

Organoids Producing Materials

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Abstract

Self-organizing tissues, such as organoids, offer transformative potential beyond healthcare by enabling the sustainable production of advanced materials¹. Resource scarcity and global warming drive the need for innovative fabrication solutions. This prospective review explores developmental biology as a manufacturing process, where the material (*e.g.* spider silk) and its production unit are self-organized (*e.g.* silk glands). Biological systems orchestrate the emergence of hierarchical materials with superior mechanical properties and biodegradability, using abundant and renewable resources. Tissue engineering enables the creation of biological systems that surpass current synthetic designs in complexity.

We highlight application opportunities, focusing on spider silk as a model to demonstrate how organs synthesize and assemble next-generation materials. The concept of growing both a material and its organ production units is exemplified by hair-bearing organoids, self-organized from induced pluripotent stem cells (iPSCs)².

Key challenges in expanding organoid research to new model species and scaling-up production are discussed alongside potential solutions. We propose a simplified description of these complex systems to help address key challenges. Furthermore, synthetic and hybrid approaches are explored, considering the ethical, societal, and technological impacts.

Though still in their infancy, material-producing organoids present a promising avenue for sustainable, high-value products, fostering new interdisciplinary collaborations among bioengineers, developmental biologists, and material scientists. This work aims to inspire further exploration into the applications of self-organized biological systems in addressing global challenges.

Keywords

Tissue engineering, organoids, living materials, biological materials, sustainability, microstructure, self-assembly, self-organization, self-microfabrication, developmental biology, systems biology, manufacturing process, microfabrication, complexity

Highlights

- Biological materials are sustainable and competitive with their synthetic counterparts.
- Organs regulate the self-assembly of materials *in vivo*.
- Organoids can produce biological materials *in vitro*.
- These self-organized living machines may create microstructures in large materials, at scale, with potential marginal cost.
- A conceptual framework discusses challenges in organoid diversification, notably the knowledge transfer from well-studied to lesser-studied organisms.

Table of contents

1.Introduction	2
2.Application opportunities for biological materials	3
2.1.Exploring new materials.....	3
2.2.How an organ regulates material self-assembly	6
3.Growing organs to produce materials	8
3.1.Principles of self-microfabrication.....	8
3.2.Material-producing organoids	10
4.Challenges in organoid development	11
4.1.Growing new organoids	11
4.2.Scaling for real-world applications.....	11
5.Theoretical considerations	12
5.1.How organs are made and maintained.....	12
5.2.Dealing with complex organs	14
6.Future outlook to address challenges	17
6.1.Growing new organoids	17
6.2.Overcoming biological limitations	18
7.Ethical, societal and technological implications	19
7.1.Societal and technological impact.....	19
7.2.Ethical considerations and contrary views.....	20
8.Summary and Conclusion	20
9.Glossary and Definitions	20
10.Acknowledgments	21
11.References	21

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1. Introduction

As the Earth's climate continues to shift and affects living conditions, human societies face the challenge of reducing their planetary impacts^{3–5}. Moreover, our high-standards of living heavily rely on limited resources⁶. Our infrastructures are predominantly made from optimized engineered materials, primarily dependent on fossil sources and unevenly distributed elements⁷. Both climate change and resource scarcity already contribute to human migrations, loss of life, economic burdens and geopolitical tensions⁸.

To mitigate these upcoming consequences, efforts have intensified in the past decades^{9,10}. But compromising standards of living¹¹ raises additional challenges¹². Given the large environmental impact of our material production industries, reducing their footprint is particularly significant¹³. However, improvements in sustainability are often accompanied with trade-offs on material performance, slowing down their implementation¹⁴. Biological materials open new avenues to keep producing high-performance and sustainable solutions¹ (Fig. 1A).

Biological materials, such as wood or spider silk, are often considered more sustainable than most conventional synthetics¹⁵. They display high mechanical properties, such as tensile strength, toughness, elasticity, adhesion, etc., while being made from globally available and renewable resources; notably transforming wastes into resources¹⁶ (Fig. 1A). Natural materials can even achieve a zero or negative carbon footprint¹⁷ and their biodegradability¹⁸ supports a circular economy¹⁹. Their production involves little to no external energy, avoids toxic chemicals, and takes place in water-based conditions²⁰. Nature's biofabrication processes for creating these materials differ significantly from conventional manufacturing²¹. Material-producing organs contain specialized cell types with complex molecular machinery that guides material self-assembly from the nano- to the macroscopic scales²², a process

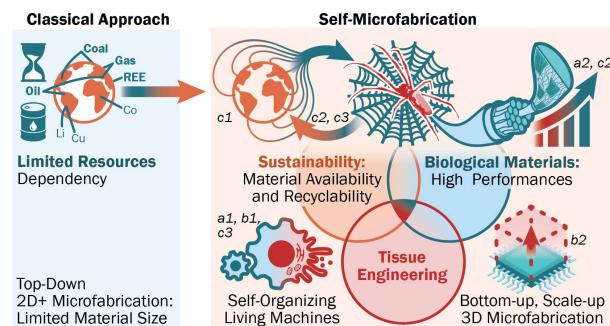
we name self-microfabrication (Fig. 1B). These refined hierarchical microstructures, optimized through evolution²³, are responsible for their outstanding properties^{24,25}. To produce them, one can use synthetic biomimicry or recombinant approaches²⁶ but difficulties remain in replicating their full complexity²⁷ (Fig. 1C). While living organs are complex biological systems that are difficult to replicate synthetically; they offer valuable insights for conventional manufacturing methods^{28,29}.

Innovations in material engineering have consistently helped to improve everyday objects and infrastructures. However, the trade-off between performance and sustainability reveals limitations in current manufacturing approaches³⁰, specifically in (a) material microstructures, (b) production processes and (c) environmental impact:

- (a1) Engineering complexity: biological systems present high levels of complexity, hierarchical control and automation that are hard to replicate synthetically^{31,32}.
- (a2) Many engineered materials may be highly optimized for specific properties (e.g. stiffness) but are often less versatile³³.
- (b1) Conventional microfabrication has high infrastructure costs, illustrated by semiconductor foundries³⁴.
- (b2) Manufacturing tools and microstructures: although current microfabrication technologies can produce complex multi-scale materials, they cannot yet produce microstructures in large materials, at scale³⁵, as nature can³⁶.
- (c1) Raw materials scarcity and energy costs: dependency on rare earth elements³⁷ and fossil-based materials³⁸.
- (c2) Sustainability: optimizing properties in engineered composites often introduces trade-offs on disassembly and recyclability³⁹, while biological materials are biodegradable.
- (c3) Significant environmental and health impacts of conventional industrial facilities⁴⁰.

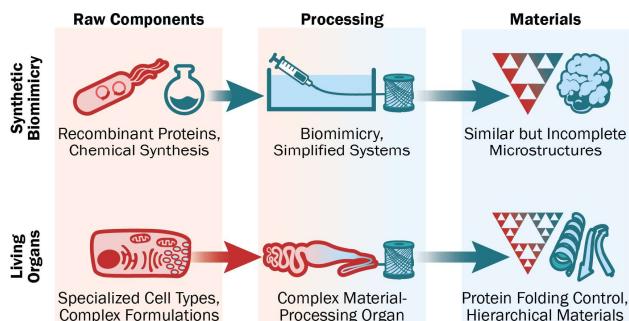
A. Biological Materials Opportunity

Performant and Sustainable



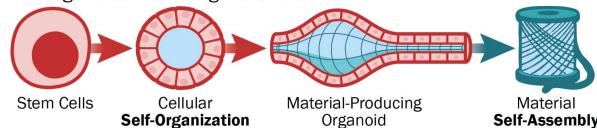
C. Making Biological Materials

Comparing Synthetic with *in vivo* Approaches



B. Self-Microfabrication Principle

Organoids Producing Materials



D. Understanding Material-Producing Organs

Research Steps

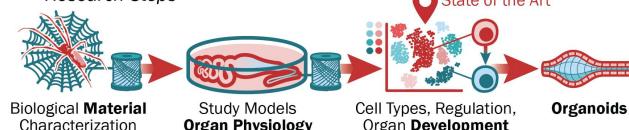


Figure 1: Self-Microfabrication for High Performance and Sustainable Materials

A. The demand for biological materials in face of resource scarcity. Integration of tissue engineering and material sciences to grow materials and overcome conventional manufacturing limitations on engineering (a), fabrication (b) and environmental impacts (c). **B.** Self-microfabrication summary, illustrated by self-organized organoids from stem cells producing biological materials. **C.** Comparison of *in vivo* material-producing organs with synthetic and recombinant approaches. **D.** Research steps to characterize the material, understand the material-processing of a specialized tissue, and its development. Red: biological systems, blue: materials, orange: sustainability aspects.

In contrast, the versatile and competitive properties of biological materials stem from their (a) refined microstructures, (b) unique manufacturing, and (c) ecological integration³³, all of which could help address these limitations if successfully replicated⁴¹.

These hierarchical materials²⁴ have mechanical properties essential in various industries⁴²; for example wood tensile strength stems from its self-organized composite microstructure⁴³. Understanding such materials to mimic them synthetically (Fig. 1D) implies to first characterize their properties, hierarchical structure and self-assembly mechanisms⁴⁴. Second, the material-producing organ must also be studied to understand its physiology⁴⁵ and development⁴⁶. Biological materials' intricate micro-architectures (a1) have been optimized through evolution for high mechanical performance and versatility^{25,47} (a2) (Fig. 1A). Organs such as the spider silk gland regulate complex processes, notably the molecular assembly of fibers⁴⁸. These organ production units are themselves self-organized following a developmental program. Instead of designing such highly complex systems from scratch, one can recapitulate the conditions guiding organogenesis⁴⁹. Starting with precise initial conditions and cell sources, highly complex tissues can self-organize⁵⁰ and produce materials autonomously⁵¹. Organoids illustrate this principle and can grow hierarchical materials, such as hair follicle organoids². These tissues, made of heterogeneous cell types differentiated from stem cells, show physiologically relevant behaviors⁵² that can mimic material-producing organs⁵³.

