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PERSPECTIVE

Intracellular 3D printing

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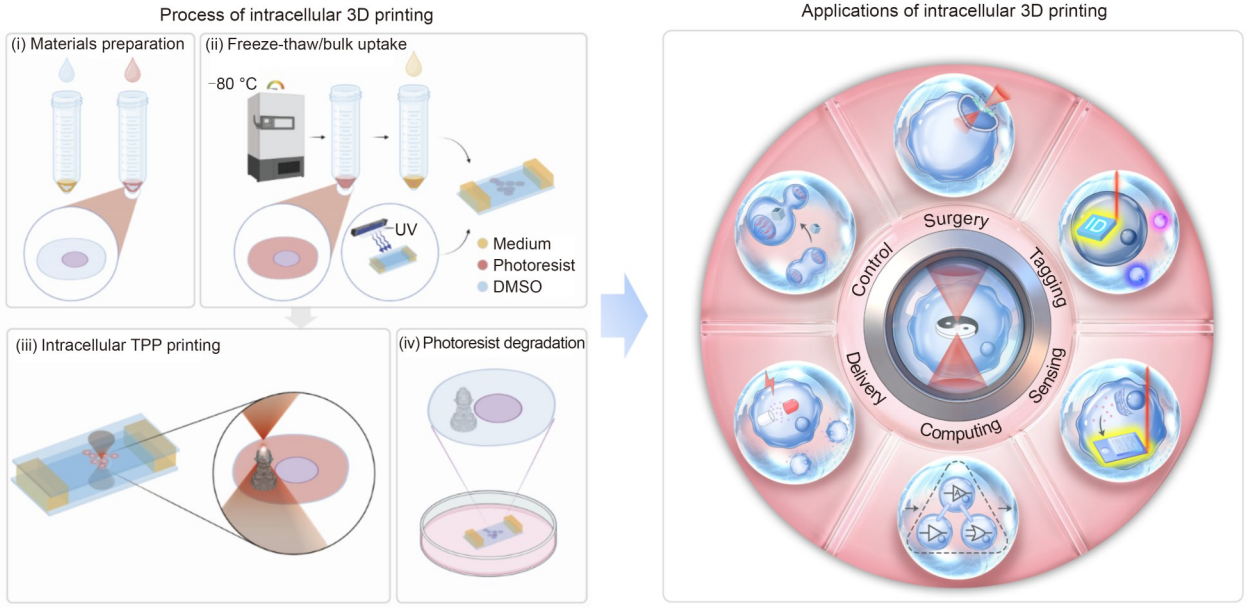
Graphical abstract



Cell engineering is transitioning from "making cells express products" to "directly manufacturing functional structures inside cells." This perspective outlines two-photon polymerization (TPP)-based direct writing of polymerizable biocompatible materials to enable programmable micron-scale three-dimensional (3D) functional architectures within living cells, thereby overcoming the limitations of simple endocytosis or phagocytosis. We highlight scalable workflows that couple bulk intracellular loading of biocompatible photoresists with automated TPP writing, and discuss how endogenous proteins, biocompatible monomers, or biomaterials can be incorporated into these platforms as crosslinking elements to mitigate immune rejection and toxicity. This paradigm elevates the cell from a mere reaction vessel to an active factory, with direct implications for in vivo sensing, tracking, and precision drug delivery. However, key challenges remain, including establishing standardized material libraries, implementing autofocus and pose-adaptive control, and co-designing device architectures together with cellular functions. We anticipate that "intracellular 3D printing" will provide a novel interface between synthetic biology and micro/nano-fabrication.

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1 Emerging approaches for intracellular 3D printing

Recent advances in 3D printing for biological systems have broadened the scope of fabrication from extracellular scaffolds toward enclosed, cell-mimicking environments [1–3]. Using TPP, well-defined hydrogel architectures can be constructed inside giant unilamellar vesicles while preserving membrane integrity, establishing synthetic cells as a controllable test candidate for biocompatible microfabrication [4]. In vivo strategies have been adapted to early embryos, where micro-implants are printed or photocured directly within developing tissues with minimal perturbation of morphogenesis [5]. Mur et al. demonstrated a related strategy by microinjecting the commercial photoresist IP-S into adherent cells and fabricating a "tiny elephant" and other benchmark structures within the cytoplasm [6]. Together, these studies outline a continuum from synthetic compartments to embryos and individual cells. Furthermore, they highlight that intracellular printing operates under the most stringent constraints on photodamage, material toxicity, and diffusion. However, designing photoresists, printing platforms, and printing workflows that maintain, or even exploit, biocompatibility at the single-cell level rather than treating biocompatibility as a mere side condition inherited from earlier TPP platforms remains to be explored.

