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# From microfluidics to hierarchical hydrogel materials

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**Abstract**

Over the past two decades, microfluidics has made significant contributions to material and life sciences, particularly *via* the design of nano-, micro- and mesoscale materials such as nanoparticles, micelles, vesicles, emulsion droplets, and microgels. Unmatched in control over a multitude of material parameters, microfluidics has also shed light on fundamental aspects of material design such as the early stages of nucleation and growth processes as well as structure evolution. Exemplarily, polymer hydrogel particles can be formed *via* microfluidics with exact control over size, shape, functionalization, compartmentalization, and mechanics that is hardly found in any other processing method. Interestingly, the utilization of microfluidics for material design largely focuses on the fabrication of single entities that act as reaction volume for organic and cell-free biosynthesis, cell mimics, or local environment for cell culturing. In recent years, however, hydrogel design has shifted towards structures that integrate a large variety of functions, e.g., to address the demands for sensing tasks in a complex environment or more closely mimicking architecture and organization of tissue by multiparametric cultures. Hence, this review provides an overview of recent literature that explores microfluidics for fabricating hydrogel materials that go well beyond common length scales as well as the structural and functional complexity of microgels necessary to produce hierarchical hydrogel structures. We focus on examples that utilize microfluidics to design microgel-based assemblies, on microfluidically made polymer microgels for 3D bioprinting, on hydrogels fabricated by microfluidics in a continuous fashion, like fibers, and on hydrogel structures that are shaped by microchannels.

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## Introduction

Hydrogels are three-dimensional (3D) networks of chemically or physically crosslinked hydrophilic polymers [1]. As a particular feature, hydrogels are able to absorb and retain significant amounts of water. Combined with the ability to process hydrogels into a variety of structures, including particles, bulk materials, and films, a vast range of applications in the fields of encapsulation, actuation, sensing, and controlled release has been developed [2,3]. In the case of microscopic hydrogel particles — often called microgels [4] — precipitation and emulsion polymerization, as well as spray drying, are well-established in yielding ton-scale amounts of microscopic particles that have been applied as super absorbers or capsules in the food industry and personal care products [5,6]. To overcome the lack of control over hydrogel properties in these large-scale processes, microfluidics has emerged as an advanced fabrication method over the past two decades. Being the science of tailoring fluid flow on a microscale, microfluidics provides precise control over the formation of microemulsions, which serve as templates for hydrogel particles and other flow patterns such as continuously co-flowing fluids (cf. below) [7].

To realize these flow patterns, the exact control over the flow cell's microchannel dimensions is as crucial as the choice of materials (e.g., hydrogel precursor, oil, surfactant). While the usage of glass microcapillaries and devices obtained by a process combining photo- and soft lithography has been the gold standard in microfluidic device fabrication, the field has been revolutionized by the introduction of microscale additive manufacturing in recent years [8,9]. Several advances in emulsion and hydrogel structure formation as well as flow cell operation have further contributed to the design of tailor-made microgels. These include the usage of macromer-based precursors for polymer-analogous gelation and homogeneous hydrogel network formation [10], the delayed addition of emulsion-stabilizing surfactants after droplet formation for improved production rates [11], and the usage of non-toxic demulsification techniques to transition from solidified emulsion droplets to microgels [12]. Additionally, droplet-based microfluidics

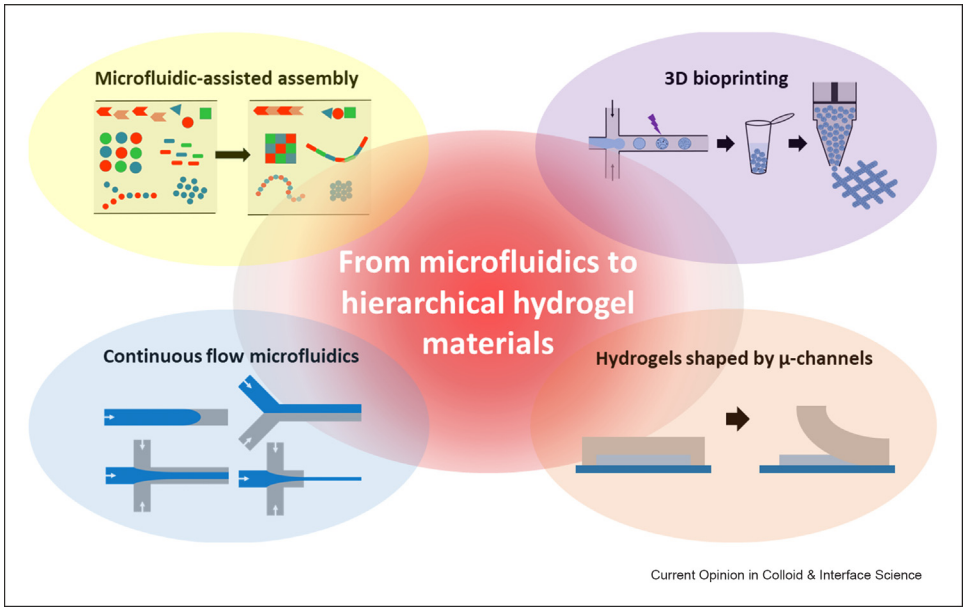
facilitates the fabrication of compartmentalized hydrogel particles deriving from multi-emulsion or co-flow strategies e.g., core-shell [13] or Janus-shaped particles [14], adding more functionality to the respective microgel species and rendering those accessible for biomedical applications.

Despite the capabilities of microfluidics-based hydrogel design, a single particle with its microscale circumference is a limitation on its own. For instance, while microgels have been utilized as individual sensor particles [15] or as microniches for single-cell culturing [16], their scale is mostly limited to a range of tens to hundreds of micrometers. Yet, handling and integrating multiple functions and stimuli would be strongly simplified by extending the scale of the hydrogels while keeping local control over hydrogel properties. These considerations have led to reviewing what microfluidics is capable in terms of hydrogel-based material design beyond the fabrication and usage of single polymer hydrogel particles. In regard to this, in Chapter 2 we will discuss recent advances in polymer hydrogel design and assembly techniques that utilize microgels as tailor-made building blocks (Figure 1). These hydrogel materials are not made of a continuous hydrogel matrix, but are hierarchical supragels that can span cross-scale and incorporate multiple functions and stimuli. Here, droplet-based microfluidics is also utilized as an assembly-assisting tool as well as a fabrication method for microgel-based inks in 3D bioprinting. Chapter 3 will then look at hydrogel structures made by microfluidics in a rather different approach, based on the second major mode of operation of microfluidic devices, which is the continuous flow at low Reynolds numbers and the mixing across co-flowing interfaces by diffusion (Figure 1). While this particular field of microfluidics has made significant contributions to elucidating early stages of nucleation and self-assembly of nanoparticles, vesicles, micelles as well as supramolecular structures, our focus will be on the design of continuously made hierarchical hydrogel structures, such as fibers. We will also highlight most recent developments on the utilization of microfluidic channels as templates that shape hydrogel precursors into complex structures and take a deeper look into smart materials made by the variety of strategies available and their potential applications. With our review, the goal is to broaden the view on microfluidics in materials science beyond its capability to provide tailor-made single microgels and move towards hydrogel structures that facilitate the incorporation of multiple functions operating side-by-side or on multiple scales.

## Strategies for controlled assembly of hydrogel building blocks

The fabrication of particle-based hydrogel structures and assembly strategies have received great attention in recent years due to the variety of benefits such hierarchical assembly structures offer compared to

**Figure 1**




This review focuses on different strategies to produce hierarchical hydrogel structures *via* microfluidic tools, either based on microgels or continuously fabricated bulk hydrogels. In the first part (top), we focus on microscale hydrogel building blocks that are either assembled *via* the support of microfluidic devices or are fabricated by droplet-based microfluidics to be applied in 3D bioprinting. In the second part (bottom), we discuss fabrication techniques of hydrogel structures utilizing continuous flow to create, e.g., fibers or utilizing templating to create sophisticated hydrogel structures that are especially interesting for tissue engineering.

conventional hydrogel fabrication in bulk. The most outstanding advantage lies in the capability of spatially tailoring material properties inside such a modular, discontinuous supragel on a microscale by utilizing different microgel species with respect to shape, properties or function [17]. The incorporation of stimuli responsiveness, e.g., towards pH, light or magnetic field, either by the intrinsic polymer properties [18] or the incorporation of functional additives [13,19] provides the basis for a vast variety of multifunctional 4D hydrogel materials.