This approach could lead to living machines⁵⁴, potentially produced in large numbers by leveraging self-organization⁵⁵ (b1). Moreover, they can grow microstructured materials at macroscopic scales, as observed in nature⁵⁶ (b2), using abundant raw materials⁵⁷ (c1). The final products can be highly complex while biodegradable⁵⁸ (c2). Organ production units can themselves be recycled, thus reducing the environmental impact⁵⁹ (c3).

While current biofabrication leverages specific aspects of biological processes, such as enzymatic reactions or the cultivation of unicellular organisms⁶⁰, it has yet to explore its full potential across all scales and material microstructures⁶¹. Self-microfabrication has the potential to complement current manufacturing technologies and achieve high-tech, low-impact materials. It takes inspiration not only from materials' production⁶² but also from the self-organization of their production units.

Collaborative efforts in tissue engineering and material science have driven significant progress, especially in creating 3D hydrogel scaffolds and biomaterials that interface with biological tissues⁶³. Material innovations have been instrumental in advancing organoid research⁶⁴. Conversely, this paper explores how organoids could improve material science⁶⁵.

Section 2 shows biological materials applications and highlights how an organ can regulate the self-assembly of materials, using spider silk as a case study. Section 3 introduces the principles of material-producing organoids, current advances and an existing proof of concept. Section 4 discusses key challenges, including organoid growth in non-model organisms and scaling up production. Section 5 presents theoretical aspects of organoid development, including tissue homeostasis strategies, the variety of developmental

trajectories, and multiscale representations for modeling purposes. Section 6 proposes future directions to overcome challenges and biological limitations. Finally, Section 7 addresses ethical, societal, and technological implications, concluding with key contributions in Section 8.

2. Application opportunities for biological materials

2.1. Exploring new materials

Biomimicry of biological materials and potential applications

Many biological materials have been characterized for their outstanding mechanical properties such as stiffness, elasticity, toughness, hardness or adhesion²⁵. These properties stem from diverse microstructures observed across species, including fibrous, layered, helical, gradual, tubular, and latticed arrangements²⁷. To broaden the perspective, Table 1 presents a diversity of biological materials as candidates for self-microfabrication, with their main properties, biological origins and potential applications.

Preprocessing materials for external self-assembly

Some materials are formed within cells, notably the hair shaft⁶⁶, or in a controlled extracellular space, such as spider silk glands. However, other biological materials form without requiring an organ for their production. Self-assembly can occur upon secretion in external environments, which generally simplifies biomimicry approaches⁶⁷, without the need for self-microfabrication. Yet some materials still depend on an organ for internal preprocessing prior to their secretion. For instance, the cuticle of insects is initially soft but hardens rapidly in contact with air⁶⁸. This chitin and protein biomolecular composite has a preformed microstructure that hardens into a tough exoskeleton through sclerotization⁶⁹. Catecholamines, such as dopamine derivatives, oxidize with air into quinones and crosslink cuticular proteins but the microstructure is performed by the epidermis⁷⁰. In other cases, materials rely on environmental conditions such as temperature changes, humidity absorption, or dehydration. Some aquatic species notably rely on their saline aqueous environment for material processing, such as barnacle adhesive⁷¹, sandcastle worm cement⁷², coral skeleton⁷³, and mussel byssus⁷⁴.

To illustrate how specialized organs help prepare biological materials for their rapid on demand solidification, we detail the mussel byssus example⁷⁵. Byssal fibers cure after release, triggered by the higher pH of saltwater compared to that of the gland⁷⁴. This fiber anchors mussels to the shore and withstands the crushing waves with its outstanding toughness and underwater adhesion properties⁷⁶. Within the mussel's foot, plaque gland cells⁷⁷ secrete plaque vesicles and metal storage particles (Fe/V) into longitudinal ducts⁷⁸. Cilia transport these concentrated droplets to distal depressions, where the material forms reversible metal-containing coordination complexes with catechol groups of dihydroxyphenylalanine (DOPA)-containing vesicles⁷⁹. After secretion from the foot, the fiber is held at its stem by billions of cilia and detaches upon neurochemical stimulation⁸⁰. While synthetic and biotechnological methods aim to mimic this hierarchical material⁸¹, self-microfabrication offers a promising alternative for replicating complex material processing.

Table 1: Potential biological material candidates for self-microfabrication

Common biological materials with a description of their most relevant properties, potential applications and tissues or cells of origin. Organized by taxonomy, including domains, kingdoms, phyla, subphyla or classes when most relevant, a focus in given to animals.