2 High-throughput intracellular 3D printing

2.1 Platform and protocol for intracellular 3D printing

Achieving high-throughput intracellular 3D printing requires dedicated optical platforms, scalable strategies for introducing photosensitive materials into living cells, and optimized printing workflows. Based on these requirements, a prototype platform was designed. Beyond a conventional TPP setup, the system enables precise control over femtosecond laser power and wavelength to achieve efficient polymerization at the lowest possible light dose, thereby limiting phototoxicity. To reliably position nonadherent cells within the focal volume, microfabricated cell traps were integrated into a redesigned culture chamber, thereby improving sealing, mechanical stability, and fabrication robustness.

Traditional single-cell microinjection, while highly precise, is intrinsically low-throughput because it is serial and labor-intensive [7]. In contrast, bulk uptake strategies, such as freeze-thaw-assisted permeabilization or concentration-gradient-driven diffusion, can simultaneously expose large cell populations to photoresist precursors, enabling parallelized intracellular printing. Building on this concept, a stepwise protocol was developed that combines bulk intracellular loading of photosensitive precursors with automated TPP-based fabrication (Fig. 1a).

To illustrate the design freedom enabled by intracellular 3D printing, a library of conceptual microstructures was constructed for future intracellular fabrication attempts. One example is a stylized "Sun Wukong" model (Fig. 1b1), inspired by the shape-shifting monkey protagonist of the classic Chinese novel *Journey to the West*, who can shrink his body to any size, symbolizing the ability to realize multiple forms and functions within a single cell. Additionally, other subcellular- or cellular-scale architectures were designed, including proteins and organelles. For example, T-cell receptor (Fig. 1b2), cytochrome (Fig. 1b3), and bacteriophage (Fig. 1b4) were designed to showcase how intracellular 3D printing could eventually generate diverse, programmable structures in living cells.

2.2 Case study for intracellular 3D printing

This case study provides workflow-level validation, demonstrating that bulk-loaded, soft hydrogel photoresists can support multi-scale intracellular manufacturing, rather than single-cell demonstrations. To benchmark this high-throughput strategy, a simple hydrogel-based photoresist was tested to evaluate its distribution across large cell populations in parallel. Subsequently, it was reshaped into a shared 3D construct. Instead of focusing on exhaustive performance metrics, this experiment represented an exploratory "stress test" of the entire workflow, from cellular uptake to printing and post-printing recovery. Cells were incubated with dimethyl sulfoxide (DMSO) to gently permeabilize membranes along with a photoresist solution containing the multiphoton photoinitiator methylene blue (MB) and poly(ethylene glycol) diacrylate (PEGDA) monomer. Then, they were subjected to a freeze-thaw cycle so that hundreds to thousands of cells could internalize the precursor cocktail in one step (Figs. 2a–2d). This parallel loading is central to batch intracellular printing, but not single-cell demonstrations.

Using this loaded population as a test bed, a PEGDA-based cubic microstructure was printed in cells and visualized using confocal microscopy to verify that it is within cell boundaries (Fig. 2e). To check whether this process is disruptive to the treated cells, fluorescence recovery after photobleaching was performed on the plasma membrane. Fluorescence intensity was recovered to approximately 90% of the pre-bleach level within 30 s, suggesting that membrane fluidity and overall integrity remain largely intact during and after printing (Fig. 2f). Scanning electron microscope (SEM) imaging provided a complementary, architectural view of the cube penetrating the cells (Fig. 2g), while wide-field optical microscopy captured the real-time evolution of the structure as it was written (Fig. 2h; Movie S1 in the supplementary information). Taken together, this case

