of compartments remain unchanged. Dynamic: the number and composition of compartment vary based on external conditions.

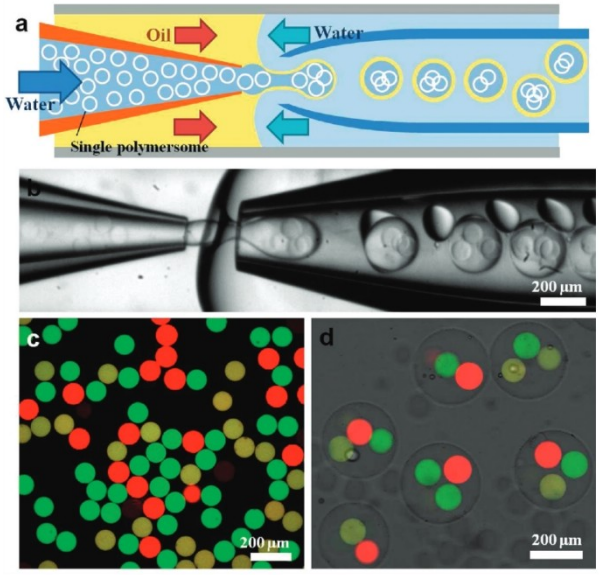

Figure 2. Formation of polymersome-in-polymersome cell-mimics by DBM. (a) Schematic of a microfluidic capillary device. (b) Light microscope image showing the formation of multi-compartment cell-mimics. (c) Confocal microscope image of individual polymer vesicles containing different dyes. (d) Confocal microscope image of dye-loaded compartments encapsulated within polymer vesicles. Adapted with permission from ref. [16]. Copyright 2011 American Chemical Society.

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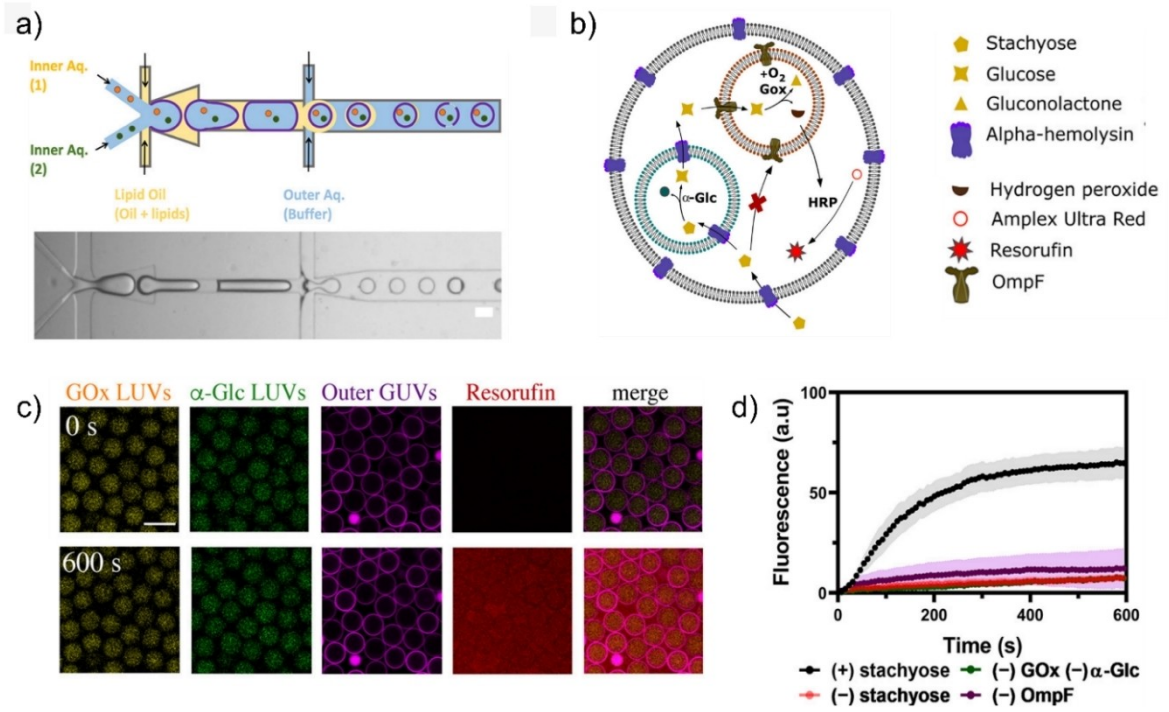

Figure 3. Lipid-based cell-mimics obtained by DBM. (a) Chip design and composition of fluids involved in the production of the cell-mimics. (b) Schematic depicting the structure and functionality of resulting cell-mimic. The scheme shows a cascade reaction involving distinct enzymes present within the different compartments. (c) Confocal microscopy showing the cascade reaction progress. The images reveal the localization of enzymes, lipid membranes, and reaction product. (d) The plot presents the reaction kinetics of the cascade reaction. The formation of resorufin is only significant in the presence of the substrate (Stachyose). Scale bars: 100 μm. Adapted with permission from reference [17]. Copyright 2021 American Chemical Society.