Recently, Feng et al. [20] and Caldwell et al. [21] allocated helpful reviews on forces driving the assembly of microgels as well as on characteristics and applications of the final hydrogel constructs. Established driving forces to spatially control building block orientation and movement are based on mechanical agitation [22–24], acoustic [25], magnetic [26,27] or electrical fields [28] as well as infrared light [29]. In this section, we want to extend this focus on reviewing strategies to spatially control either single particles or arrays of particles within higher-ordered or larger-scaled hierarchical hydrogel structures and particularly look at those that make use of microfluidics either as assembly or fabrication tool, respectively. For that, we have identified two categories of assembly strategies that are capable of controlling the geometry and macroscale composition of microgel assemblies. In section *Microfluidic-assisted assembly techniques of hydrogel building blocks* we cover assembly techniques that utilize microfluidic platforms and liquid flow to spatially organize particles. In particular, microgel arrangements can be obtained by various aspects, including building block geometry, channel geometry, microfluidics-coupled non-uniform electrical fields or particle sequencing *via* specific microfluidic layouts. Section *Microfluidics as fabrication tool for microgel-based inks in 3D bioprinting* refers to fabrication techniques, where inks consisting of particles produced *via* droplet-based microfluidics are extruded through a nozzle to create particle assemblies in predefined patterns. This fabrication method is referred to as extrusion-based 3D bioprinting, as the processed hydrogel materials are envisioned to be applied in biomedical applications, especially as their mechanical properties are similar to tissue and due to their high cell compatibility. Here, the spatial resolution relies on different mechanical or physical parameters like step motor precision, applied pressure, nozzle diameter and mechanical properties of the microgel-based inks. While 3D bioprinting setups are mostly automated and thus, relatively easy to operate, approaches referring to section *Microfluidic-assisted assembly techniques of hydrogel building blocks* include rather elaborate setups that offer higher precision of single building block control.

## Microfluidic-assisted assembly techniques of hydrogel building blocks

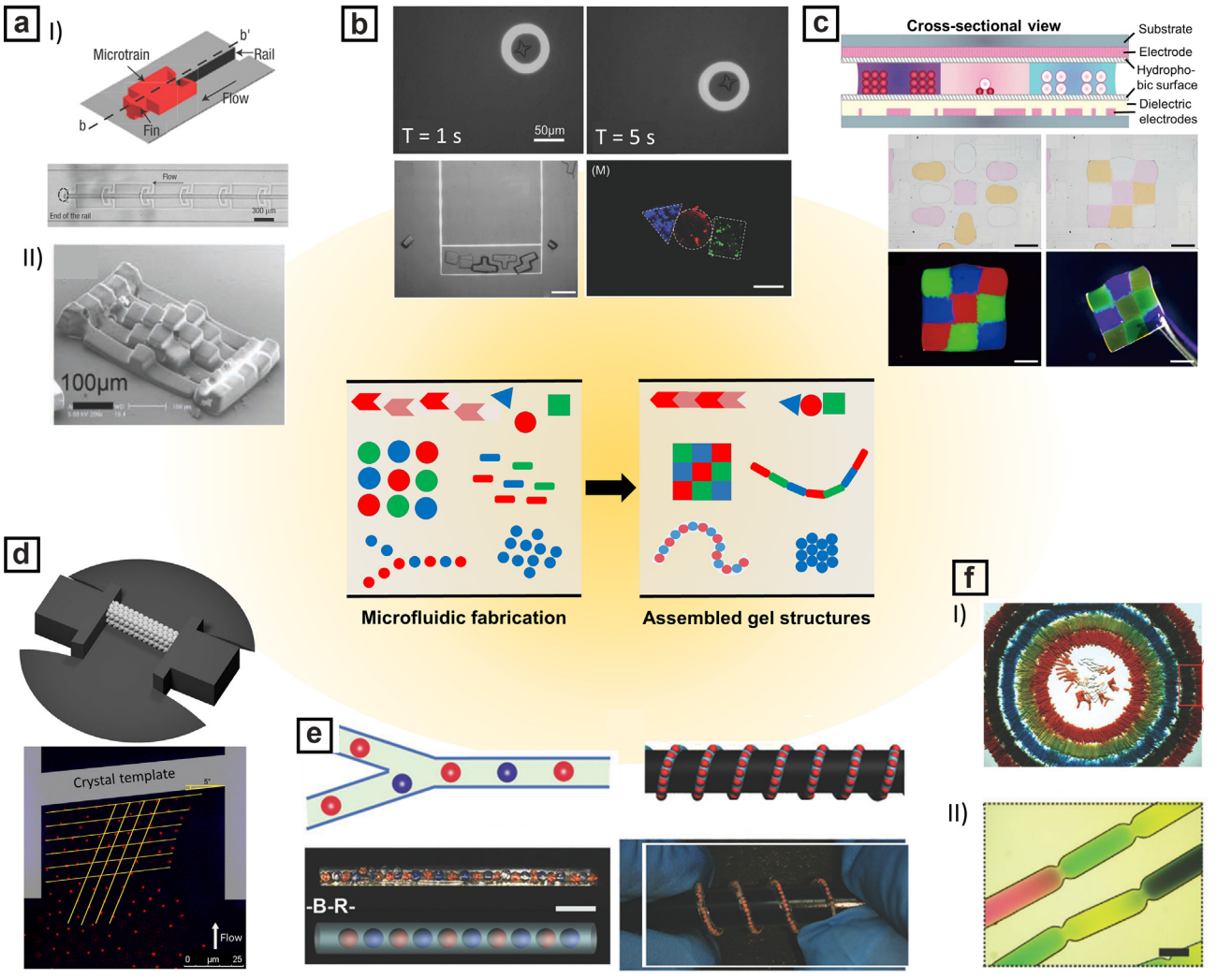
Microfluidics provides exceptional control over flow pattern formation on a microscopic scale that is not only widely used for shaping materials or tailoring the assembly of nanoparticles or vesicles, as discussed above, but also to spatially organize microgels *via* flow-induced motion. Precision and speed of the local arrangement can be manipulated and controlled by the design of the microfluidic channels [30–32], the flow rates, the coupling with external fields [33,34] or the integration of special templates [35]. Coupling the microfluidic setup as the microgel organization tool with a 3D printing system enables the fabrication of millimeter to centimeter scale objects with defined shapes, while the single microgels are locally pre-organized in-situ [36–38]. Hence, adding more possibilities with respect to shape and size of the fabricated object.

### *Assemblies requiring specific building block geometries*

Earlier examples of controlled microstructure organization in fluidic devices are known as “railed microfluidics” [30–32]. The group of Kwon established this concept as a specialized tool for building well-ordered microstructures based on grooved fluidic channels (“rails”) guiding microstructures occupying the respective counterpart (“microtrain”, Figure 2a I). These microstructures were fabricated *via* optofluidic maskless lithography [39], and the ends of the rails served as assembly sites. This concept was applied for the controlled arrangement of linear and sheet-like structures that were utilized as tissues carrying living cells and for silicon microchip packaging [30] as well as a sorting instrument and for assembling flipped and rotated complex hydrogel structures based on poly(ethylene glycol) diacrylate (PEGDA) [31]. As these early examples were limited to the assembly in only one plane, the concept was further extended towards 3D constructs by integrating a channel feature that provided axis translation of building blocks, enabling the fabrication of three-layered cubic constructs consisting of two different materials (Figure 2a, II) [32].

In two different approaches, structured hydrogel building blocks were required for the creation of cell-laden tubular structures, e.g., in a multi-areal poly(dimethylsiloxane) (PDMS)-based microfluidic device [40] or for air-bubble induced collection on a microneedle [41]. All of the above-discussed examples can be considered largely independent of the hydrogel material being processed, but do need to fulfill requirements in terms of hydrogel building block size and shape. Additionally, the overall assembly structures are limited in size by the constrained space inside a microfluidic chip or by the dimensions of the microneedle.

**Figure 2**




Microfluidic-assisted assembly techniques of hydrogel building blocks. **a**) I) Internal structure of "railed microfluidic" devices, where a "microtrain" is moving on a "rail". Building blocks are then exemplarily assembled in a line onto these rails utilizing fins matching the respective grooves [30]. II) Fabrication of 3D-constructs utilizing an axis translation feature in the microfluidic device [32]. **b**) Hydrogel building block motion control utilizing optically induced dielectrophoresis (top). Illustration of assembly versatility by combining differently shaped blocks (scale bar indicates 50 µm) and combining differently dyed materials (bottom). Scale bar indicates 100 µm [33]. **c**) Side view of an electromicrofluidic platform hosting different liquid precursors (top). Spatial control of droplet precursors on surface and polymerization producing a free-standing hydrogel sheet (bottom). Scale bar indicates 1 mm [34]. **d**) Computer-aided design (CAD) of a hexagonal crystal structure made of a photoresist *via* nanolithography located inside a microfluidic chip (top). Orientation of microgels inside the microfluidic device upon blocking at the colloidal crystal template (bottom) [35]. **e**) Utilization of Y-shaped channels to alternate differently colored microgels (left). Fabricated flexible hydrogel fibers (right). Scale bar indicates 1 mm [36]. **f**) I) Fabricated multi-colored and aligned rod structures. Scale bar indicates 2 mm [37]. II) Free-standing fibers consisting of rod-shaped building blocks with different colors. Scale bar indicates 300 µm [38].