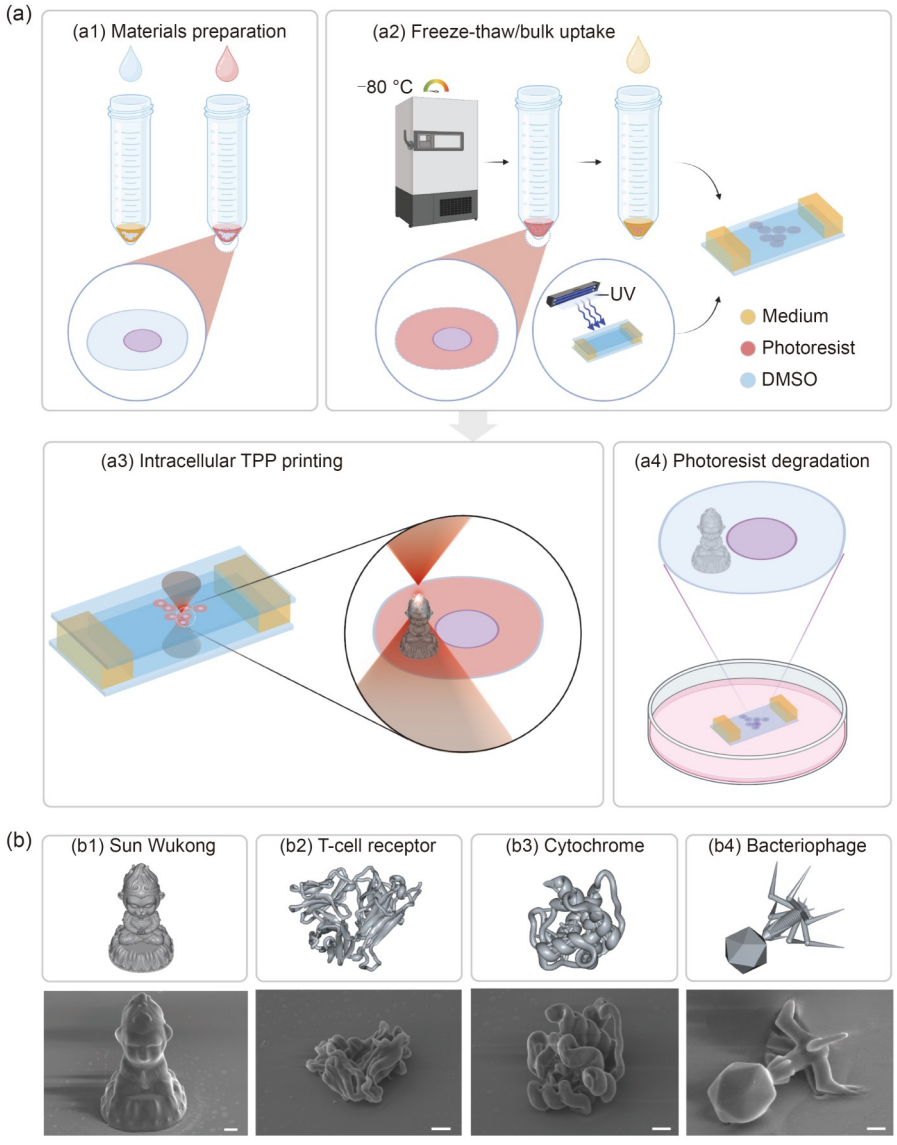

Fig. 1 Workflow and representative structures of intracellular two-photon 3D printing. (a) Schematic diagram of the intracellular printing process: (a1) materials preparation; (a2) freeze-thaw/bulk uptake; (a3) intracellular TPP printing; (a4) photoresist degradation. (b) Printed models (upper) and scanning electron microscope (SEM) images (lower) of the Sun Wukong (b1), T-cell receptor (b2), cytochrome (b3), and bacteriophage (b4) models. Scale bars: 2 μm

study illustrates that a relatively simple PEGDA/MB system, combined with bulk uptake via DMSO, enables batch-mode intracellular 3D printing, generating intracellular 3D constructs across many living cells. Therefore, with additional automation, such as multibeam parallel writing and auto-focusing/positioning, intracellular devices can eventually be manufactured in batches rather than one cell at a time.