large unilamellar vesicles (LUVs) containing different enzymes were used as subcompartments and encapsulated within giant unilamellar vesicles (GUVs) using DBM. To enable catalytic reactions between the subcompartments, the researchers introduced pore-forming proteins into the lipid membranes, allowing the diffusion of small molecules and substrates between the compartments, mimicking the functionality of natural cells. By integrating different pore proteins, the researchers achieved control over the sequence of reactions by exploiting the size selectivity of the pores. In the context of cell-mimics, droplet-based microfluidics offers remarkable flexibility in the choice of compartments and sub-compartments. For example, Zhang and colleagues, used a one-step microfluidic method for the formation of multi-compartment alginate microgels encapsulating natural cells.[18] This example illustrates the versatility of DBM methods to create hybrid hierarchical systems that bridge soft matter and biology.

In particular, nanocapsules have attracted considerable attention as subcompartments for cell-mimics due to their desirable compartmentalization properties, including size control, high encapsulation efficiency, surface functionalization, and tunable permeability.[19] A recent example from the Landfester group describes the use of core-shell silica nanocapsules as nanoreactors within cell-mimics constructed using polybutadiene-b-polyethylene oxide (PB-PEO) polymersomes (Figure 4).[20] The enzyme-loaded silica nanocapsules (nanoreactors), measuring approximately 300 nm in diameter, featured a porous silica shell permeable to small molecules. These nanoreactors were subsequently encapsulated in giant polymersomes using DBM (Figure 4 a–b). The researchers used oleyl alcohol as the organic phase, which exhibited excellent compatibility with PB-PEO and did not require additional surfactants to control dewetting. This robust approach facilitated the rapid formation of polymersomes with internal nanoreactors within seconds of exiting the microfluidic device. The nanoreactors were able to perform a cascade reaction to produce resorufin (Figure 4 c–d). In general, The use of enzymatic nanoreactors as subcompartments is an effective strategy to create cell-mimics with catalytic properties.[21]

3. Cell-mimics incorporating membraneless sub-compartments

A recent approach to engineering multicompartmentalized cell-mimics involves the utilization of liquid-like coacervate droplets as membraneless sub-compartments. Coacervates have emerged as versatile candidates for replicating the dynamic nature of biomolecular condensates in eukaryotic cells.[22] Coacervates form through the liquid-liquid phase separation (LLPS) of macromolecules, proteins, or nucleic acids, into dense, molecularly crowded liquid droplets dispersed in a dilute phase. One key function provided by coacervates is the spatial and temporal localization of biomolecules through selective sequestration and concentration. This function offers an effective

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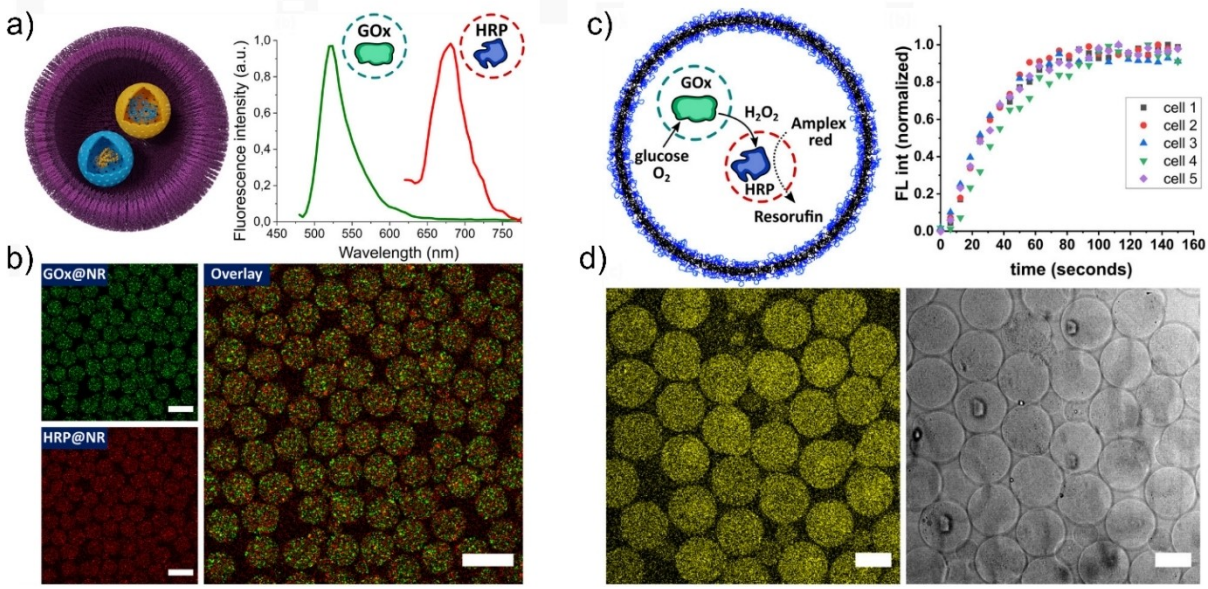