Taxonomy	Material	Function	Material Properties / Description	Biological Systems	Potential Applications	Ref
Bacteria	Magnetite in Magnetotactic Bacteria	Geomagnetic navigation	Controlled size and morphology of magnetite (Fe_3O_4) crystals; organic outer layer creating a homogeneous dispersion in aqueous solution	Fe^{2+} captured from the intermembrane space with vesicle encapsulation within magnetotactic bacterial cells (e.g., <i>Magnetospirillum magneticum</i>)	Biotechnologies like high-sensitivity immunoassay, drug screening and cell separation, targeted drug delivery using magnetic guidance; heavy metals removal	82,83
Fungi	Fungal Cell Walls	Structural support and protection	Made of chitin, β -glucans, and glycoproteins; rigid and dynamically adapting to the environment; resistant to turgor pressures (1-8 MPa); thickness (~100 nm)	Complex enzymatic pathways including chitin synthase, glucan synthases and specific assemblies at the cell membrane	Hydrophobic coatings (notably using hydrophobin proteins); antifungal drug development	84,85
Protists	Diatom Frustules	Protective silica shells	Hydrated, layered, porous, amorphous silica with pores and spines. Absorb mechanical stress; Lightweight and durable; Stiffness (22.4 GPa), compressive strength (155-680 MPa)	Diatoms synthesize silicic acid transporters and silica-forming proteins (phosphorylated silaffins, cingulins, and silacidins), long-chain polyamines and chitin	Lightweight, impact-resistant materials; microlenses, optical sensors and biosensors; drug delivery systems	86,87
	Radiolarian Skeletons	Structural support and protection	Mainly made of hydrated amorphous silica (98 %) within an organic matrix with traces of Mg, Ca, Al, and Na; particles around 10-50 nm assembling hierarchically in lamellae and polysaccharide plates joined by protein fibrils	Captured monomeric orthosilicic acid is concentrated within cells; a synthesized organic matrix guides the mineralization and prevents initial crystallization	Lightweight and resilient materials	88
	Coccolithophores	Protective shell; buoyancy	Calcite scales (coccoliths) increasing light scattering in the water; Contribute to 1-3 % of primary productivity, sequestering carbon	Biomineralization in Golgi-derived vesicles within coccolithophores	Optical scattering, detectable by satellite monitoring; structural material; carbon sequestration	89,90
Plants	Cork	Protective barrier; reduces water loss	Buoyant, impermeable to water; anisotropic elastic (10-20 MPa) and resilient under compression; low thermal conductivity; lightweight (0.1 g/cm ³); Mainly composed of suberin (~52 %)	The phellogen (cork cambium), a meristematic tissue continuously generates phellem (cork cells) in a periderm layer	Sealing (wine industry); Insulating material; construction, aesthetic	91,92
	Wood (various timber wood)	Structural support; water transport	Anisotropic, aligned fibers; Density (120-1200 kg/m ³); stiffness (softwoods: 7-10 GPa, hardwoods: 20 GPa), tensile strength (100 MPa), compressive strength (35-90 MPa), toughness, low thermal conductivity	Produced by the cambium layer (tracheid, vessels, fibers and parenchymal cells in); made of cellulose, hemicellulose and lignin	Construction (beams, flooring, and framing), industries	93,94
Mollusks	Suckerins	Sucker ring teeth stiffness to hold prey	Tunable high elastic modulus, 6-8 GPa (dry), 2-4 GPa (hydrated); Self-assembling nanoscale β -sheet and amorphous domains	Found in squid ring teeth epithelial cells in squids and cuttlefish	Hydrogels, films, tunable load-bearing implantable biomaterials	95,96
	Nacre	Inner shell layer; protection	Crack deflection; fracture toughness (3-9 MPa.m ^{1/2}); elastic modulus of 60-70 GPa, hardness of 4.4 GPa, high toughness; Microstructure: mineral bridges, polygonal nanograins, nano-asperities, and interlocked brick in organic matrix	Secreted by nacre-forming epithelial cells in the mantle of mollusks (e.g., oysters, abalone)	Tough, lightweight composites; bone graft substitutes; wear-resistant coatings; optical devices	97,98
	Byssus	Secure mussels to rocks in intertidal zones	Mechanical gradient; stiffness (core: 900 MPa), hardness (cuticle: 100 MPa) tensile strength up to 48 MPa, resilient, self-healing (sacrificial His-Zn bonds); metal coordination (Fe, Zn, V); underwater adhesion	Mussel's foot glands; core gland: collagenous proteins (strength and elasticity); cuticle gland: DOPA-rich proteins (outer layer hardness and toughness); plaque gland: adhesive proteins	Biomedical adhesive, biocompatible material, underwater adhesive, marine coating, self-healing material, technical textile	74,76
	Squid Beak	Feeding apparatus to carve preys	Stiffness gradient: hard and stiff tip (5 GPa), soft and compliant base (0.05 GPa); self-assembly; chitin, histidine-rich proteins, and His-DOPA cross-linking catecholamines	Secreted by buccal mass beccublast cells within cephalopod tissues	Gradient materials; high-strength lightweight composites; biomedical devices; peptide-derived self-assembled drug delivery	99
	Chiton Radular Teeth	Grazing on hard rocky surface, algae scraping during feeding	Hardened (9-12 GPa), stiffness (90-125 GPa); wear resistance, crack deflection, self-sharpening with a mechanical gradient; outer hard magnetite nanoparticles embedded in a chitinous matrix, inner softer core	Formed by mineralizing cells in the radula sac of chitons, a conveyor-belt-like organ. Mineralization through the deposition of magnetite and iron phosphate	Ultra-hard materials; biomimetic abrasive tools; wear-resistant coatings, self-sharpening cutting tools, low energy production	100
Cnidarians	Scleractinian Coral Skeletons	Rigid structural support for a symbiotic habitat	High porous mineral microstructures facilitating liquid flow (low density); Elastic modulus (~60-70 GPa) from aragonite fibers; hardness (~5 GPa).	Specialized cells in the calicoblastic ectoderm secreting an organic matrix in "centers of calcification" guiding aragonite deposition, from which fibrous aragonite radiates.	Biocompatibility, porosity for bone grafting and regeneration or tissue scaffolding; Environmental monitoring (impacting the structure)	73,101–103
Crustaceans	Crustacean Exoskeleton	Protection; structural support, water retention	Lightweight, high-strength, multilayer: exocuticle (stiffness ~9 GPa, hardness: 130-270 MPa), endocuticle (stiffness ~4 GPa, hardness: 30-55 MPa); Bouligand microstructure made of chitin and calcium carbonate (mix of crystalline and amorphous).	Single epidermal layer deposition of chitin-protein matrix inducing CaCO ₃ biomineralization.	Chitin and chitosan are used in biomedical (wound dressing, scaffolding, drug delivery, biocompatibility), biodegradable packaging, edible film, textile.	104,105
	Barnacle Cement Proteins	Underwater adhesive to hold on substrate	High adhesive strength in aquatic environment (on hydrophobic surface: 21 nN, on hydrophilic surface: 7.2 nN), tensile strength ~930 kPa	Cement glands in the barnacles secreting lipids first to exclude water, followed by the cement proteins	Marine industry (underwater adhesives, biofouling-resistant coatings, anticorrosion), biomedical adhesives	71,106
Annelids	Sandcastle Worm Cement Proteins	Bind minerals for shelter	Water resistant adhesive, biocompatible, solid foam (0.2-5 μm pores). Oppositely charged co-polypeptides coacervates rapidly curing underwater.	Cement glands (<i>Phragmatopoma californica</i> , <i>Sabellaria alveolata</i>)	Water-resistant, biocompatible, and strong adhesive (surgical glues, tissue repair) while being biodegradable and non-toxic.	72,107
	Marine Worm Jaw Proteins	Sharp tool in feeding and defense (<i>Nereis</i> or <i>Glycera</i> jaws)	Zinc-enriched jaws at the tip increasing the stiffness (7.5-17.75 GPa) and hardness (0.39-1.31 GPa). halogens like chlorine, bromine, and iodine, contributing to cross-linking and hardness.	Produced in the jaw structure. The proteins are histidine-rich facilitating zinc binding, as well as other elements.	Tunable mechanical properties, responsive hydrogels, shape-memory polymers.	108,109
Echinoderms	Sea Urchins spines	Structural support; protection form predation	Amorphous regions and Mg-calcite nanocrystals (10-40 nm) with elongated particles (100-300 nm long, 50 nm wide) enhancing toughness and flexibility at the microscopic scale; glass-like conchoïdal fracture behavior	Sclerocytes secreting amorphous calcium carbonate particles that then crystalize into calcite. They also secrete the organic macromolecules regulation crystallization	Lightweight, impact-resistant composites; high-strength and toughness materials with alternating amorphous-crystalline mesostructures	110,111
	Sea Urchins teeth	Feeding on hard surfaces (like rocks)	Self-sharpening design: controlled fracture to sharpen the edge; Mg-rich calcite arranged in plates, needle-prisms and lamellae balancing high strength, hardness and toughness	Odontoblasts secrete amorphous CaCO ₃ , later crystalizing in calcite. They form a syncytium guiding the microstructure growth	Durable self-sharpening cutting tools: high strength composites, wear resistant and resilient tools	112
Insects	Silkworm Fibroin	Cocoons protection	Stiffness: 10-17 GPa, tensile strength: 300-740 MPa. β -sheet crystallites in an amorphous matrix	Secreted by silk glands in silkworms (<i>Bombyx mori</i>)	Tunability, biocompatibility (sutures, scaffolding, drug delivery), processing versatility	113