3 Functional structures at cellular scale via biomaterials

By integrating geometry, mechanics, and molecular transport, functional subcellular architectures can be created. Soft, water-rich matrices preserve cytoplasmic rheology and molecular exchange, whereas rigid, hydrophobic thermosets perturb mechanotransduction and hinder diffusion [8]. These constraints translate directly into material requirements for intracellular TPP. In practice, the performance and cytocompatibility of an intracellular photoresist are largely determined by two coupled factors: (i) the photoinitiator, which sets the excitation window, initiation efficiency, and reactive oxygen species (ROS) generation and phototoxicity burden, and (ii) the monomer/base matrix, which dictates the hydration, mechanical compliance, and molecular permeability of the printed network. Accordingly, we first discuss photoinitiator selection and then compare candidate monomer/base materials for intracellular 3D structuring.

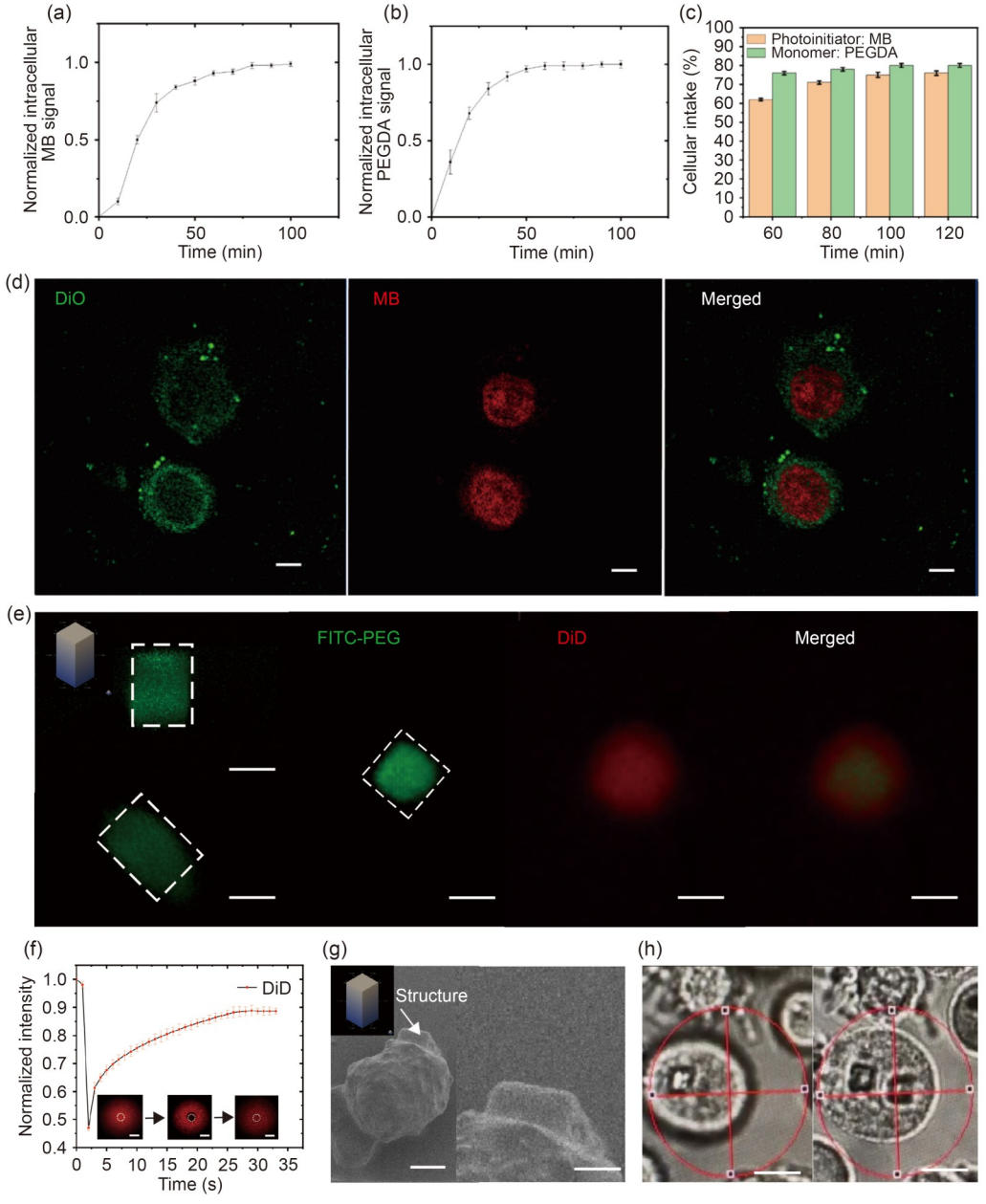

Fig. 2 Intracellular printing of photoresist and related structural characterization. (a) Relative concentration of the photoinitiator methylene blue (MB) permeating cells over time. (b) Relative concentration of the monomer PEGDA permeating cells over time. (c) Proportion of each component of the photoresist infiltrating cells over time. (d) Microscopic fluorescence images of the photoresist after permeation into cells (DiO: λ_{ex}= 488 nm; MB: λ_{ex}=633 nm). Scale bars: 2 μm. (e) Microscopic fluorescence images of the intracellular printed structure (FITC-PEG: λ_{ex}=488 nm; DiD: λ_{ex}=633 nm). Scale bars: 5 μm. (f) Photobleaching curve of the fluorescence intensity of the cell membrane after intracellular printing. Confocal fluorescence images of the top plane of the cell are shown (red, λ_{ex}=633 nm): (left) before photobleaching of a circular area (white dashed line), (middle) 1 s after photobleaching, and (right) 30 s after bleaching. The normalized mean intensity within the bleaching area is plotted over time (scale bars: 3 μm). (g) Scanning electron microscope images after intracellular printing (the model penetrates the cell to show the structure), showing a partial enlarged view of the side of the penetrating structure (right). Scale bars: 2 μm. (h) Light microscope images of the intracellular printing process, from left to right: before and after printing (scale bars: 10 μm). Data in (a–c, f) are expressed as mean±standard deviation (n=3). DiO: 3,3'-dioctadecyloxacarbocyanine perchlorate; FITC-PEG: fluorescein isothiocyanate-polyethylene glycol; DiD: 1,1'-dioctadecyl-3,3,3',3'- tetramethylindodicarbocyanine perchlorate

3.1 Photoinitiator selection

Intracellular TPP requires photoinitiators that are efficient under near-infrared (NIR) excitation and compatible with the cellular environment. Small, water-soluble dyes, such as MB, Eosin Y, and Rose Bengal (RB), are widely used because they combine low molecular weight with strong visible absorption [9–11]. MB (approximately 320 Da) exhibits