Figure 4. Silica nanocapsules as subcompartments in polymer-based cell-mimics. (a) Left: schematic representation of the cell-mimic. Silica nanoparticles carrying enzymes, acting as nanoreactors, are encapsulated within a polymer vesicle. Right: UV-vis spectra of nanoreactors. GOx-containing nanoreactors were tagged with FITC and HRP-nanoreactors with CY5. (b) Confocal microscopy images of nanoreactors showing their distribution within the polymer vesicles. (c) Left: scheme illustrating an enzymatic cascade reaction carried out by the cell-mimics. Right: fluorescent intensity of resorufin, the product of the cascade reaction. (d) Left: confocal microscopy image of resorufin distribution inside the cell-mimics after completion of the cascade reaction. Right: bright-field image of cell-mimics. Scale bars = 50 μm. Adapted from ref. [20]. Copyright 2021, with permission from Wiley-VCH.

means to regulate the internal chemistry and architecture within cell-mimics, resembling the function of biomolecular condensates in eukaryotic cells.[23,24]

DBM methods offer a significant advantage in the design and analysis of dynamic systems, such as coacervate-based cell mimics. They allow precise tuning of critical variables such as droplet volume, interfacial areas, and component concentrations within well-defined compartments.[25–27] A notable example was described by the Dekker group.[28] The study describes the use of liposomes as the main compartments (Figure 5a). The precise incorporation of components required for coacervation was achieved through droplet-based microfluidics, enabling high encapsulation efficiency and monodispersity.

To create the coacervate subcompartments, positively charged poly-l-lysine (pLL) was encapsulated in giant unilamellar vesicles (GUVs). To prevent premature coacervation, the negatively charged component adenosine triphosphate (ATP) was introduced through a chamber integrated into the microfluidic chip design. The inclusion of α-hemolysin pores in the liposome membrane facilitated the diffusion of ATP, resulting in the formation of coacervates with a size of approximately 1–2 μm within a few minutes (Figure 5b). The precise encapsulation achieved using DBM allowed the size of the coacervates to be regulated by controlling the concentration of pLL within the liposomes (Figure 5c). The precise encapsulation of coacervates by DBM in liposomes has also been used to study coacervate-membrane interactions with a high degree of control.[29]

The dynamic formation of sub-compartments allows the development of more complex systems, offering a strategy to create materials with adaptive properties. A notable attribute of coacervate-based compartments is their ability to utilize dynamic compartmentalization for the control of biochemical reactions within cell-mimics. This capability was demonstrated by the Tang group.[30] In their study, coacervate-forming components, namely polylysine (pLL) and ATP, were encapsulated within liposomes using DBM at a pH above 10.5 to prevent premature coacervation. The internal coacervation process could be regulated by decreasing the pH below the pKa of pLL, causing the polymer to acquire a positive charge that triggered coacervation with the negatively charged ATP. This mechanism allowed for the reversible assembly and disassembly of coacervates in response to pH changes. In this approach, all components were precisely encapsulated within the lipid vesicle, while the signal molecule could cross the vesicle membrane. The same study also described the use of dynamic coacervation as a mechanism to control enzymatic reactions by manipulating the local concentration of enzymes and substrates. Droplets obtained by DBM can be used as compartments that allow the precise study of the dynamic behavior of coacervates in pL volumes, providing important insights into the variables that influence phase separation. Linsenmeier and colleagues used this strategy to show that the timescale of phase separation of synthetic organelles formed by the DEAD-box ATPase Dhh1 and RNA decreases linearly with increasing compartment volume.[31]