Taxonomy	Material	Function	Material Properties / Description	Biological Systems	Potential Applications	Ref
	Resilin	Elastic energy storage	High resilience 95%; flexible; low stiffness (0.1-3 MPa); stretchable (300 %); thermal stability; tyrosine cross-linking	Synthesized in the cuticle regions by epidermal cells at elastic joints (e.g., wing hinges)	(fibers, textiles, films, sponges, hydrogels, optical devices)	
	Chitinous Insect Cuticle	Protective outer layer, exoskeleton	Mechanical versatility: soft membranes (stiffness: 1 kPa) or fully sclerotized (Stiffness: 20 GPa, hardness: 0.25-0.8 GPa); light: (1 kg.m ⁻³); multilayer exocuticle and endocuticle (aligned chitin fibers). Epicuticle (no chitin): waterproof waxes and lipids.	Produced by the integumentary system (epidermal cells)	Elastic polymers; soft robotics; bio-inspired springs; elastic coatings; biomedical applications	114,115
	Butterfly Wings	Flight; water repellent, visual colors	Aerodynamic benefits, super-hydrophobicity; structural colors through optical interference (high reflectance), iridescence (single lamella thickness ~70-90 nm)	The cuticle presents two distinct layers of scales, each developing from single epidermal cells.	Bioinspired solar cells, photonic devices for their high reflectance and wavelength specificity; anti-counterfeiting; water-repellent.	116,117
	Beetle Elytron (wing cover)	Protection of the wing and armor	Wide range of properties depending on species and tanning stage; Layered structure for waterproofing and rigidity; stiffness can reach 2.3 GPa; flexural strength (<i>Phloeodes diabolicus</i> : 338 MPa)	Two layers of epidermal cells producing the multilayered exocuticle, endocuticle, trabecula, and hemolymph spaces	Impact-resistant materials, lightweight armor combining flexibility and toughness	118,119
Velvet Worms	Velvet Worm Slime	Prey capture and immobilization	Rapid reversible liquid-solid transition, viscoelasticity; stiffness: 4 GPa, tensile strength: 100 MPa, high extensibility; coalescent nanodroplets; disordered structure with β -sheet domains and disulfide bonds	Secreted by slime glands near oral papillae containing a reservoir and secretory duct	Biomedical adhesives; spontaneously forming fibers, liquid-liquid self-separation	120,121
Arachnids	Spider Silk Dragline, Spidroins	Web construction; prey capture	Stiffness: 10-12 GPa, tensile strength: ~1 GPa; toughness: 130-200 MJ/m ³ , breaking strain: 30 %, supercontraction; biocompatibility; β -sheet nanocrystals and amorphous regions	Abdominal major ampullate glands; tail region: spidroin synthesis; ampulla: storage, coating; duct: processing, coating; spinneret: extrusion	High-performance technical fibers and textiles (bulletproof vests, safety gear); biomedical (sutures, ligament repairs, scaffolds, drug delivery, cell compatibility)	122-126
	Spider Fangs	Venom injection needles	Gradient: stiffness (13-20 GPa) and hardness (0.6-1.3 GPa). Chitin-protein composite in a layered cuticle; Zn and Cl ions-enriched tip enhance hardness and wear resistance	Epidermis producing the epicuticle, exocuticle and endocuticle; histidine-rich proteins binding to metal ions for reinforcement	High strength injection needles: advanced biocomposites reinforced with metal ions; impact and wear-resistance	127,128
Fish	Fish Scales	Protection; hydrodynamic efficiency	External mineralized layer (puncture resistance), internal collagenous layer (Bouligand pattern for high resilience); Stiffness (dry: 2.2 GPa), tensile strength (dry: 93 MPa); Fracture toughness (hard-soft structure)	Epidermis and dermal layers; matrix vesicles in the external layer, outer limiting layer collagen-free organic matrix, collagen-base mineralization in the internal layer, Mandl's corpuscles heterogeneous mineralization	Flexible, lightweight armor materials; protective coatings; hydrodynamic surfaces, antifouling	129
	Hagfish Filaments, Slime	Defense mechanism, rapid expansion	Rapidly expanding fibrous network with high elasticity (hydrated stiffness: 6 MPa, 8 GPa through post-processing) and extensibility (failure strain at 220%), tensile strength: ~180 MPa; thread diameter: 1-3 μ m.	Gland thread cells (producing the threads for structural integrity), gland mucous cells (producing the mucin vesicles for the rapid expansion in contact with water)	Biomedical (biocompatible suture, scaffolds), filtration, underwater self-sealing materials, high stretchable fibers, coatings	130,131
Reptiles	Reptile Scales	Protection barrier; water retention	High wear resistance and low deformation (β -keratin outer layers); Alpha-keratin softer inner layer; for legless reptiles, ventral scales have denticulations or fibrils reducing friction for their mobility	Keratinocytes in the epidermis going through cornification	Friction-modulation surfaces; protective coatings, abrasion resistant materials; hard and flexible materials for potential prosthetics	132,133
	Turtle Shells	Protective shield	Elastic modulus (ventral cortex 18 GPa, dorsal cortex 16.5 GPa, cancellous interior 12 GPa); hardness (ventral cortex 0.65 GPa, dorsal cortex 0.65 GPa, cancellous interior 0.5 GPa); hydration softening (50-60 % E modulus reduction)	Dermal bone tissue covered with epidermal keratinous scutes. Bone cells produce mineralized collagen, and keratinocytes form the outer protective scutes layer	Impact-resistant materials; surface load bearing, energy absorbing with a "soft-softer-hard" design	134,135
Birds	Eggshells	Protective barrier of the chick embryo	Composite of calcite (95 %) organic components (3.5 %); the protein osteopontin increases hardness (2.79 GPa); multilayer structure with variable grain size (30-74 nm)	The eggshell membrane is formed in the isthmus; calcification occurs in the shell gland (uterus) with high ion concentration and regulating proteins (osteopontin, ovocleidins)	Protective coatings; absorbent for removing contaminants; membranes	136,137
	Bird Feathers	Flight; insulation; protection; communication	Central shaft (rachis) and branches (barbs) are multilayered, balancing stiffness (2.5 GPa), flexibility, resilience (crack-stopping points), low density (foam-like medullary core, gas filled cells) and improved buckling resistance.	Stratified, squamous epithelial tissue producing the β -keratin of the cortex. The foam-like core of the rachis is formed through cell vacuolization, creating a porous and gas-filled structure	Lightweight, durable design (aerospace, protective gear, energy-absorbing structures); high efficiency foams (crash resistant designs); deployable structures; directional airflow	138,139
	Peacock Tail Feathers	Visual signaling for mating	Iridescent colors from a multilayered structure made of melanin granules (130-140 nm); The shaft is lightweight (0.037-0.133 g/cm ³), foam-filled (dry stiffness: 17 MPa), surrounded by a stiffer cortex layer (dry: 4.13 GPa)	Specialized keratinocytes create the feather barbules and rachis	Structural colors for durable pigments and reflective; materials; lightweight resilient materials; porous scaffolds	140,141
Mammals	Armadillo Armor	Protection against predators; energy dissipation	Keratin layer and underlying osteoderm hexagonal tiles (hexagonal or triangular bony tiles interconnected by non-mineralized Sharpey's fibers; stiffness (dry: 425 MPa, hydrated: 150 MPa), tensile strength (dry: 23 MPa, hydrated: 13 MPa), toughness (dry: 1.1 MJ/m ³ , hydrated: 0.53 MJ/m ³)	Four tissue layers: epidermis (with keratinocytes), papillary dermis (osteons with osteocyte lacunae), reticular dermis (numerous porosities), and hypodermis (encased in collagen matrix with surrounding blood vessels)	Composites combining toughness and flexibility, lightweight protective gear or armor materials	142,143
	Skin/Leather (Cows and other mammals)	Protection, Structural support	Matrix of collagen fibers processed by tanning; flexible, resistant to biodegradation and tear; water-resistant	Derived from the skin's dermis layer; contains collagen, elastin, and other ECM proteins	Fashion (shoes, bags, garments), furniture, automotive interiors, filtration membranes	144
	Articular cartilage (human)	Low friction; load distribution and absorption	Biphasic porous composite: solid matrix (mainly collagen and proteoglycans) and an interstitial fluid phase (mainly water); viscoelasticity (instantaneous Young's modulus: ~2.28 MPa, equilibrium Young's modulus: ~0.69 MPa), strain-responsive permeability	Chondrocytes embedded within the cartilage matrix, balancing collagen-proteoglycan content.	Biomedical (implants, joint repair and regeneration); wear resistant coatings with low friction (lubricated coatings)	145,146
	Tendons (human)	Elastic energy storage; muscles-bones interface	Self-assembled collagen fibers (hierarchically aligned), elastic modulus 5-7.75 GPa, viscoelasticity (energy absorption)	Tenocytes and tenoblasts (specialized fibroblast differentiated from mesenchymal stem cells) producing type I collagen, elastin and proteoglycans matrix	Biomedical (implants); High-strength composites with high strength-to-weight ratios; elastic energy storage devices, mechanical actuators	147,148
	Ligaments (human)	Stabilizing joints; connecting bones	Parallel collagen fibers cross-linked together; stiffness (1-2 GPa), tensile strength (50-150 MPa), strain (5-7 %, some ligaments enriched with elastin: >30 %)	Ligamentocytes: fibroblast-like cell specialized for synthesizing collagen and the ECM that supports ligaments (originate from mesenchymal stem cells)	Biomechanics and prosthetics; soft robotics	149,150

Taxonomy	Material	Function	Material Properties / Description	Biological Systems	Potential Applications	Ref
Menisci (human knee)	Cushioning of knee joint; absorbing shocks	Composed mainly of water (72 %), type I collagen (22% dry weight) and proteoglycans like aggrecans (water retention for cushioning); shock absorption, load transmission, joint stability, nutrition and lubrication	Fibrochondrocytes produce the ECM and the fibrocartilaginous structure (resilience); other fibroblast-like cells in the outer vascular region (tensile strength)	Prosthetic joints; shock-absorbing materials; biomedical (meniscus repair and regeneration)	151,152	
Bone (human)	Load bearing structure; mineral storage	Anisotropic layered hierarchical design with relatively low density; stiffness (macro: 14-20 GPa, meso-scale osteons: 12 GPa in tension, micro-scale lamellar bone 22 GPa)	Osteoblasts (mesenchymal stem cells-derived); Osteocytes (embedded osteoblasts); Osteoclasts (hematopoietic stem cells-derived)	Biomedical (implants, prosthetics, bone regeneration scaffolds); lightweight, high-strength materials	153,154	
Dentin (human)	Mechanical support; bulk of the teeth	peritubular (mineral-rich) and intertubular dentin (collagen-rich) regions; 50% hydroxyapatite mineral, 30% type I collagen, and 20% water by volume; stiffness (18-25 GPa), hardness (KNH 5.8-6.8 MPa), strength (52-105 MPa), fracture toughness (K _c 1.8-3 MPa.m ^{1/2})	Odontoblasts (differentiate from dental pulp cells, produce dentin by secreting predentin, which mineralizes)	Biomedical (dental restoration, repair, grafts); protective coatings, wear resistant materials	155,156	
Enamel (human)	Protective outer tooth layer; wear resistant	Anisotropic densely packed keyhole-shaped rods of apatite crystals; stiffness (parallel: 87.5 GPa, perpendicular: 72.7 GPa); hardness (parallel: 3.9 GPa, perpendicular: 3.3 GPa).	Ameloblasts (originating from the inner enamel epithelium); post-embryonic development developmental routes from odontogenic epithelial stem cells or human keratinocyte stem cells	Biomedical (tough and durable fillings, crowns and veneers); wear resistant coatings	157,158	

2.2. How an organ regulates material self-assembly

Spider silk production

In this section, we explore the spider silk gland to illustrate how an organ tightly regulates material self-assembly¹⁵⁹. Its physiology¹⁶⁰, as the silkworm's¹⁶¹, have been extensively studied, making both excellent candidates for self-microfabrication. Spider silk is a prime example of a sustainable biological material with high mechanical performance and industrial applications¹²⁸. Tougher than Kevlar¹⁶² and not dependent on fossil fuels, spider silk has been extensively studied in various species¹²⁷ for its potential uses, notably in bulletproof vests or composites¹²⁸. Replicating the silk's intricate microstructure synthetically has posed a challenge for decades, notably due to its complex processing conditions⁴⁸ (Fig. 2A).

Chemical microenvironments (ChemuEnv), such as the pH and salt concentrations, guide the self-assembly of biological materials through thermodynamics principles^{163,164}. Spider silk glands use specialized cell types to synthesize and secrete precursor proteins (spidroins) into the extracellular space. Other cells subsequently regulate the extracellular ChemuEnv¹⁶⁵, driving the proper folding of proteins and material assembly⁴⁸. For these reasons, the spider silk gland example is detailed to showcase the role of multicellular tissues in hierarchical material production. However, an in-depth understanding of spider biology is not required in the following sections.

In a spider, up to seven types of glands can produce silk with different properties, such as the tough dragline from the major ampullate (MA) glands or sticky fibers from the aggregate glands. Furthermore, environmental adaptations across 50,000 spider species have diversified their silk properties^{166,167}, including hydrophobic motifs in underwater spiders¹⁶⁸. We focus on *Larinoides sclopetarius* and *Nephila* golden orb weaver MA silk glands, due to the large literature available on these species, the high mechanical properties¹²⁷ and versatile applications of their silk¹²⁸.