### *Non-contact assembly* via *dielectrophoresis*

A versatile system that enables both the fabrication of hydrogel-based building blocks for supragel assemblies of various shapes (e.g., triangular, star shape or square shape) and their rapid assembly is based on the combination of optofluidic maskless lithography and optically induced dielectrophoresis [33]. When a non-uniform electrical field was generated in a liquid medium (deionized water), the position of dielectric hydrogel particles could be spatially controlled *via* a light pattern that was projected onto the area of a photoconductive film inside a separate chip (Figure 2b, top). The created force and the motion velocity of the microgels made from PEGDA were dependent on the applied frequency of the electrical field. By that, the organization of differently shaped hydrogel building blocks as well as differently dyed, cell-laden microgels was demonstrated (Figure 2b, bottom). Here, the control over building block motion without direct contact to the assembly-driving tool provides a significant benefit

compared to other methods that create disruptive forces (e.g., nozzle-based extrusion) or rely on incorporation of cell-harming additives.

Alternatively, exploiting electrowetting in combination with dielectrophoresis on a single electro-microfluidic platform (Figure 2c, top) enabled the formation of programmable hydrogel sheets accompanied by low material consumption [34]. In this example, various liquid precursors occupying different reservoirs in the microfluidic chip were precisely transported, positioned and merged by controlling the electrical field (Figure 2c, bottom). The process was used to fabricate hydrogel patterns exhibiting different color coding and consisting of three different chemically crosslinkable precursors, PEGDA, Matrigel and poly(acrylamide) (PAAm), that were exemplarily utilized as patterned templates for fibroblasts and cardiomyocytes. The method allows for processing and combining various hydrogel materials. Hence, this system has potential to complement additive manufacturing of hydrogel microstructures, where multi-material prints on a microscale are still challenging. However, the process lacks fabrication of complex-shaped 3D structures, as the resulting geometries are limited to sheets and stacking was only shown for two distinct layers. Additionally, both approaches are also restricted in terms of scalability as the microgel assembly took place inside the respective devices.

### *Studying long range order in microgel assemblies*

Apart from combining distinct micrometer-sized building blocks in a controlled fashion to build up supragel-like structures, the long-range order or crystallinity of microgel assemblies has been in the recent focus of research and was investigated in microfluidic systems [35,42,43]. Wessling and coworkers exploited soft microgel assemblies as model systems of filter cakes to study transport phenomena, filter cake mobility and microgel assembly crystallinity inside microfluidic devices for a better understanding and optimization of membrane filtration processes. More precisely, they implemented a hexagonal colloidal crystal structure that was fabricated *via* 3D nanolithography and exhibited a tilted angle of 5° respective to vertical channels inside a PDMS-based microfluidic device (Figure 2d, top) [35]. Subsequently, the device was filled with core-shell microgels with the core consisting of trifluoroethyl methacrylate and the pH-responsive shell made of poly(*N*-isopropylacrylamide-*co*-acrylic acid) (P(NIPAAm-*co*-AAc)), whereas the colloidal crystal structure served as a blockade for the microgel suspension. They showed that the resulting microgel orientation is in good accordance with the tilted colloidal crystal structure (Figure 2d, bottom) while compression and subsequent relaxation of the microgel-based filter cake yields smaller particle-to-particle distances, indicating a particle rearrangement. Although these studies may not yet show a high degree of control over the order of microgel assemblies, they bear interesting potential with respect to the ordinance across broader length scales.

### *Sequential assembly* via *Y-channel geometry*

As a specialized microfluidic feature, Y-shaped microchannels provide control over the sequencing of different materials and building blocks and allow for the production of alternating structures. As a prime example, colloidal crystal suprastructures were implemented into a hydrogel matrix to yield flexible photonic fibers with tunable colors (Figure 2e) [36]. These supraspheres derived from a microfluidic assembly approach that relied on random packing of nanometer sized core-shell particles made from poly(styrene)@poly(2-hydroxypropylacrylate-co-*N*-vinylimidazole). Dependent on the supracolloidal structure size, different reflection spectra with maxima at wavelengths ranging from 439 nm to 618 nm were recorded with the supraspheres exhibiting various colors (blue, green, red, yellow). To make use of the supraparticle arrangement, gelatin methacrylate was used as a scaffold surrounding the photonic supraballs for the production of a self-healable hydrogel exhibiting angle-independent reflectance of light. Additionally, the photonic hydrogels were able to insulate heat upon reflective cooling when exposed to sunlight.

Microfluidic Y-geometry was likewise utilized to fabricate assemblies of quantum dots (QD)-containing self-healing non-aqueous gel particles with different fluorescence. By utilizing a microfluidic printing device, hydrogel constructs with dual sensitivity to pH and amines were successfully fabricated on PDMS substrates, illustrating the potential of the method for the fabrication of sensor systems [44]. Although employing Y-channels is beneficial in the creation of alternating structures or specific sequences consisting of two distinct materials by matching the respective flow rates in the supply channels, utilization of more than two supply channels exacerbates the control over sequencing as flow rate adaption becomes more elaborate.

### *Assembly of hydrogel rod structures*

Poly(1,1,2,2-tetrafluoroethylene) (PTFE) tubings of small diameter are commonly used for transferring liquid in or out of a microfluidic device, but can also be used as confining spaces to order hydrogel-based buildings blocks with a rod-like shape into hierarchical structures [37,38]. Gelatin methacrylate (GelMa) hydrogel microspheres and rods were obtained at elevated temperatures (37 °C) upon varying flow ratios while cooling the end of the tubing to induce gelation of the formed structures in an immiscible oil phase (Figure 2f, I) [37]. By controlled deposition of the hydrogel structures on a surface utilizing a triple axis micromanipulator unit, parallel and circular rod arrangements were obtained illustrating the great potential of this droplet microfluidics-based 3D

printing method. Further modification of the microfluidic system enabled the fabrication of GelMa-based microrod chains with each rod segment being differently colored (Figure 2f, II) [38]. Here, the rods were pre-organized by the utilization of a syringe pump and a three-axis robot to yield free-standing strings by extruding single rods directly sticking to each other at the outflow port under release of the oil phase. Both approaches display great alternatives to form multimaterial hydrogel structures and tissue models in a 3D printing manner by combining microfluidics with robotic manipulation. However, building block geometries are limited to rod-like (and spherical) as the tubing serves as a formative unit.

Generally, microfluidic-assisted approaches allow for fabricating supragel structures spanning from hundreds of micrometers [33] to several centimeters [37]. The examples above have shown microfluidics to be versatile regarding the creation of various supragel structures consisting of different materials that are envisioned to be applied in biomedicine, e.g. as tissue or sensor systems. As discussed in *Sequential assembly via Y-channel geometry* and *Assembly of hydrogel rod structures*, microfluidics can be coupled with 3D printing to fabricate structurally defined, free-standing microgel-based constructs. Although this enables the *in situ* organization of single microgels within the supragel, there are certain drawbacks, e.g., lack of mechanical property adjustment or potentially insufficient purification. Thus, microfluidic hydrogel fabrication and 3D bioprinting can be separated to fabricate mechanically defined and more functional supragel structures, which will be discussed below.