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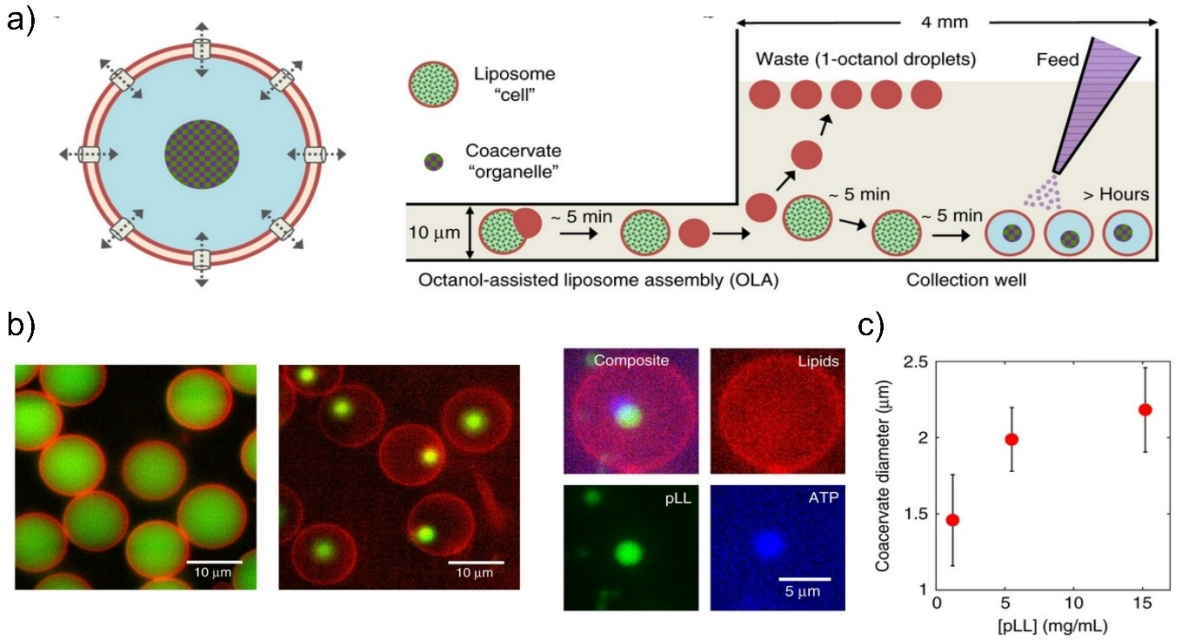

Figure 5. DMB for assembling cell mimics with dynamic subcompartments. (a) Schematic of the cell mimic. Prior to coacervation, only one of the two coacervation components is present inside the vesicles. The second component is introduced from the outside and enters the cell-mimic through a pore protein. The microfluidic chip has an opening that allows waste to be removed and components to be introduced. (b) Cell mimics before (left) and after (middle) coacervation induced by the addition of external ATP. The encapsulated component pLL is labeled with FITC (green). The different components of the cell mimic are shown in the right panel. (c) The size of the coacervates can be controlled by the concentration of pLL inside the cell mimics. Adapted from reference [28]. Copyright 2019, with permission from Springer Nature.

4. Summary and outlook

Droplet-based microfluidics has emerged as a robust and versatile method for constructing cell-mimics, expanding the range of building blocks and components that can be used. This advancement has enabled the incorporation of droplets, vesicles, coacervates, nanocapsules, and hydrogels into the toolbox for creating sophisticated cell-mimics. In addition, droplet-based microfluidics provides precise control over the composition and structure of cell-mimics, facilitating detailed studies of complex behaviors such as cascading reactions and adaptive restructuring. A key advantage of DBM is the precision achieved, which greatly reduces variability between individual cell-mimics, improving data analysis and reproducibility. This precise assembly also allows the programming of cell-mimics for specific tasks, such as the integration of enzymes and nanoparticles to design new hybrid chemical systems and expand the possibilities in catalysis.

Another notable strength of droplet-based microfluidics is its high-throughput capability, which enables the production of cell-mimics at kHz rates. This is particularly advantageous for applications that require large quantities of cell-mimics, including studies involving communication between cell-mimics or with biological cells, and the exploration of emergent properties in large populations of communicating cell-mimics.

Finally, by incorporating organelle-like subcompartments, droplet-based microfluidics offers precise control over the spatial organization of enzymatic reactions, introducing a new level of chemical control comparable to natural cells. Thus, the use of cell mimics as a platform for designing the next generation of synthetic biochemical systems represents a breakthrough approach at the intersection of biology and materials science. Despite well-established advances in DBM technology, several challenges remain. These include high-throughput screening of large droplet populations, integration across multiple devices, droplet leakage, and scalability.[32]

As cell-mimics become more sophisticated, they hold tremendous potential as versatile alternatives to natural cells in diverse applications including tissue-like materials, biosensors, and biochemical reactors. The development of precise cell-mimics and lab-on-chip technologies enabled by droplet-based microfluidics will further facilitate the detailed study and use of these systems. Overall, the emerging field of droplet-based microfluidics has made remarkable progress in assembling monodisperse cell-like compartments, leading to the development of hierarchically organized multi-compartment systems. The versatility, precision, high-throughput capabilities, and programmability of cell-mimics produced by droplet-based microfluidics open new avenues for synthetic biochemical systems and offer exciting opportunities for applications in synthetic biology, biotechnology, and materials science.

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Conflict of Interests

The authors declare no conflict of interest.

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