Despite significant progress in spider silk research, no current technique can replicate the gland's complex material processing, encouraging efforts to develop spider silk gland organoids in the future. When trying to reproduce a biological material, approaches of various scales should be considered. At the organism scale, farming silkworm colonies industrially is efficient¹⁶⁹ but impractical for spiders, owing to their cannibalistic nature, as revealed by early attempts in the late 18th century¹⁷⁰. At the molecular scale, fully synthetic approaches can mimic specific aspects, such as spider silk discoveries improving nylon's properties¹⁷¹. Recombinant

expression of silk protein (spidroin) has been developed in various hosts to better replicate the material composition¹⁷²⁻¹⁷⁴. Many challenges associated with that approach have been addressed in the past decade¹⁷⁵, including preventing aggregation in highly concentrated spidroin solutions^{48,176}. However, the yield and scalability continue to be significant bottlenecks¹⁷⁷. Furthermore, the native silk dope composition is more complex than a few recombinant spidroins: including peptides, lipids, glycoproteins that serve functions such as lubrication, antibacterial and more¹⁷⁸.

While the synthesis function of silk glands can be simplified synthetically (e.g. recombinant silk solutions), the process of transforming the liquid phase into a solid fiber has not been fully replicated¹⁷⁹. Wet spinning, dry spinning, and electrospinning¹⁸⁰ can produce tough threads but often induce aggregation instead of proper protein folding, reducing the resulting properties⁴⁸. Biomimetic aqueous spinning using microfluidics is the most promising synthetic approach yet that may control the ChemuEnv¹⁸¹. However, it does not match the *in vivo* multicellular regulation of the spinning process¹⁶⁵ where MA glands regulate the pH, salts, water content and shear forces⁴⁸.

To address the spinning challenge at a tissue scale, silkworm glands have been genetically engineered to secrete spidroin^{182,183}. Despite not fully mimicking the spider glands, transgenic silkworms present a promising strategy for large-scale¹⁸⁴, high-performance silk production¹⁸⁵. It further highlights the importance of a multicellular organ for hierarchical material processing. These examples at various scales can be generalized to other biological materials and organs.

Tissular scale: multifunctional production units

This section details how the spider silk MA gland regulates material synthesis and assembly at the tissue, cellular, and molecular scales. At the tissular scale, the MA gland, located in the spider's abdomen, is organized in three regions: the tail for spidroin secretion, the ampulla for storage and coatings, and the duct for solid material formation¹⁸⁶ (Fig. 2B). The tail is a long, widening tubular epithelium on the anterior side of the organ (zone A). It synthesizes and secretes spidroin vesicles in the lumen¹⁸⁷. The ampulla stores the liquid silk dope at high concentrations, enabling rapid, on demand, spinning⁴⁸. The ampulla is itself segmented in two regions, zone B and C, secreting each different coatings layers¹⁸⁷. These middle and outer layers wrap the core silk dope produced in the tail, creating a concentric meso-structure. The third part of the organ, the duct, can be seen as an extruder and is specialized in

converting the silk dope from liquid phase to solid fibers. To do so, it regulates the Chem μ Env in the lumen, which guides spidroins' proper protein folding¹⁸⁸.

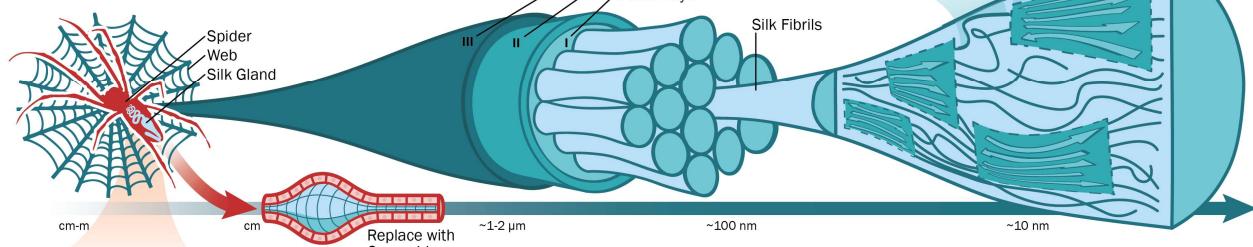
Pulling the hanging thread at the posterior side, exiting the spigot, initiates the process. Pulling the fiber manually, namely forced silking, also induces spinning. Tensile forces propagate via intermolecular interactions, from the spigot to the ampulla, initiating the flow¹³. A ratchet and pump mechanism is

hypothesized to restart spinning if the fiber breaks within the gland¹⁸⁹.

The solidification of silk solution into fiber occurs as it flows from the ampulla and through the duct. The tapering funnel and duct induce shear forces¹⁹⁰ and align the molecules¹⁹¹, improving the resulting material properties^{192,193}. The funnel's thick cuticle connects the flexible duct to the more stable ampulla¹⁹⁴, and is hypothesized to prevent the dope from

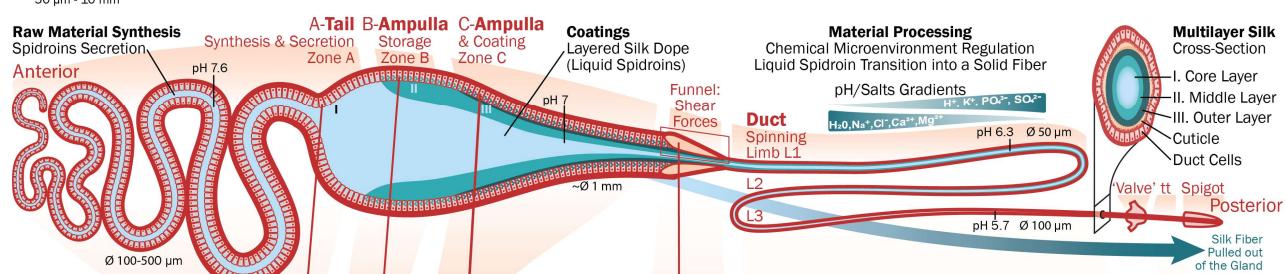
A. Biological Material Scales

Hierarchical Microstructure
1 nm - 1 m



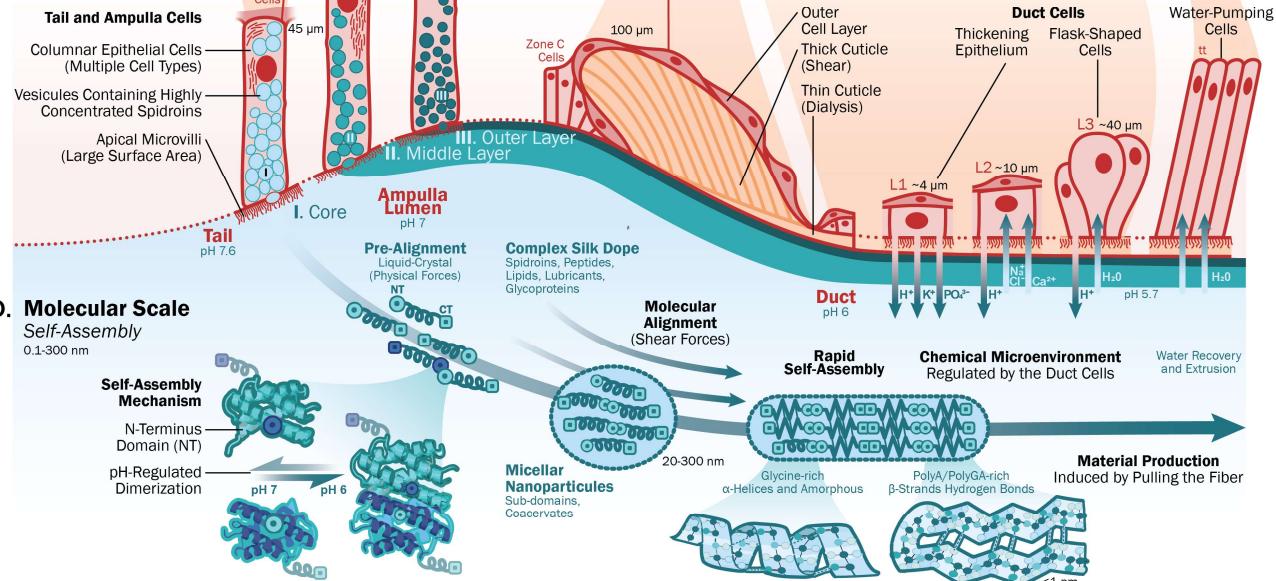
B. Tissular Scale

Spider Silk MA Gland
50 μm - 10 mm



C. Cellular Scale

Specialized Cells
1-100 μm



D. Molecular Scale

Self-Assembly
0.1-300 nm

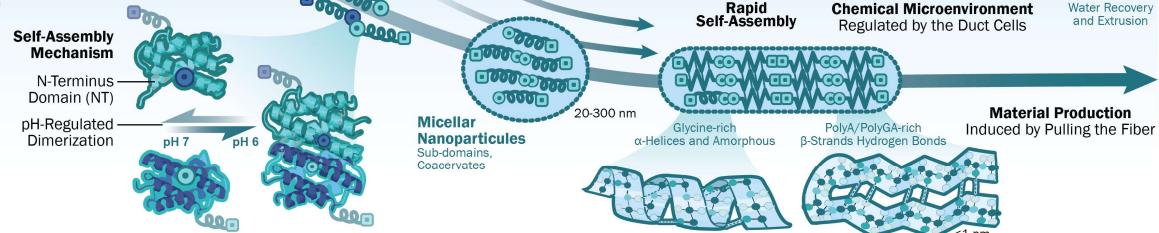


Figure 2: Spider Silk-Producing Gland Hierarchical Physiology (Material, Tissular, Cellular, Molecular Scales)

A. Hierarchical structure of spider silk with its crystalline and amorphous phases. Self-microfabrication aims to eventually replace the gland with an organoid. **B.** *L. sclopetarius* and *Nephila* spider silk major ampullate (MA) gland and its tri-sectional anatomy, including the tail, ampulla and duct. **C.** Cell type localizations and function within the gland. Tail and ampullar cells produce the spider silk proteins (spidroins) in layers (core, middle, outer). **D.** Molecular self-assembly of the spidroins. Pre-alignment in the ampulla, coupled with a lock-and-trigger mechanism enabling a rapid self-assembly in the final high-performance microstructure. Terminal tubules (tt), limbs 1-3 of the duct (L1-3). Original schematics, compiling findings from Rising, Vollrath et al. on *L. sclopetarius* and golden orb weavers, as observed in other species. Red: cells and biological systems, blue: materials and precursors, orange: cuticle.

excessive shearing when the spider moves around¹⁶⁰. The thicker cuticle also helps to oppose the induced forces from the flow. The duct regulates ChemyEnvs, establishing gradients of salts, pH and water content along its length¹⁹⁵. As it flows through these conditions, the dope self-assembles in a hierarchical material⁴⁸. To complete the conversion to solid fiber and reduce water losses, terminal tubules on the posterior side pump remaining water¹⁹⁶ and the spigot's lips retain the aqueous phase inside¹⁶⁰. This example shows how a multi-sectional organ can perform coordinated functions for material production.