## Microfluidics as fabrication tool for microgel-based inks in 3D bioprinting

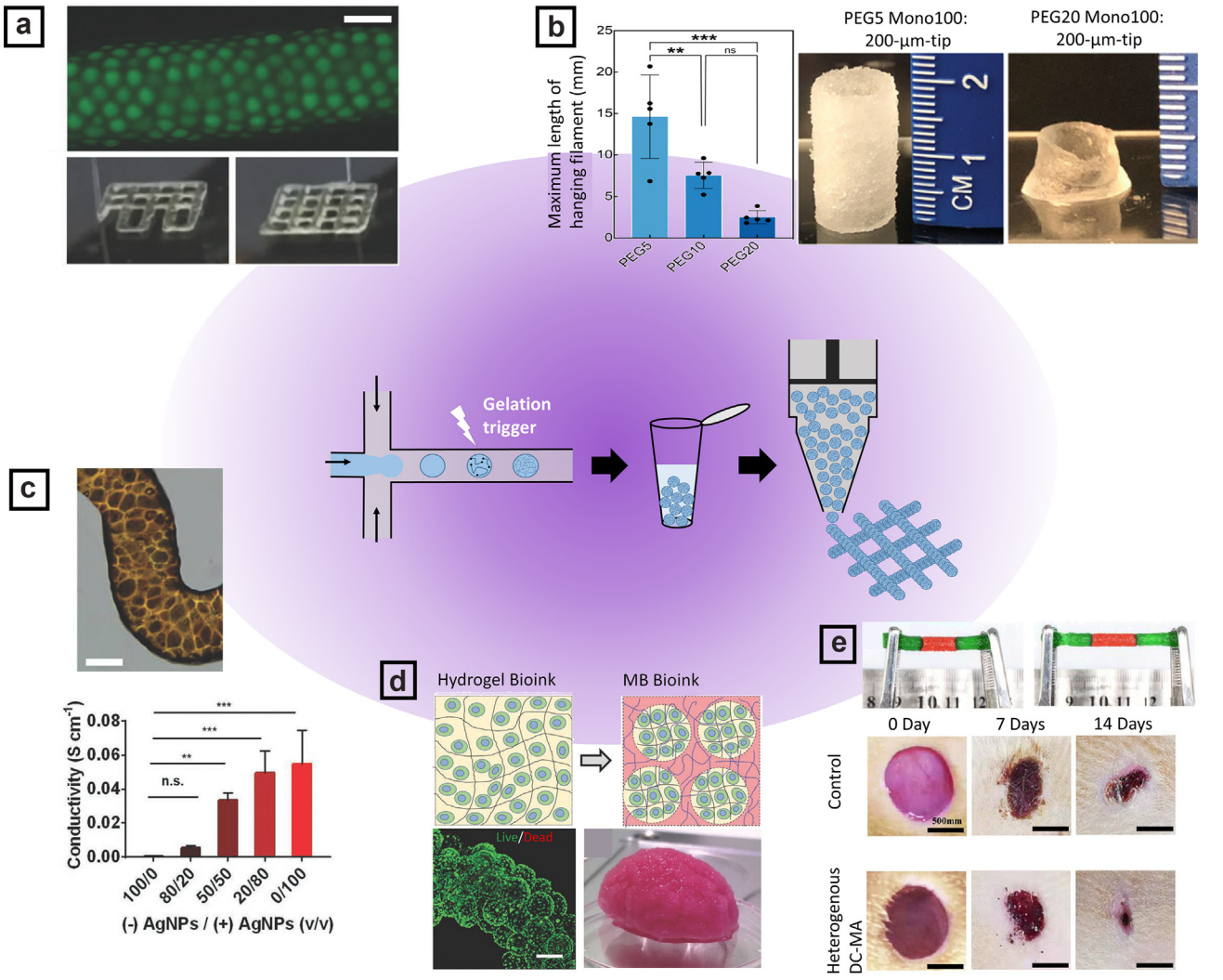
3D bioprinting has emerged as a versatile and reliable tool to fabricate various hydrogel structures that are applicable as tissue-like materials [45,46] or sensors [47–49] due to micro-to millimeter precision. Additionally, the users have the capability to fabricate complex geometries as well as the ability to process various hydrogel-based materials. Here, supragels made from individual microgel-based building blocks exhibit several benefits over bulk hydrogels made from a continuous material matrix, including locally controllable modularity, printability, and porosity [17,50]. The shear-thinning behavior of hydrogel particle-based inks benefits the injectability and printability, as printed strands are less compromised to spread uncontrollably on the surface after ejection due to the solid-like behavior. Meanwhile, the ejection is facilitated due to liquid-like behavior upon applied stress. The mechanical stability and printability of the microgel-based inks can be further improved by addition of crosslinkers and UV-initiators and subsequent post-curing [51] or by utilizing a support medium preserving the structural integrity. Porosity is not only defined by the polymer network of each microgel, but the supragel itself exhibits micropores due to interparticle spacing and thus, providing an additional degree of permeability for nutrient flow as well as improved cell mobility and attachment [17,20]. These overall features render multiparametric microgel assemblies [17] especially interesting for biomedical applications, e.g., as drug delivery models or for tissue repair [50,52]. The properties of supragels are also dependent on the fabrication method of the building blocks, e.g., *via* microfluidics, batch emulsion polymerization or fragmentation [53]. In plenty of 3D bioprinting-based approaches with microgel-based inks droplet-based microfluidics is the fabrication tool of choice due to the precise control on gel size accompanied by a narrow size distribution as well as the capability of producing heterogeneous, functional particles, e.g., core-shell particles. Due to certain drawbacks of microfluidics, particularly low particle production rates and laborious device fabrication, emulsion polymerization [54–56], mechanical crushing of gelatin-based hydrogels [57,58], and electro-spraying of PEG-based microgels [59] serve as alternative fabrication methods for microgel-based bioink preparation.

### *Jammed particles as inks for 3D bioprinting*

In 2019, the group of Burdick established the concept of "jammed" microgels for 3D bioprinting [60]. Upon vacuum filtration microgels are densely packed and behave like solids accompanied by a shear-thinning behavior that is beneficial for nozzle-based extrusion processes (Figure 3a). Exemplarily, the microgels required to form jammed particles were readily made by droplet microfluidics from norbornene-modified hyaluronic acid (NorHA), PEGDA and agarose, respectively. By that, the authors tuned the mechanical properties of both individual particles as well as the particle jam regarding storage and loss modulus as well as viscosity. While structures made from microgel-based building blocks were initially rather fragile since the jammed particles were primarily held together by physical interactions, the addition of a crosslinker and photoinitiator led to stable structures subsequent to UV post-curing. The microgels could be extruded into a support gel to create differently colored patterns as well as multimaterial filaments. The jammed agarose gels could be utilized to create microchannels in the support hydrogel made of adamantane-and norbornene-functionalized HA and cyclodextrin-modified HA by post-removal at elevated temperatures in the presence of agarase.

A detailed investigation on the printability of jammed microgels dependent on the nozzle diameter, microgel size and mechanical properties was conducted by Xin et al. utilizing PEG-Nor/PEG-dithiol-based microgels [61]. The printability correlated directly with the microgel size for a given nozzle diameter while larger jammed particles ruptured when ejected through a comparably thin nozzle. As another key insight, it was

**Figure 3**




3D bioprinting of microgel-based inks fabricated *via* microfluidics. **a**) Dense packing of microgels *via* vacuum filtration leading to "jamming" (top). Scale bar indicates 200 µm. Fabrication of grid structures without support matrix (bottom) [60]. **b**) Filament length's dependent on the molar mass of four-arm PEG-Nor (left). Stability of cylindric structures dependent on the molar mass of four-arm PEG-Nor (right) [61]. **c**) Filament of the conductive supragel (top). Scale bar indicates 100 µm. Conductivity dependency on the ratio of microgels loaded and not loaded with Ag nanoparticles (bottom) [62]. **d**) Scheme of the microgel-based biphasic ink consisting of a hydrogel matrix (red) and incorporated microgels made from a cell-laden hydrogel bioink (yellow, top). Cell viability of stained microgel fibers (bottom left). Scale bar indicates 200 µm. 3D-printed brain model prepared from a biphasic ink (bottom, right) [63]. **e**) Self-healed, multi-material hydrogels illustrating stability at the healed interfaces during tensile testing (top). Wound-healing effect of a dynamic microgel ink on rat skin compared to normal saline treatment (bottom). Scale bar indicates 500 mm [65].

found that particles being uniform in size were printable up to a nozzle diameter of twice the particle size, while polydisperse particles required a three times larger tip diameter compared to the average particle diameter. These insights highlight the benefit of droplet-based microfluidics for uniform particle formation in 3D printing of jammed hydrogel structures. Additionally, it was shown that higher Young's modulus and yield stress of the denser crosslinked, lower molecular weight PEG-Nor species produced longer filaments as well as more stable cylindrical objects compared to the PEG-Nor species with higher molecular weights (Figure 3b).

Burdick and coworkers also exploited the concept of jammed particles for the fabrication of conductive supragels (Figure 3c) that are especially interesting for electrophysiological applications like biosensors [62]. Microgels were formed *via* droplet microfluidics from HA modified with aromatic gallol groups that enabled the reduction of silver ions. In this process the storage modulus of the jammed microgels increased from 25 to 130 Pa upon silver coordination. Interestingly, the conductivity of the jammed microgels (0.05 S $cm^{-1}$) was significantly larger than in bulk (0.01 S $cm^{-1}$) or compared to milled hydrogel pieces (0.028 S $cm^{-1}$) due

to the overall higher silver content in the densely packed microgel constructs. Additionally, the conductivity could be further tailored by simply varying the ratio of silver-loaded and non-loaded microgels in the supragel matrix. The fabrication of a stable, two-layered grid from these microgels was realized, and the supragel was even injected in-between two isolated skeletal muscles to work as an electrically conductive bridge.

*Microgel-bulk hydrogel composite inks*

Instead of utilizing inks of purely jammed particles, which may only exhibit a limited mechanical stability without additional covalent or supramolecular interactions between individual particles biphasic inks comprising of microgels (phase 1) and a hydrogel precursor solution (phase 2) combine printability with high mechanical stability of the hydrogel particle ink [63—65]. Along these lines, Fang et al. presented a biphasic ink consisting of cell-laden GelMA microgels made by flow-focusing droplet microfluidics and embedded these particles in a GelMA matrix (Figure 3d) [63]. The capability to fabricate complex, functional microgel-hydrogel constructs was examined by fabricating tubular and human anatomical models, e.g., a brain model, while mechanical testing revealed hyper-elastic behavior of the printed biphasic bioink with low hysteresis over 1000 compression cycles. To more closely model the complexity of the human tissue comprising of various cell types, the authors incorporated different cell types in the microgels and the hydrogel precursor ink to create a heterogenous tissue environment and additionally demonstrated the expression of genes and proteins. This example greatly connects to the afore-discussed potential of microgel-based inks to set up multiparametric, functional cell culture environments [17].