strong absorption around 665 nm, is highly water-soluble, and can permeate cell membranes efficiently. Eosin Y and RB also exhibit strong visible absorption and excellent aqueous solubility but can generate substantial ROS upon illumination, increasing phototoxicity. MB and Eosin Y have relatively small two-photon absorption cross-sections (on the order of approximately 10 GM). Even so, under femtosecond NIR excitation, these dyes can be photoactivated within living cells to drive localized photodynamic effects in situ. MB is particularly notable for its small size, membrane permeability, and relatively low cytotoxicity at appropriate doses, making it a practical and validated initiator for intracellular 3D printing. Given the confined intracellular environment, photoinitiator concentration and laser exposure should be empirically optimized based on cell-viability measurements. Furthermore, longer-wavelength excitation, combined with efficient, water-soluble initiators, can reduce the total light dose and heat/ROS burden.

3.2 Comparison of monomer/base materials

Two main types of photoresists are considered for intracellular 3D structuring: hydrophilic hydrogel-forming monomers, such as poly(ethylene glycol) (PEG) diacrylate (PEGDA), PEG methyl acrylate, 2-hydroxyethyl methacrylate, bovine serum albumin, and commercial acrylic-based IP-series resins (e.g., IP-Dip, IP-L). Here, we take PEGDA as a representative example, as its hydrogels form soft, water-rich networks with tunable elastic moduli in the kilopascal range that closely match cytoplasmic mechanics. Therefore, these hydrogels support molecular diffusion of metabolites and signaling factors. PEGDA is biocompatible, optically transparent, and can incorporate degradable linkers, making it suitable for transient intracellular constructs. To balance polymerization efficiency with cell viability, optimizing the resin formulation to 15%–20% (150–200 g/L) PEGDA dissolved in isotonic phosphate-buffered saline (PBS) or phenol red-free culture medium is preferable. Using PBS as the solvent is crucial for maintaining isotonicity (approximately 300 mOsm/L). Pure water or hypotonic buffers cause cell swelling and lysis, whereas high monomer concentrations (>30%) create a hypertonic environment, leading to cell crenation (shrinkage) and death. In contrast, IP resins polymerize into stiff (2–3 GPa), hydrophobic, and nondegradable thermosets [12, 13]. Moreover, their poor water solubility and rigid structure make them incompatible with intracellular environments, potentially leading to mechanical stress, metabolic interference, or cytotoxicity. They typically require organic-solvent-based development/cleaning and contain proprietary photoinitiators that are not intended for direct contact with living cytoplasm.