Cellular scale: specialized functions acting in a collective

At the cellular scale, specialized cell types have been localized¹⁹⁴ and characterized by single-cell sequencing^{159,186}. The core of silk fibers¹⁵⁹ is secreted by three columnar epithelial cell types localized in the tail (zone A). The middle and outer layer coatings are secreted by two cell types in zone B and C of the ampulla (Fig. 2C). The columnar epithelia are filled with spidroin vesicles, secreted to the lumen from their apical side¹⁸⁷. Each cell type produces a different combination of spidroins, used to define their identity¹⁵⁹, and realizes post-translational modifications¹⁹⁷ impacting their self-assembly¹⁹⁸. Another cell type is scarcely present in both the tail and the ampulla, and does not seem to be directly involved spidroin expression¹⁵⁹; we therefore hypothesize its role in supporting its surrounding cells or for tissue homeostasis.

The duct consists of a thickening epithelium along its length, as revealed by histology, electron microscopy and single-cell sequencing, which has identified two duct cell types¹⁹⁴. A cuticular intima separates the cells from the lumen but enables the diffusion of molecules with its pore-like structure¹⁹⁹. The duct cells regulate the lumen's ChemyEnv, notably the pH with high carbonic anhydrase expression levels¹⁶⁵; they are filled with vesicles and have dense apical microvilli¹⁹⁶. At the posterior side, flask-shaped cells contain secretory granules and may add an additional coating layer¹⁸⁹. Water is continuously pumped out of the lumen during spinning, notably with terminal tubule cells¹⁹⁶. The specialized cell functions in spider silk glands exemplify the complexity of material-producing organs, challenging their biomimicry using conventional recombinant approaches.

Molecular scale: regulation of self-assembly

At the molecular scale, the spidroins are high molecular weight proteins with repetitive domains, driving their self-assembly in nanometer-scale structures²⁰⁰(Fig. 2D). The silk dope is itself highly complex, made of many components¹⁷⁸. Each cell types secretes different composition and quantities of spidroins¹⁵⁹, tuning the material properties at each layer¹²⁷. The silk dope also contains a heterogeneous group of non-spidroin proteins with low molecular weight, named spider-silk constituting elements (SpiCE)²⁰¹. Peptides, lipids²⁰², glycoproteins²⁰³, and more²⁰⁴ have also been reported in the silk dope.

The hypothesized functions of the main components are: mechanical properties for spidroins; plasticity and support for SpiCE proteins; water balance, lubrication, and pliancy for glycoprotein coatings; and antibacterial protection and social signaling for outer-layer lipids²⁰⁵. In most MA spidroins, crystalline regions are formed by polyA and polyGA domains, while glycine rich domains give an amorphous phase²⁰⁶. The ratio and size of these domains affects the stiffness and extensibility of the fiber²⁰⁷.

Spidroins are stored in the ampulla at high concentrations, up to 50% w/v²⁰⁸, higher than most artificial spinning⁴⁸. Spidroins self-assembly¹⁷⁸ can be described according to three models:

micellar¹⁹³, liquid crystalline²⁰⁹, and liquid–liquid phase separation²¹⁰ (LLPS). Terminus domains (NT and CT) play a major role in this structure: NT dimerizes spidroins and transfers tensile forces, while CT contributes to the rapid, on demand polymerization of spidroins⁴⁸. Shear forces in the duct and drawdown effects further align spidroin nanoassemblies, stabilized in β-sheets structures¹⁹¹.

Once again, the spider silk gland showcases the intrinsic complexity of biological material composition and processing *in vivo*. To mimic silk self-assembly with recombinant expression and artificial spinning, the conditions should be greatly simplified. It is unclear if such reduction in complexity will be capable of producing the proper microstructure and versatile properties of biological materials, such as spider silk. Self-microfabrication, using tissue engineering, offers a complementary approach, aiming to grow material-producing organoids². Insights from spider development^{46,211,212}, at the single-cell resolution^{213,214}, are encouraging contributions toward this goal.

3. Growing organs to produce materials

3.1. Principles of self-microfabrication

Producing materials at the tissular scale

We have seen how organs can regulate complex material self-assembly. This section explores how to grow such multicellular tissues, notably from stem cells. Biological systems consist of numerous interacting components organized across scales, including molecules, cells, organs, and entire organisms²¹⁵. At the macroscopic scale, top-down approaches extract materials directly from organisms, such as tree trunks, cotton, or silkworm cocoons. At the microscopic scale, bottom-up manufacturing produces recombinant proteins (*e.g.* bio-based polymers²¹⁶) or guides material production (*e.g.* concrete biohealing²¹⁷). Despite ongoing advancements²¹⁸, biofabrication approaches often depend on monoclonal colonies²¹⁹. These systems may lack the intracellular and intercellular complexity required by specialized cell types and organs, as exemplified by the spider silk gland example. Bacterial consortia partially address this limitation, notably in biomimetic mineralization^{220,221}, but solutions remain to be found for material-producing multicellular organs^{48,222}, which are not covered by current engineering approaches³². This leaves a research gap at intermediate scales, between top-down and bottom-up biofabrication strategies. A rational approach to biofabrication may bridge this gap, by directing resources exclusively toward a necessary and sufficient organ, without requiring an entire organism.

For instance, snake venom gland organoids produce toxins for anti-venom research without the need to develop other organs, such as the brain^{223,224}. This approach could also enable new functionalities and benefits; *i.e.* removing the risk of accidental bites from traditional snake breeding²²⁵. To rationalize biofabrication even further, tissues can themselves be edited and improved²²⁶, such as multicellular engineered living systems (M-CELS)²²⁷.

We propose to define such rational approach as self-microfabrication: the process of fabricating structures at microscopic scale through self-organization. Conventional microfabrication in the semiconductor industry already creates desired patterns²²⁸, but barely uses self-organization²²⁹. Self-microfabrication also builds microstructures guided by DNA-encoded patterns, and achieves an unprecedented level of control over complex material self-assembly²³⁰. This property

differs from passive thermodynamic processes²³¹, such as phase transitions in metals, with its common use of energy-dependent molecular chaperones or nanoreactors²³². Thus, self-microfabrication occurs at multiple scales: self-organizing both production units (organogenesis) and materials (molecular self-assembly). This article explores these principles, exemplified by organoids producing materials (Fig. 3A).

Regulation by the microenvironment

Self-organization processes are heavily influenced by surrounding conditions. Cells and organs regulate Chem μ Envs in microscopic compartments²³², enabling precise spatiotemporal control over material assembly (Fig. 3B). Synthetic approaches mimic these conditions and explore beyond natural processes²³³. Nevertheless, cellular collectives tune Chem μ Envs at microscopic scales and higher complexity than synthetics, and thus achieve hierarchical structures that are difficult to mimic¹⁸⁷.

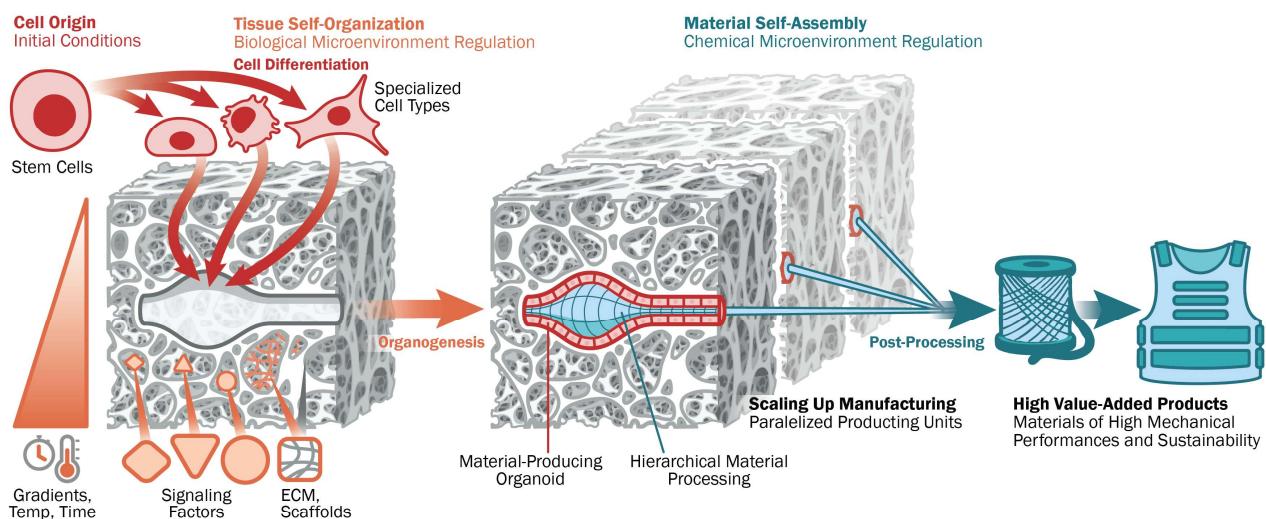
The formation of such biological tissues, or organogenesis, is a complex orchestration process²¹. Previous reviews have explored the principles of organoid self-organization^{52,234,235}. We focus on how environmental conditions influence their development²³⁶. To introduce a distinction from chemical microenvironments (directing the self-assembly of materials), cellular microenvironments (Cell μ Env) describe the conditions regulating cell self-organization²³⁷ (Fig. 3B). Cell μ Envs use various conditions, communication pathways, diffusing