A similar approach was followed by Chai et al., who utilized a biphasic ink consisting of cell-laden collagen/alginate core-shell particles embedded in methacrylated silk fibroin (SilMA) and GelMA for bone repair [64]. They investigated different ratios of SilMA and GelMA and the influence on pore size, swelling degree, elastic moduli, compression strength and degradability. It was found that mixtures of GelMA/SilMA hydrogels with core-shell particles of collagen (core) and alginate/$Ca^{2+}$ (shell) had a positive effect on cell proliferation. This was due to the protection of the bone marrow mesenchymal stem cells inside the microgel core during hydrogel processing and extrusion compared to bulk GelMA/SilMA hydrogel matrices, where cells were distributed unprotected.

Beyond stabilizing matrices or covalent bonds between microgels permanently, mechanically stable supragels can be likewise formed utilizing dynamic crosslinks, which can improve tissue adhesion and provide the microgel assembly with self-healing properties [65,66]. Exemplarily, Feng et al. developed microgels consisting of phenylboronic acid-modified hyaluronic acid methacrylate (HAMA-PBA) and GelMA, which were blended additionally with dopamine-modified HA as a dynamic crosslinker. By that, viscosity and printing fidelity could be greatly improved compared to jammed particles made from the same formulation, but omitting dopamine-modified HA [65]. 3D-printed structures could be cut repeatedly and reprinted again with no obvious flaw in the newly assembled constructs. The strong adhesion of the printed parts to skin and various animal organs was promoted by the dopamine reacting with hydroxyl-and amino groups on the tissue surface. The self-healing ability enabled the creation of multi-component materials. Moreover, in combination with the microporosity and good tissue adhesion, the material was applied as a wound-healing dressing (Figure 3e).

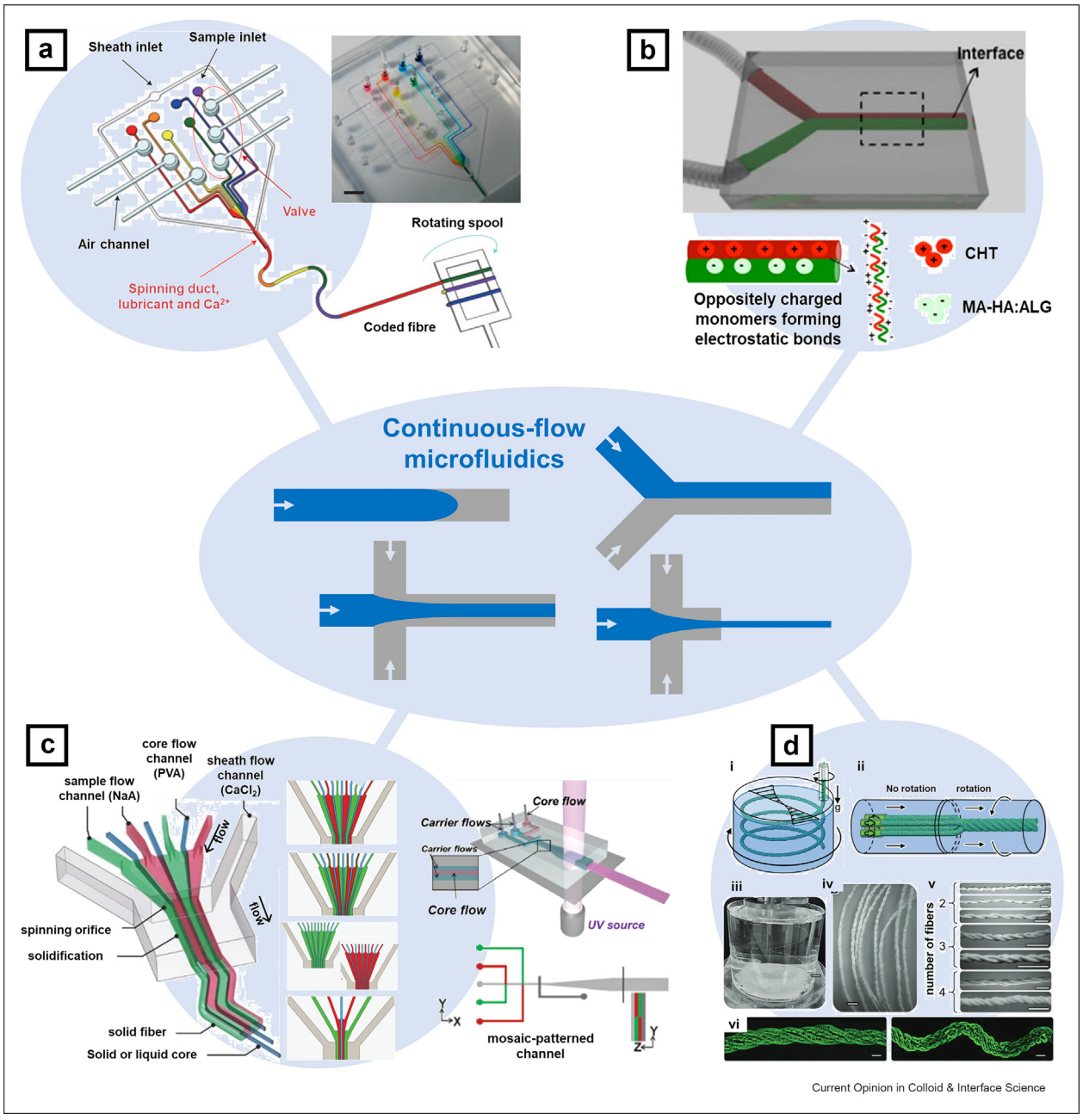
Generally, 3D bioprinting facilitates the fabrication of centimeter-scale microgel-based constructs with various geometries due to the freedom of design choice, generating great potential for tissue applications. To be adequately printed, the ink needs to fulfill certain requirements in terms of viscosity and mechanical stability, while the ingredients of the ink should be stable against shear forces. Compared to the approaches discussed in Microfluidic-assisted assembly techniques of hydrogel building blocks, the deposition and thus, the location of single building blocks within the supragel network are barely controllable as the microgels are rather randomly distributed or jammed together inside the inks. However, the process offers more possibilities for producing larger hydrogel constructs.

## Fabrication of continuous hydrogel structures utilizing microfluidics

### Continuous hydrogel formation and assembly into polymer microfibers

Beyond their broad application as a production platform for uniform droplets and microgels, respectively, microfluidic channel networks provide a likewise unique environment for tailoring flow patterns of miscible fluids and their gelation in a continuous fashion. With that, hydrogel constructs become available that extend the size range of single microgel particles by orders of magnitude and are particularly powerful for forming discrete gradients of concentration, group functionalization, porosity, and mechanics. Especially, by tuning the above-mentioned conditions, different morphologies may be coded in one continuously made hydrogel and collected conveniently from the outflow port [67] (Figure 4a) or tailored in shape and size by the microchannel networks [68].

**Figure 4**




Schematic illustration of various examples of continuous flow patterns formed in microfluidic devices and their utilization for fabricating hydrogels. (**a**) Conceptual description of a process for generating coded hydrogel fibers. The extruded fibers were continuously wound onto a motorized spool [67]. (**b**) Oppositely charged solutions (negatively charged in green and positively charged in red) were injected into separate microchannels that formed a stable interface inside a microfluidic chip [72]. (**c**) Left: microfluidic chip for fabricating heterogeneous hollow microfibers from calcium-alginate, and exemplary flow designs for forming multiple compartments [73]. Right: formation of a tri-layered and mosaic-patterned laminar flow to be photo-polymerized downstream [80]. (**d**) Continuous collection of microropes: i: Schematic depicting the collection of microropes in a water-filled, rotating cylinder. ii: Schematic depiction of delayed microfluidic twisting. iii: Photograph of microrope collection. Scale bar indicates 1 cm iv, v: Micrographs of collected and photopolymerized microropes. Scale bar indicates 0.5 mm. vi: Confocal micrographs of straight and undulated fibers. Scale bar indicates 100 μm [77].

Generally, the gelation of a continuously flowing hydrogel precursor stream inside a microfluidic channel can be triggered and mediated by physical or chemical crosslinking, which can be precisely controlled under microfluidic conditions [69]. In one example, the transition from liquid to solid was exemplarily triggered at the liquid-liquid interface of two precursor solutions flowing side-by-side in a laminar fashion, and the

resulting hydrogel is then extruded continuously at the outflow port of the microchannel network (Figure 4b) [70—72]. In this process, extrusion was facilitated by forming a sheath flow around the gelling fluid flow that then acted as a lubricant [71] while a diffusion-based co-flow allowed for continuous Janus fiber formation to retain the structure polarity. Control over the shape of flow patterns, and thus the shape of a continuously fabricated hydrogel structure is defined by the height, width as well as the geometry of the microchannel (e.g., round, square). Complexity of the hydrogel structures was further increased by utilizing multiple inflow streams that are independently controlled and enable the formation of multiple compartments [67,73].