For intracellular use, PEGDA-based systems can be formulated in isotonic culture medium or in buffered saline to match the osmolarity and ion strength with the cytosol. If DMSO is required to carry hydrophobic components, its volume fraction should be kept below approximately 1% to ensure cell viability. While direct cytoplasmic delivery via microinjection can overcome constraints associated with membrane permeability and monomer size, submicron injection tips are highly sensitive to viscosity: as PEGDA concentration increases, higher pressures are needed. This increases the chances of clogging, compromising injection success and cell viability [14, 15]. Consistent with the case study in Fig. 2, a modest-molecular-weight PEGDA formulated at near-aqueous viscosity, paired with MB under femtosecond NIR excitation, provides a biocompatible and experimentally validated baseline for functional intracellular architecture.

4 Intracellular 3D printing toward biomedical applications

4.1 Intracellular scaffolds for steering cell behavior

Intracellular 3D printing has several potential biomedical applications (Fig. 3). One exciting prospect is designing subcellular scaffolds that can modulate cell behavior. Cell polarization, migration, or differentiation might be guided by internal printed frameworks that impose spatial cues or mechanical constraints on organelles and the cytoskeleton. For instance, a printed microstructure could anchor or partition specific cytoplasmic regions, inducing a controlled asymmetry similar to natural cell polarity cues [16]. By physically interacting with the cell's architecture, even deforming the nucleus, such internal structures could influence mechanotransduction pathways and gene expression, providing a new toolkit for programming cell fate from within, beyond traditional genetic or biochemical approaches. However, the stiffness and dimensions of these intracellular scaffold structures must be carefully optimized to avoid overly rigid or bulky constructs that could disrupt cellular metabolism or elicit excessive immune responses.

4.2 Disease modeling and organelle repair from within

Disease modeling and organelle repair are other compelling avenues. Using intracellular 3D printing, synthetic organelles or pathological proxies can be created inside a cell. Inert microdeposits that mimic protein aggregates can be printed to study neurodegenerative disease mechanisms at the single-cell level or fabricate a functional organelle substitute to rescue a cell with a damaged mitochondrion or lysosome. Indeed, artificial organelles have been explored

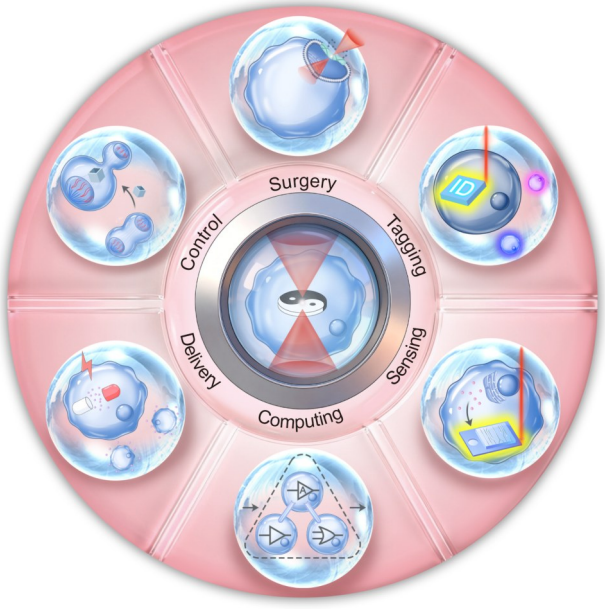

Fig. 3 Application domains of intracellular functional microstructures: surgery, tagging, sensing, computing, delivery, and control

as a medium to add or restore cellular functions. For example, synthetic DNA-based "organelles" have been designed to trap and sequester telomerase in cancer cells, suppressing their division [17]. Such structures require smaller dimensions, which means that the initiators used must have sufficient initiation efficiency to print fine structures while also having good degradation properties. In the future, such therapeutic concepts could be realized more directly by printing the requisite nanostructures on demand within target cells, enabling precision cell therapy for diseases involving intracellular dysfunction.