biochemicals²³⁸, extracellular matrix (ECM), mechanical^{239,240} or bioelectric cues²⁴¹, to name a few. Stem cell niches illustrate Cell μ Envs, where surrounding signals either maintain stemness or induce cell differentiation²⁴². They guide embryonic development, adult homeostasis, regeneration, and more²⁴³. For instance aged cells can be rejuvenated when placed in a biologically “younger” environment²⁴⁴, such as blood or skeletal cells²⁴⁵. When the blood circulations of a young and an old mouse are connected through parabiosis, systemic rejuvenation of the older mouse’s tissues is observed²⁴⁶. Key factors expressed by certain cells can also reprogram a tissue’s identity, notably the thickening of skin upon volar fibroblast transplants²⁴⁷.

In many cases, only a few factors are necessary and sufficient to guide cell behavior and organoid development. For instance, only four Yamanaka factors are sufficient to reprogram differentiated cells into iPSCs²⁴⁸. As a second examples, four key signaling factors guide Lgr5-positive stem cells to grow intestinal organoid²⁴⁹, not mentioning a few more essential parameters such as the ECM⁶³, culture medium and small molecules²⁵⁰. Tissue engineering leverages this ability of complex biological systems to arise from relatively simpler external inputs. By leveraging both tissue self-organization and organ-regulated material self-assembly, self-microfabrication aims to create high-value products, such as spider silk-based body armor²⁵¹.

A. Self-Microfabrication Manufacturing

Self-Organized Production Units and Materials



B. Principles

Key Steps and Components

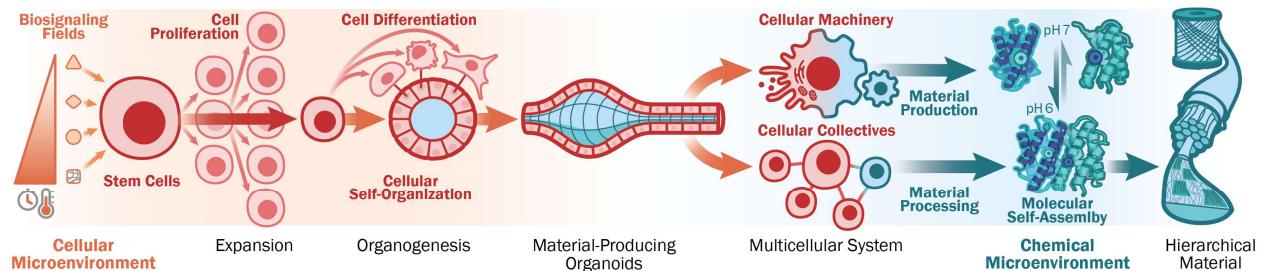


Figure 3: Self-Microfabrication Overview

A. General steps: self-organized living machines may enable the scalable production of high-performance materials for high value-added applications, such as spider silk for technical fibers and bullet-proof vests. **B.** Key components of self-microfabrication: the cellular microenvironment directs stem cell expansion or differentiation into organoids, while the chemical microenvironment (regulated by the organoid) guides hierarchical material self-assembly. T: temperature, ECM: extracellular matrix. Red: biological systems, blue: materials, orange: cellular microenvironment and signals guiding self-organization.

3.2. Material-producing organoids

Proof of concept: self-organized production units

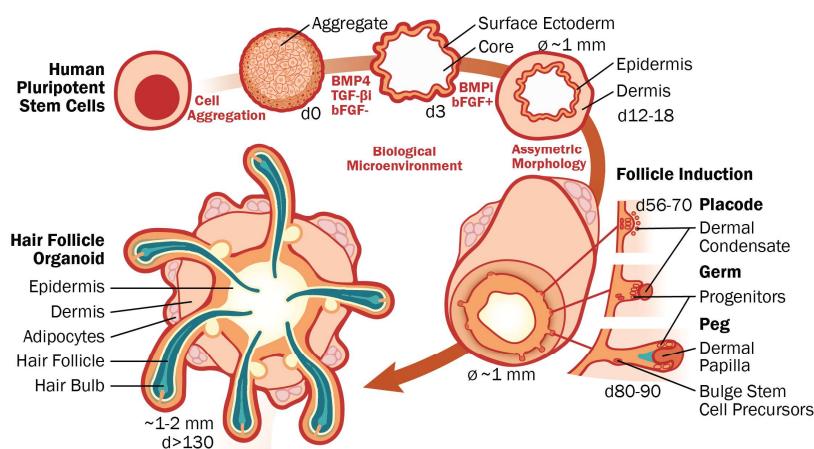
Self-microfabrication has yet to be fully established. While many examples exist to demonstrate parts of the approach^{1,234,252,253}, the hair follicle organoid is the most comprehensive example yet². This organoid self-organizes from human pluripotent stem cells (hPSCs) to produce a hierarchical material: the multilayered hair shaft. It illustrates how relatively simpler engineered conditions can give rise to a highly complex organ producing material⁵¹ (Fig. 4). The hair complements the spider silk example by demonstrating a material produced within cells, rather than externally.

We describe the hair follicle organoid development in detail to showcase the complex autonomous processes occurring during

organogenesis. Hair organoid *in vitro* growth begins with the aggregation of hPSCs, recapitulating normal stages of embryonic development²⁵⁴ by differentiating into various cell lineages²⁵⁵ (Fig. 4A). A spheroid forms and creates an inner cavity²⁵⁶. Mesenchymal cells migrate outwards and self-organize in the dermis while the inner surface ectoderm gives rise to the epidermis². Hair placodes appear, develop into hair germs and bulge out in hair pegs to form the dermal papilla (DP) and bulge²⁵⁶. Hair-bearing follicles eventually grow out, each containing tissue-specific stem cells that can be maintained *in vitro* for half a year⁵¹. Within each follicle, a hierarchical material is produced – the hair shaft – implying a complex multicellular regulation of the keratinization process²⁵⁷. Hair follicle organoids replicate cell types found *in vivo*²⁵⁸ and mimic the 3D organization of the real organ, such as DP, melanocytes,

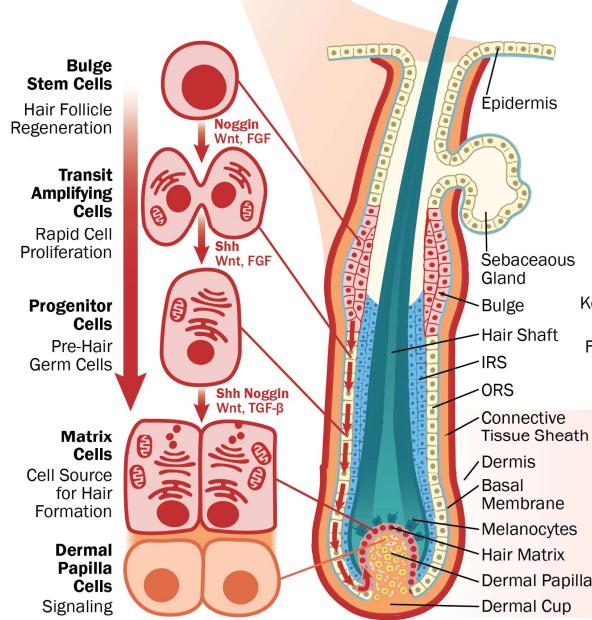
A. Organoid Self-Organization

Recapitulating Embryogenesis



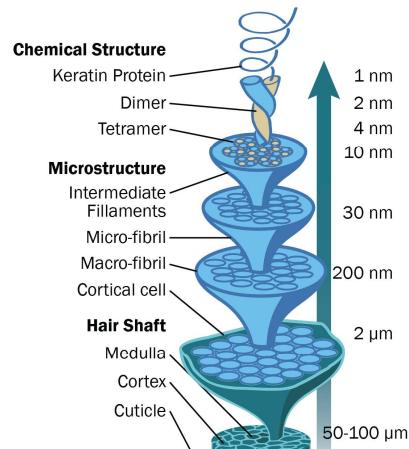
B. Tissue Self-Maintenance

Hair Follicle Stem Cell Homeostasis



D. Biological Material

Hierarchical Microstructure



C. Material Self-Assembly

Hair Shaft Keratinization

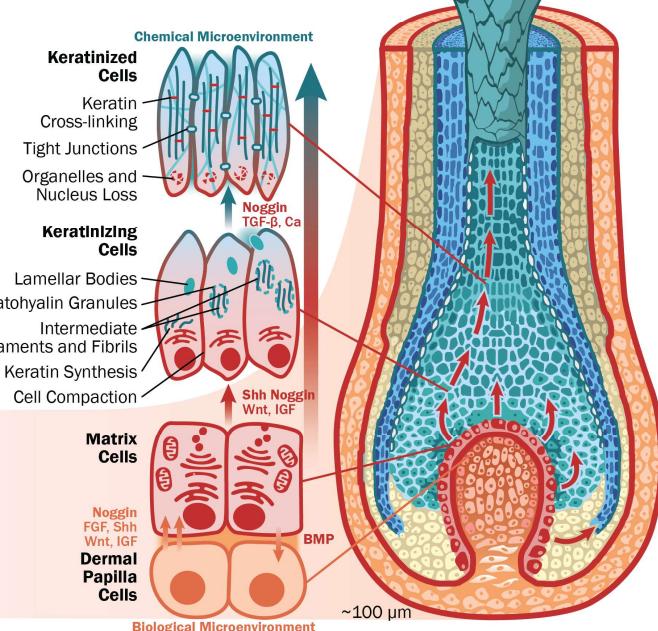


Figure 4: Tissue Self-Organization and Hierarchical Material Self-Assembly in Hair-Bearing Organoids