A typical technique for generating microfibers from microfluidics is defined as microfluidic spinning [68]. Generally, such a device is composed of several inlet microchannels that merge into a longer outlet-channel. The device allows fluids to form coaxial or sheath flows, which can be shaped by controlling the fluid dynamics and lead to the continuous generation of microfibers or -tubes exhibiting defined sizes and geometries [74]. As a result of the so-called rope-coil effect, diffusion-based mixing and crosslinking at the interface induces spiral formation of the core flow when the flow rate ratio between the shell and the core reaches a certain limit [75]. Thus, continuous hydrogels were fabricated and switched between straight and helical fibers by adjusting the flow rates, which could be potentially applied in tissue-engineering [74,75]. By employing multiple core channels in the microfluidic device, hydrogel microtubes with multiple channels were fabricated (Figure 4c). Compared to single core/shell hydrogel microtubes, the introduction of the extra core provided more diversity of morphologies by tuning the flow rates of each core [74,76]. Exemplarily, Khara et al. fabricated twisted microropes by using centrifugal force, and systematically analyzed effect factors to enable the assembly of microropes with enhanced mechanical flexibility (Figure 4d) [77].

Besides solid fibers continuous hydrogels were designed as hollow- or tubular-shaped fibers that are especially interesting for tissue engineering applications. Onoe et al. fabricated metre-long hollow gel fibers with encapsulated proteins and cells by using a microfluidic device exploiting double-coaxial laminar flow. Furthermore, these microfibers were assembled by weaving and reeling into macroscopic cellular structures with different spatial patterns. This strategy can improve the safety of medical transplantation and may serve as a template for the reconstruction of e.g., muscle tissue [78]. Xie et al. reported the synthesis of a knot-shaped hollow gel fiber to study glomerular filtration barriers. Hollow microfibers with knots were fabricated within minutes by microfluidics for mimicking microcurved features of the looping capillaries. Endothelial cells were seeded in the perfusable lumen to generate the vascular barrier. The permeability of albumin from the vascular channel to the ultrafiltrate side was tested, demonstrating the successful fabrication of the filtration barrier [79].

### Hydrogel structures templated by microfluidic and microchannel networks

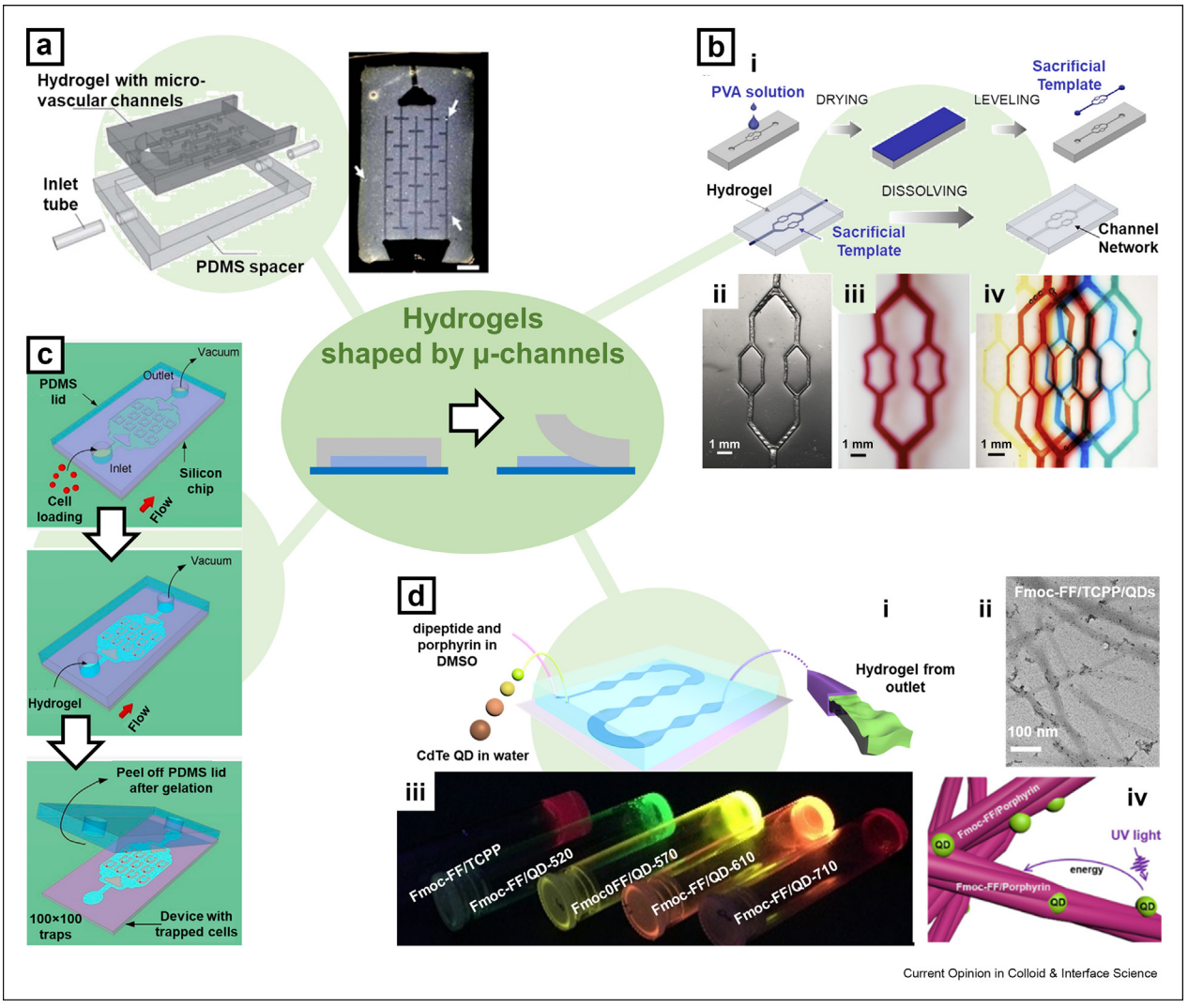
Besides constructing hydrogel fibers by extrusion, microfluidics also provides other strategies for hydrogel formation *in situ*. With the assistance of templates (e.g. molds) and photopolymerization, sophisticated hydrogel patterns were processed that are widely applied as engineering tissue models *in vitro* [68].

Replica molding is a straightforward approach to construct various architectures. For example, Koo et al. presented a light-driven biomimetic reactor consisting of an agarose hydrogel matrix with embedded photocatalytic $TiO_2$ nanoparticles (Figure 5a) [81]. Inspired by the natural structures of leaves, where water and minerals are uniformly distributed in a venation network, they utilized a PDMS-based reactor where the agarose-nanoparticle hydrogel was embedded as interdigitated channel networks that were formed by replica molding. The hot liquid agarose with suspended $TiO_2$ was poured on a patterned mold (photoresist SU-8) and was cooled down to room temperature. The $TiO_2$-embedded hydrogel with the branched channel network was enclosed by a PDMS spacer and sandwiched by two glass substrates. Due to the high porosity and moisture of the hydrogel as well as the high surface area provided by the microfluidic channels, such a device allows for uniform permeation of the liquid and enhances the reagent mass transfer. The efficiency of these microfluidic reactors was estimated by calculating the degradation rate of the dyes under dark and illumined conditions.

Utilizing sacrificial templates is another suitable way to obtain complex vascular geometries in synthetic, homogeneous and large size scaffolds. For example, poly(vinyl alcohol) (PVA) was employed exploiting this strategy due to its biocompatibility and easy machinability [82]. Here, the aqueous PVA solution was cast on the mold and allowed to dry. The dried PVA layer was leveled in order to remove the polymer excess from the microfluidic track. After drying, the sacrificial template was gently demolded and encapsulated into a liquid matrix. After the matrix was crosslinked, the template was dissolved in water, yielding a monolithic hydrogel with embedded channel networks (Figure 5b). As a result, fabricated microfluidic scaffolds were successfully integrated in a 3D cell culture to demonstrate the adaption and effectiveness in vascularized thick tissues.

In a different study provided by Wong et al., hydrogels were formed and patterned in microchannels relying on thermal curing. Here, a matrigel precursor solution was

**Figure 5**




(**a**) Schematics of the light-driven microvascular gel reactor. The gel with the microfluidic channels was enclosed in a PDMS spacer, sandwiched between two glass substrates, and connected to the inlet and outlet tubing [81]. (**b**) i: Scheme of sacrificial template fabrication and microfluidic channel network: The aqueous PVA solution was cast on the mold and allowed to dry. The dried PVA layer was leveled in order to remove the polymer excess from the microfluidic track. The mold was then dried a second time and the sacrificial template was gently demolded. The sacrificial template was encapsulated into a liquid matrix. After the matrix crosslinking, the template was dissolved in water, yielding a monolithic gel with embedded channel network. ii: Optical images of the single microfluidic hydrogels. iii-iv: Optical images of single (iii) and multilayer (iv) microfluidic gel perfused with dyed solutions [82]. (**c**) Working principle of the injection molded microfluidic approach: cells were loaded into the device by applying vacuum at the outlet to form a single cell array, after which the hydrogel solution was injected into the device by vacuum and allowed to cure. After curing, the PDMS lid was peeled off [84]. (**d**) i: Continuous fabrication of a supramolecularly assembled N-fluorenylmethoxycarbonyldiphenylalanine (Fmoc-FF) hydrogel by microfluidics. ii: Transmission electron microscopy (TEM) images of hydrogels embedded with molecules as fabricated by microfluidics. iii: Fluorescence microscopy images of QD and 10,15,20-(tetra-4-carboxyphenyl)porphyrin (TCPP) entrapped in Fmoc-FF hydrogels collected from the outflow port of a microfluidic device. iv: Energy transfer in Fmoc-FF/porphyrin/QD hydrogels [85].