4.3 Embedded microdevices for sensing and therapeutics

Microdevices can be embedded within cells for sensing or drug delivery, thereby enabling a direct method for manufacturing intracellular devices for sensing and actuation. Researchers have successfully placed tiny optical resonators (microlasers) inside cells to act as unique spectral barcodes and monitor physical conditions [18]. Injectable rigid silicon chip sensors have been used to measure intracellular pressure changes [19]. Intracellular 3D printing will enable the fabrication of such sensors or drug-loaded capsules in situ, minimizing invasiveness. Therefore, it is possible to print a smart nanoparticle or hydrogel capsule within a cell that gradually releases a drug or responds to a biochemical trigger to modulate cellular activity, provided the materials exhibit certain responsive properties. Similarly, printed microstructures with electronic or photonic functionality could continuously report on a cellular metabolic state or force environment, turning the cell into a self-monitoring system.

4.4 Toward programmable and hybrid "cyborg" cells

Looking ahead, intracellular 3D printing could enable programmable cell engineering synergistically with synthetic biology. This technology provides a physical platform for organizing and constraining biological processes inside the cell, facilitating the construction of spatially arranged enzyme cascades or gene networks that would be impossible to achieve with gene editing alone. Early efforts using synthetic cells have already shown this potential: 3D-printed membrane pores were used to control molecular transport into protocells. Extending these concepts to living cells, intracellular printing could potentially enable the fabrication of intracellular modules for biocomputation and the spatial organization of regulatory processes. Future efforts in intracellular printing could lead to "cyborg cells," in which each cell contains built-in microdevices that empower its functionality, from programmable metabolic factories to self-healing cellular components [20]. This forward-looking integration of 3D printing and cell biology considerably expands cellular capabilities, heralding a new era of engineered living materials.

5 Challenges and future perspectives

Over the past three years, we have pursued intracellular 3D printing as an ambitious yet experimentally testable concept. We finished the preliminary results, as shown in Fig. 2 in June 2024 and demonstrated the feasibility of constructing complex 3D microstructures inside living cells. We filed

a patent entitled "A method for laser additive manufacturing within cells," which covers key aspects of this approach in April 2025 (Application number: CN202510492240.6). In parallel, Mur et al. reported similar work on creating functional microstructures inside living cells in January 2026, during the revision process of this perspective [6].

Compared to their work, our platform emphasizes three features that we believe enable the construction of more complex intracellular architectures. First, instead of serial microinjection, we rely on bulk freeze-thaw cycles to simultaneously load photoresist precursors into multiple cells. This diffusion-based uptake is gentler on the membrane and distributes monomer and photoinitiator throughout the cytoplasm rather than confining the printable volume to a narrow region near the needle tip. Second, our experiments use suspended, roughly spherical cells, which provide a larger isotropic intracellular volume for 3D constructs. The implications of suspended versus adherent geometries are discussed in detail in Sect. 5.6. However, adherent cells are generally easier to locate and image than suspended cells, facilitating real-time observation and downstream functional analysis. Third, we employ a PEGDA-based hydrogel system as the intracellular matrix, in contrast to the rigid IP-S resin used by Mur et al. This soft, water-rich network is more compatible with cellular physiology and better suited for assembling functional subcellular structures. Still, many technical difficulties remain, especially for large-scale cellular manufacturing.

5.1 Printing technology optimization and automation

Current TPP setups are not designed for intracellular administration and therefore require major adaptation. Active autofocus/feedback control is needed to compensate for cell drift. Pose monitoring should be incorporated to track rotation or deformation so the laser hits the intended volume. Because TPP is a serial, point-by-point process, multibeam parallelization or faster scanning could improve throughput. Microfluidic trapping or cell-array platforms with image recognition can immobilize and re-identify cells post-printing, improving repeatability for downstream analysis.

