

## Multi-scale fabrication of hierarchical architectures in hydrogels with novel functions

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Living systems exhibit extremely sophisticated and dynamic properties. Therefore, there is a growing demand for novel biomimetic designs to introduce such complex functions into artificial materials. In sharp contrast to conventional synthetic materials, living systems are composed of hierarchical structures spanning multiple length scales from the molecular ( $\sim$ nm) to the cellular ( $\sim$  $\mu$ m) and further to the tissue/organ scale ( $>$ mm). For example, a single cell contains countless biomolecules (e.g., proteins, DNA, and lipids) that can precisely recognize one another and self-assemble into distinct hierarchical structures, including membranes, cytoskeletons, and ribosomes, etc. At larger length scales, different cell types self-organize into complex tissue architectures, such as anisotropically aligned muscle fibers and skin patterns. These hierarchical architectures are essential for enabling diverse chemical reactions in a single system and underline the remarkable functional complexity of living systems. My research focuses on developing fabrication methodologies to reproduce such biological hierarchical structures across length scales, from molecular to tissue level, with the ultimate goal of creating novel materials that exhibit life-like, sophisticated functions.

### (1) Cell-inspired fabrication of supramolecular hydrogels via self-sorting phenomena

In living cells, multiple fibrous cytoskeletal components, such as actin filaments and microtubules, orthogonally "*self-sort*" into different networks, where they play distinct roles in molecular transport, cell motility, and morphogenesis. Inspired by this biological principle, I investigated that "*self-sorting*" of synthetic low-molecular-weight-gelators (LMWGs) to create unique supramolecular hydrogels with advanced functions. For instance, I developed self-sorted supramolecular networks of photo-responsive peptidetype LMWGs and non-responsive lipid-type LMWGs. These systems generated complex macroscopic patterns upon light exposure, through out-of-equilibrium process where the diffusion and interactions of monomers were involved (JACS 2022). I also extended the "*self-sorting*" concept to composite hydrogels of supramolecular nanofibers and macromolecular networks (e.g. agarose polymer). In this work, I discovered that their network can be classified into four different patterns based on fiber morphology and spatial localization, which control their mechanical properties of the resulting hydrogels (Nat. Commun. 2023). These works establish design guidelines for utilizing self-sorting to create synthetic, multi-component hydrogels that mimic cell-like structural and functional complexity.

### (2) Tissue scale fabrication of soft materials based on 3D printing for novel biofabrication

Beyond cell-scale structures, I have explored the fabrication techniques of tissue-sized structures from cells or cellular-sized materials using novel 3D bioprinting technologies. In this context, I've explored the use of granular hydrogels formed by jamming microgels, which exhibit unique shear-thinning property and porosity that make them suitable for extrusion-based 3D bioprinting. I designed various stimuli-responsive microgels and 3D printed these microgels into multi-component objects with specific patterns to program shape morphing of the objects or regulate biological functions of cells embedded in the objects. For example, I developed temperature-responsive microgels composed of poly(N-isopropylacrylamide) polymers. These dynamic microgels are extruded with a 3D printer into a support bath of non-responsive microgels to create multi-material granular hydrogels that undergo actuation upon heating, governed by the responsiveness of individual microgels and the printed patterns (Adv. Mater. 2024). This strategy was further extended to chemically responsive microgel systems based on  $\beta$ -dextrin–adamantane supramolecular crosslinks with stem cell spheroids, enabling

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spatiotemporal regulation of cellular migration within printed objects (Adv. Sci. 2025). This bottom-up assembly approach, combined with 3D printing, provides a powerful platform for the programmable fabrication of dynamic tissue-like objects that respond to external stimuli, with promising applications in soft robotics and tissue engineering.