uniformly injected into the PDMS microchannels, and heated for complete gelation [83]. The produced hydrogel slabs are spatially tailorable and function as cell culturing substrates. Li et al. developed an injection-molded microfluidic approach for single cell analysis. First, microfluidic devices were primed with cell media and the PEG hydrogel mixture was introduced to the device with the trapped cells. The device was maintained in a cell culture incubator for 20 min to allow the hydrogel to crosslink, after which the PDMS lid was peeled off. As a result, the hydrogel pattern had stronger adhesion to the silicon chip, and the cells remained with the silicon substrate (Figure 5c). By this method, cells were organized and characterized in order to analyze the functional and genomic heterogeneity within biological systems [84]. Our group recently reported a short peptide self-assembling and encapsulating system that was constructed by integrating water-

soluble QD of different sizes and porphyrin molecules pre-dissolved in dimethylsulfoxide (DMSO) into the same gel carrier to achieve organic-inorganic energy transfer in hydrogels (Figure 5d) [85]. The unique combination of bottom-up self-assembly of short peptide constructs and top-down microfluidic control of hydrogel morphology and nanoparticle embeddability provides the basis for integrating multiple molecules in a coordinated system to implement a tailored circulation matrix for stable and uniform capture of target compounds. This system may provide a reference for the development and utilization of low molecular weight gelator (LMWG)-based peptide drug carriers.

## Towards smart materials for cell culturing, drug delivery and sensing

### *Materials for microfluidics-based continuous hydrogel formation*

The material basis from which hydrogel materials have been fabricated by continuous flow microfluidics is vast, ranging from synthetic to natural sources, while network formation is based on covalent, ionic, or supramolecular crosslinking. As a natural polysaccharide, alginate is a widely used hydrogel material in food, pharmaceutics, biomedicine, or wearable sensors due to its biocompatibility, biodegradability, and highly efficient crosslinking. The gelation can be rapidly induced by the electrostatic interaction between negatively charged alginate and a variety of cations e.g., $H^+$, $Ca^{2+}$, $Mg^{2+}$ or $Ba^{2+}$ to form polyelectrolyte complexes [86]. Such fast ionic crosslinking that proceeds normally within seconds determines its unique fabrication strategy through microfluidic spinning to form hydrogel fibers [68]. In here, either sodium alginate or $CaCl_2$ is injected into a core channel, while the other solution is induced into the outer sheath channel (Figure 6ai) [87]. At the interface between the two fluids thin film-like crosslinks form, resulting in a typical hydrogel microfiber. The Alginate-based hydrogel is optically clear, has good mechanical performance and a similar structure to the extracellular matrix in living tissues [88], enabling its application in cell encapsulation, wearable sensors, or wound repair. Wound dressings made from alginate hydrogel exhibit excellent hygroscopic and antibacterial properties. In particular, with water content up to over 90% of the total mass, hydrogels are highly porous, allowing diffusion of molecules through the network [89,90]. 3D network structures provide hydrophilic multicompartments for drugs, especially small-sized proteins, enzymes or growth factors embedded, and are also applicable for time-dependent release. For instance, anti-infective agents or growth factors can be encapsulated for recovery acceleration and reinforcement of the repairing ability [91].

Meanwhile, to satisfy different demands regarding morphologies and properties towards different applications in tissue engineering, researchers developed diverse approaches based on alginate spinning. By tailoring the chemical conditions, mechanical properties [92,93], antibacterial properties [94], or cell compatibility [92] can be optimized. Besides solid fibers, multiple structures including tubular, porous, and hybrid fibers have been developed [71]. Liang et al. recently conducted a series of innovative works on creating structurally diverse alginate fibers by microfluidic spinning [68,74,87]. In particular, they developed a microfluidic approach for controllable fabrication of necklace-like microfibers with diverse knot structures, such as spindles, hemispheres or petals. Besides, straight channels, perfusable Janus channels and helical channels were obtained inside knotted microfibers, inducing diverse morphologies. Moreover, cells were directly encapsulated in the knotted microfibers for culturing with potential in bioengineering and biomedical applications [87]. Apart from alginate, other natural materials such as chitosan, collagen, and gelatin also play important roles in cell seeding and tissue engineering [68,95].

Although natural hydrogel materials have excellent biocompatibility, their properties (e.g., mechanical, optical or thermal) are still limited. In contrast, synthetic polymers are highly engineered and, may thus provide extended tunability and substitutability for specific demands, such as enhanced mechanical strength of wearable sensors, modified surfaces for cell adhesion and stimuli-responsive hydrogel valves [68]. Typical synthetic materials such as PEG, PEGDA, poly(lactide-*co*-glycolide) (PLGA), PVA, poly(caprolactone) (PCL), and PAAm can be applied using a microfluidic spinning strategy to fabricate functional microfibers [68]. For instance, water-soluble PVA is compatible with biomaterials, and allows for easy and repeatable generation of complex vascular patterns. By using PVA as a sacrificial vascular scaffold, a tissue engineering model containing a vascular channel was fabricated for primary endothelial cell seeding [96]. The functionality of the microfluidics-based formation of hydrogel fibers can be extended by the introduction of composites, e.g., to combine electro-response and enhance mechanical property. Along these lines, Hu et al. fabricated hydrogel fibers with the core consisting of graphene oxide (GO), and the sheath consisting of alginate/$CaCl_2$ [97].

Different crosslinking types, densities, and morphologies of static hydrogels influence their chemical and physical characteristics, which qualifies them for different applications [70]. In contrast to hydrogels crosslinked by covalent bonds, supramolecular hydrogels based on organized intermolecular self-assembly are unique materials due to the reversible and weaker non-covalent intermolecular interactions (e.g., hydrogen bonding, host-guest interaction, metal-ligand coordination, and electrostatic interaction) [98–100]. Exemplarily, Li

et al. fabricated supramolecular hydrogel fibers by microfluidic spinning where self-healing fibers were assembled non-woven into fabrics through non-covalent host-guest interactions. To obtain supramolecular hydrogel fibers, $\beta$-cyclodextrin and *N*-vinylimidazole were chosen as host molecule and guest molecule, respectively. By utilizing differently designed microreactors, beaded, cylindrical and knotted fiber structures were obtained. In particular, they constructed multidimensional (2D plane, 3D bulk, and 3D spiral textile) materials by using self-healing fibers as building blocks. By virtue of the host-guest supramolecular assembly, fibers exhibit high flexibility combined with high strength and long-term stretching behavior [101]. Highley et al. also investigated non-covalent crosslinked hydrogels to be used for 3D bioprinting [102]. The self-healing hydrogel deformed when a syringe needle was inserted to inject the hydrogel ink and rapidly healed around the printed ink, which retained the printed structure within the support gel. Thus, the process allowed the printing of supramolecular inks into any position within the space that was initially occupied by the support gel. The dynamic nature of the supramolecular crosslinking that permitted both shear-thinning and self-healing was essential and is particularly useful in biomedical applications to mimic or reproduce features of cellular environments.

### *Combined functions towards 4D hydrogel materials for soft robotics*

Hydrogels are playing an increasingly important role in various applications, such as soft robotics [103,104], smart drug delivery and release [105,106], tissue engineering [107], and biosensors [108,109]. Compared to bulk hydrogel fabrication, microfluidic hydrogel fabrication provides a continuous platform to achieve uniform control, particularly for the integration of different materials inside one hydrogel, which result in different responsivities and various hydrogel morphologies. For instance, Takeuchi et al. recently fabricated microfibers with an axial pattern of stimuli-responsive and non-responsive hydrogels by microfluidics. By using the thermo-responsive material PNIPAAm-*co*-AAc the programmed pattern of stimuli-responsive regions on the microfiber enabled the fiber to locally bend upon temperature increase over the entire microfiber (Figure 6b) [110]. Finally, they demonstrated the utilization of the programmable microfiber as a soft actuator, expanding possibilities of fiber-based materials in biomimetics and soft robotics. Liu et al. reported a segmented 3D-printed hydrogel tube composed of PNIPAAm and a passive non-responsive gel (PAAm), exhibiting different swelling behaviour [103]. Notably, such an elaborately designed tube exploits two functions simultaneously, namely elongation and gripping in response to temperature, which plays an important role in soft-robotic endoscopic applications. Zhang et al. developed a smart hydrogel with responses to multiple triggers including moisture, multivalent cations, and pH, while exhibiting high stretchability, shape memory and self-healing properties [104]. Based on the mismatch due to volume change after dehydration, they fabricated a series of "plastic flowers" with various patterns by assembling hydrogel strips with hydrophilic PDMS films. With multifunctionality and stretchability, this smart hydrogel broadens the scope of functional materials and improves the versatility of hydrogel applications, which have great prospects in the fields of actuators, soft robotics and electronic skins. Duan et al. *presented* a self-lubricated spinning strategy for large-scale fabrication and weaving of electro-responsive hydrogel fibers. Enhanced mechanical flexibility enabled the fiber to be knitted into various complex geometries (Figure 6c) [111]. The polyelectrolyte inside endowed the hydrogel fiber with electro-responsiveness, further promoting the actuation behaviour.