5.2 Material library standardization

A primary challenge is the lack of a standardized library of polymerizable biomaterials for intracellular applications [21]. Different applications require well-characterized, biocompatible photocurable materials that are nontoxic both before and after polymerization and do not persist as inert inclusions, but can instead be degraded, cleared, or remodeled by cells. PEG-based hydrogels are usually more cytocompatible than rigid, highly crosslinked acrylates that persist as inert inclusions. However, in the absence of standards, these experiments rely on ad hoc formulations and extensive testing, slowing progress and increasing risk.

5.3 Biosafety and long-term effects

Long-term biocompatibility remains unclear. We must test whether printed inclusions elicit stress responses, immune-like reactions, or gene-expression changes over hours to days, and whether the residual photoinitiators/monomers are cytotoxic. The capability of cells to degrade or expel the printed polymers via proteasome or autophagy is also unknown. Time-lapse live-cell assays and biochemical analyses will be needed under realistic conditions.

5.4 Optical and physical challenges

Accurate delivery of two-photon light inside a living cell is difficult. Although NIR TPP light can penetrate cells, refractive index mismatches at internal interfaces, such as photoresist droplets or organelle boundaries, can distort the focus and reduce precision. Scattering and aberrations from cellular structures and the curved membrane further blur the focal spot. Beam shaping or adaptive optics may be required for in situ correction.

5.5 Cell–device co-design

Printed microstructures must be co-designed with host-cell biology to avoid disrupting essential processes. Internal scaffolds/sensors should tolerate division, organelle trafficking, and metabolic exchange while maintaining function. Where possible, designs could leverage cellular machinery that anchors to the cytoskeleton or uses motor proteins for positioning. This integration requires close collaboration between cell biologists and device engineers.

5.6 Suspended vs. adherent cells

The physical shape of the target cell significantly influences the structures. Adherent cells can flatten to a thickness of only a few microns, restricting printed features to planar or thin-sheet geometries inside the cell. In contrast, suspended cells typically remain roughly spherical, with diameters of approximately 10–20 μm, providing a larger internal volume for truly 3D architectures. Thus, printing in suspension facilitates the construction of volumetric microstructures, whereas printing in adherent cells is limited to flatter designs. The optimal mode depends on the specific application and cell type.

5.7 Future perspectives

Despite these challenges, intracellular manufacturing offers exciting possibilities for bioengineering. For example,

digital identifiers or optical tags could barcode individual cells for tracking. The use of embedded components can enable new forms of intracellular sensing or actuation [22]. Intracellular printing may also transform tissue engineering and personalized medicine. Instead of relying only on external scaffolds, one can directly print cellular building blocks within a tissue matrix or even in vivo. Patient-derived cells with tailored intracellular microarchitectures may provide highly accurate models for drug screening or promote tissue regeneration after injury. Embedding nanoscale sensors, microelectronic elements, or optical components inside cells could enable unprecedented real-time monitoring and control of cellular function during development or therapy.

Looking ahead, advances in artificial intelligence and robotics can accelerate these developments. Machine learning algorithms can be used to optimize microstructure geometries and placements for specific cell types, whereas robotic microscope systems execute high-throughput intracellular printing. Revolutionary concepts such as a fully "3D-printed synthetic cell" have even been proposed, in which every component of a cell is engineered using additive methods. While fully printed cells remain a long-term goal, the ongoing advances in fabrication technologies, biomaterials, and computational design can expand the scope of applications.

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Author contributions JRH: conceptualization, methodology, investigation, and writing—original draft. AR: data curation. XYL: data curation. HYY: resources, supervision, and funding acquisition. LM: conceptualization, project administration, and writing—review & editing. All authors have read and agreed to the published version of the manuscript.

Declarations

Conflict of interest HYY is an editor-in-chief of *Bio-Design and Manufacturing* (*BDM*). LM is an academic editor of *BDM*. They were not involved in the editorial review or the decision to publish this article. The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human or animal subjects performed by any of the authors.

Data availability The data supporting the findings of this study are available from the corresponding authors upon reasonable request.

Use of generative AI tools The authors did not use any generative AI or AI-assisted technologies in the preparation of this manuscript.

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