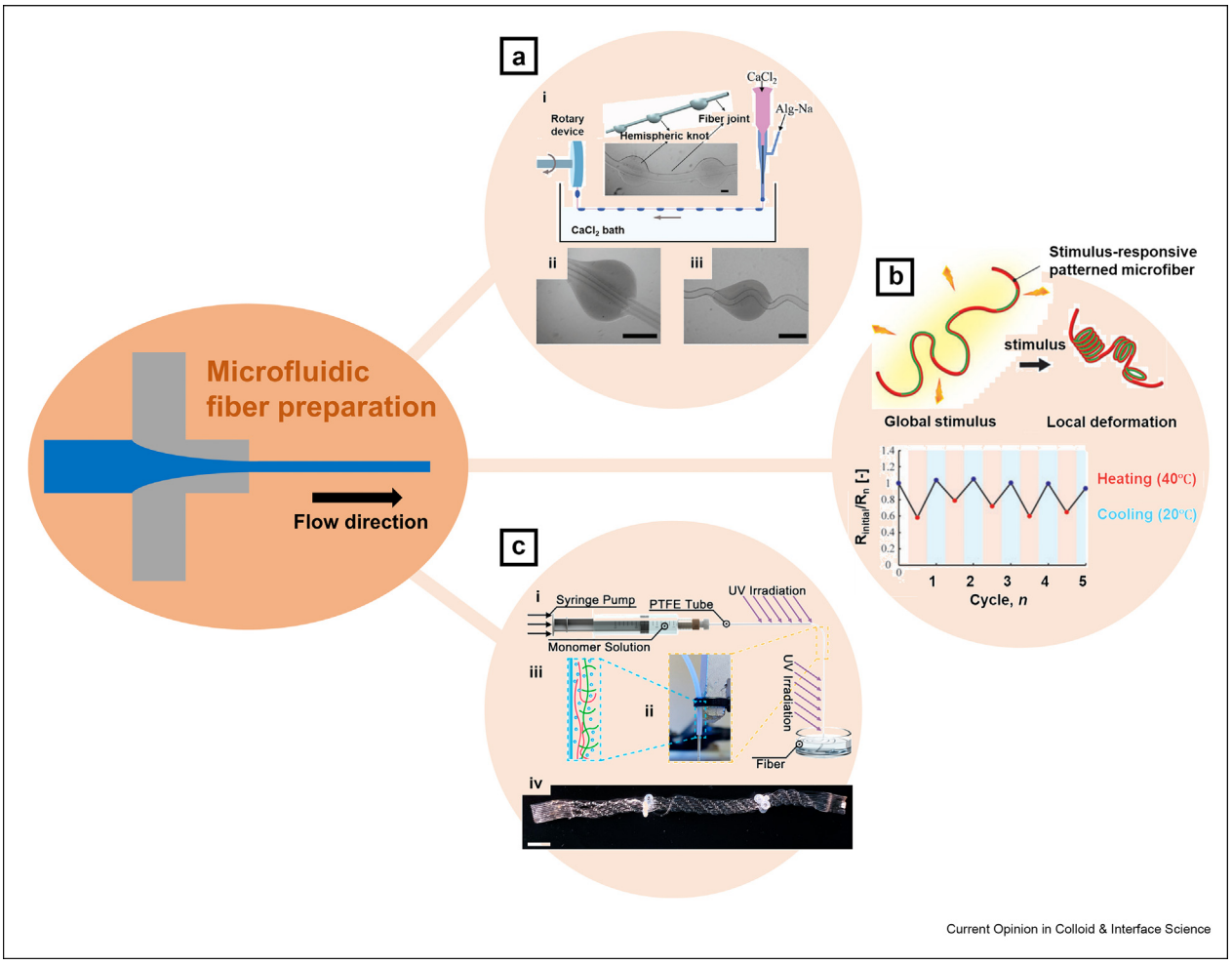
### *Drug delivery*

Drug delivery is a promising application field for hydrogel materials due to their general biocompatibility and especially due to material specific responsivities to stimuli like pH or temperature [112]. Through general molecule diffusion, hydrogels create favorable conditions for drug release, especially for controlled release through controlling porosity or configuration of fibers, e.g., folded, tied, or weaved structures [113]. Wei et al. prepared core-shell hydrogel fibers and scaffolds and designed structures for drug delivery and controlled release. Briefly, poly(dopamine) (PDA) mixed with alginate constitute the shell, drug-loaded thermos-sensitive hydrogel is injected as the core part, both of which are co-injected as coaxial fibers to be further injected into tissue for treatment. Due to the high specific surface area and hydrophilic nature, these nanoscaled fibers are suitable to trap drugs. Under near infrared (NIR) irradiation, photothermal PDA raised the temperature of the fibers, facilitating the gel-sol transition of the core gels, which resulted in the release of the drug from the loosened network. These photothermal hydrogels are especially promising for the treatment of breast cancer [106].

### *Sensors*

Due to the biocompatibility and stretchability of most hydrogels many works have been concentrated on the development of flexible electronic skins, energy storages, and wearable sensors [111,114]. Kim et al. fabricated a stretchable and strain-sensitive hydrogel sensor, where acrylamide and sodium alginate were mixed with conductive aqueous poly(3,4-ethylenedioxythiphene)-poly(styrenesulfonate) (PEDOT:PSS) [114]. Microfibers with an approximate size of 50 cm were directly fabricated by microfluidics exhibiting high stretchability and motion sensitivity to detect finger, walking and running motions, or plant growth, respectively. Besides the above-mentioned applications of smart hydrogels, the application field may be broadened to industrial

**Figure 6**




(**a**) i: Schematic diagram of a microfluidic platform for preparing and collecting hemisphere-knotted hollow microfibers. Scale bar indicates 200 μm. Bright-field images for the spindle-knot on a microfiber with (ii) Janus channels and (iii) helical channel. Scale bar indicates 500 μm [87]. (**b**) Concept of microfiber-shaped, programmable hydrogel materials made by microfluidic extrusion. Change in ratio of curvature radii, $R_{initial}/R_n$, of microfibers against cyclic thermal stimulus [110]. (**c**) i: Apparatus for fiber fabrication by using the self-lubricated spinning strategy. ii: Side view of the outflow of the PTFE tube. iii: Section diagram of ii illustrating self-lubricating behavior of poly(2-acrylamido-2-methylpropanesulfonic acid) (PAMPS)/PAAm gel fibers (thick blue line: tube wall, green line: PAAm network, red line: PAMPS chain, blue dots: water molecule). iv: Spun fibers. Scale bar indicates 1 cm [111].

fabrication of clothing, food manufacturing and cosmetic industry [115].

## Conclusion and outlook

Over the past two decades, tailor-made microfluidic devices have been established as a major platform in material science to design complex structures like vesicles, microgels or droplets templated by a discontinuous, segmented flow. At the same time, the precise control over flow pattern formation at low Reynolds numbers has been the key to shed light on early stages of rapidly progressing nucleation, growth and self-assembly processes at continuously flowing liquid-liquid interfaces. Despite this broad range of strategies microfluidics has to offer, we observe a growing number of demands and challenges in materials and life sciences that do not just require the fabrication of single entities that are precisely tailored by microfluidics, e.g., polymer microgels, vesicles or droplets. Recently, the focus has shifted towards microfluidics as a manifold tool for the fabrication of microgel-based assemblies as well as continuous hydrogel structures, e.g., fibers that possess great potential in biomedical applications.

Exemplarily, in the field of cell biology and tissue engineering, microgels have been established as individual niches to tailor the growth, migration and differentiation of single cells. Yet, cell tissue spans beyond a few micrometers and commonly incorporates billons of cells of various types. Taking this into account, the view on microgels in cell biology steadily shifts from being a platform for single cell culturing towards becoming a

multiparametric building block that — by cross-scale assembly into 3D particle matrices — allow for the closer study of the architecture and cross-scale heterogeneity of cell matrices. These so-called supragels (or cellular materials) could likewise be a significant step forward in the design of biomimetic systems in cell-free biotechnology and synthetic biology that help to improve biological systems' understanding and to translate design principles optimized by nature into artificial platforms. We foresee exciting developments, e.g., at the interface of polymer hydrogel design by microfluidics and life sciences. Here, the transition from a continuous hydrogel to a hierarchically structured, discontinuous hydrogel system will provide multifunctional polymer hydrogel particle assemblies as well as fiber-type structures that are able to conduct complex operations based on multiple stimuli. By interfacing these with living tissue, biological metamaterials will come to life, in which living cells and hydrogel materials will form hybrid networks to physicochemically or mechanically interface and interact with each other to advance cell replacement, tissue repair, or drug delivery and release.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andreas Fery reports financial support was provided by German Research Foundation.

## Data availability

Data will be made available on request.

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