A. Self-organization of hair-bearing organoids derived from human pluripotent stem cells (hPSCs). Red annotations represent key signaling pathways involved in the relative cell differentiation between each step. **B.** Bulge stem cell migration, proliferation and differentiation into matrix cells, supporting hair follicle homeostasis *in vivo*. **C.** Zoom on the hair follicle bulb. Matrix cells differentiate and undergo keratinization in the formation of the hair shaft. Small red arrows represent cell migration trajectories. **D.** Hierarchical microstructure of the hair shaft. Inner root sheath (IRS), outer root sheath (ORS). Original figure compiling findings from Koehler et al. Red and orange: biological systems, orange (B-C): supporting cells, blue: materials. Sizes and developmental timings are indicated.

and surrounding connective tissue²⁵⁹. Even the follicles' patterning is reproduced, with regular intervals between them²⁶⁰. This example demonstrates that complex production units can self-organize from stem cells and assemble microstructured materials.

Self-maintained production units

Beyond their development, organoids have integrated mechanisms to self-maintain their function through their lifespan. The hair-bearing organoid homeostasis mechanisms are described to illustrate this unique property of self-microfabrication production units. *In vivo*, hair follicles contain bulge stem cells that differentiate and eventually replenish the hair matrix cells, which will form the solid hair shaft²⁶¹ (Fig. 4B). This stem cell homeostasis strategy shares common characteristics with other adult tissue homeostasis²⁶². A small pool of cells remains quiescent, maintaining their stemness via microenvironmental signals from their niche, including bone morphogenetic protein (BMP), transforming growth factor beta (TGF β) and Wnt inhibition²⁶³. The anagen phase activates bulge stem cells²⁶⁴, which migrate downward through various Cell μ Envs guiding their differentiation²⁶⁵. They become transit amplifying cells for rapid proliferation, and then progenitors before reaching the DP and giving rise to matrix cells²⁶⁶. At the dermal side of the hair follicle bulb, DP cells regulate signaling and nutrient supply, influencing the surrounding Cell μ Env²⁶⁷ (Fig. 4C). DP cells interact with matrix cells using diffusing signals through the basement membrane and regulate their differentiation²⁶⁸.

Matrix cells proliferate rapidly and undergo a keratinization process while migrating away from the DP signals^{257,269}. They increase the expression of type I and II keratin proteins, which assemble in heterodimers, then tetramers and finally align head-to-tail in intermediate filaments²⁷⁰. Keratohyalin granules begin to form, increasing keratin's concentration and storing it within the cells in preparation for their solidification. Inside the granules, filaggrin and trichohyalin proteins help bundle filaments into microfibrils while transglutaminase stabilizes them by cross-linking cysteines into disulfide bonds²⁷¹, which contributes to the mechanical stiffening and hardening of the hair²⁷². During cell migration, keratinocytes' nuclei and organelles slowly degrade, halting metabolic activity. The cells are progressively transformed and compacted together in a multilayer solid material composed of microstructured keratin fibers²⁶⁹.

The hair-bearing organoid is currently used as a model in development, wound repair, and hair loss research and creates opportunities beyond medical applications²⁵⁹. A keratinization organoid model offers a promising foundation for studying other keratin-based biological materials found in vertebrates (*e.g.* nails, horns, scales, shells, beaks, feathers, and hooves²⁷³) and invertebrates (*e.g.* marine organisms²⁷⁴). The hair organoid produces a hair shaft with all seven concentric keratinized cell layers found *in vivo*² (Fig. 4D). None of the material processing steps, including the keratinization or crosslinking, have been directly engineered nor regulated as it is in artificial systems. The complex organogenesis and maintenance of this material-producing organoid require minimal inputs and leverages existing self-organization programs²⁶⁰. To the best of our knowledge, no synthetic system can autonomously regulate the formation of such hierarchical material at this scale, nor its production unit, highlighting the innovative potential of self-microfabrication. However, developing organoids in new species raises fundamental challenges²⁷⁵, developed in the next section.

4. Challenges in organoid development

4.1. Growing new organoids

Exploring non-model species

Most biological materials of interest are typically found in species less studied than model organisms (Table 1). However, growing an organoid relies on preliminary achievements such as cell culture conditions, stem cell identification and a certain understanding of growth factors²⁷⁶. This poses a central challenge to material-producing organoids, introduced here and further addressed with emerging solutions in following sections. Intraspecies variability already illustrates the difficulty of generalizing findings between individuals, notably in personalized medicine²⁷⁷. This issue is further complicated by interspecies variability, notably with greater phylogenetic distances²⁷⁸.

Collegial efforts are necessary to unravel new cell identities²⁷⁹, signaling cues²⁸⁰, gene regulatory networks²⁸¹ and differentiation pathways²⁸², to cite a few. The development of the first organoid relied on decades of research on dissociation-reaggregation experiments, embryoid bodies, 3D culture systems and iPSCs²⁸³. In comparison, recent developments of organoid protocols in new tissues have accelerated rapidly in the past fifteen years²⁷⁵. For instance, hair follicle organoids have advanced due to progress in tissue regeneration^{284,285}, growth factor discoveries²⁸⁶, niche characterization²⁸⁷, embryonic cell aggregation^{288,289}, stem cell differentiation media²⁹⁰, and patterned hydrogel scaffold development²⁹¹.

The "missing body problem": cellular microenvironment

When trying to grow a tissue outside its native environment, a basic question is: what is lacking for its survival? In a nutshell, the rest of the body is missing. In practice, only a finite number of cues are sufficient to guide a tissue's development and maintenance. For instance, the self-renewal and proliferation of many stem cells is regulated by their niche²⁹², which can be replicated *in vitro*²⁹³. Characterizing a new tissue's Cell μ Env is challenging due to its complexity and potential differences from established systems²⁹⁴. Defining these dynamic environments involves the understanding of signals from surrounding cells²⁹⁵, diffusing molecules gradients^{296,297}, ECM²⁹⁸, mechanical²⁹⁹ and bioelectric cues³⁰⁰. To enable self-microfabrication, addressing the "missing body problem" by maintaining functional tissues *ex vivo* is a crucial initial proof of concept that the organ may eventually produce material autonomously, which has been achieved with spider silk explants.

4.2. Scaling for real-world applications

Biotechnology costs and scaling-up challenges

The technology readiness level of self-microfabrication is between 2 and 3³⁰¹ when considering the hair follicle organoids as proof-of-concept. Scaling up organoids for medicine has revealed significant challenges, but potential solutions can be leveraged for material-producing organoids^{302,303} (Table 2). Unlike medicine, self-microfabrication faces fewer regulatory constraints but emphasizes cost-efficiency³⁰⁴. Focusing solely on costs at this stage would be shortsighted, as it overlooks future innovations, automation and economies of scale. Much is to learn from the cultivated meat sector^{305,306} that has even stricter cost requirements³⁰⁷. Biological materials may balance the cost by focusing on high value products³⁰⁸ that exhibit high mechanical performance²⁵.

Table 2: Challenges in scaling-up organoids

Challenge	Description	Potential solutions	Refs
Biological	Organoid size	Limited by the diffusion of oxygen through larger tissues potentially leading to necrotic cores	Vascularization Microfluidic devices for oxygenation, nutrient delivery and waste removal 309 310
	Multicellular complexity and tissue maturation	Cell origin, culture duration	Co-culture systems (with immune, endothelial, stromal cells, etc.) Enhancing cell maturation with signals from other tissue lineages 311 234,312–314
	Dynamic microenvironment regulation	Adapt signaling during development	Spatiotemporal signaling Signaling gradients, microfluidics 315 316
	Reproducibility and standardization	Variable cell sources, genetic and epigenetic variants, ECM batches, culture conditions and stochastic differentiation	Synthetic ECM and serum-free media with defined and consistent properties Robust cell lines (notably for iPSC) Standardized protocols and automation 317–319 320 321–323
Technological	Organoid lifespan	Tissue degeneration or cell death	Long term cultures of organoids 324
	Culture conditions and bioreactor systems	Nutrient delivery as waste removal, CellμEnv regulation in large bioreactors, with reduced hydrodynamic shear stress	Perfusible bioreactors Low-shear suspension cultures 325 325,326
	Automation and monitoring	Complex protocols and manual steps prone to variability	Reducing steps and simplifying protocols Automated procedures with liquid handling systems and robotics (seeding, passing, etc.) Continuous monitoring with real-time sensors (e.g., pH, oxygen) and feedback control 327 323 328
Industrial	Costs and economic feasibility	High skilled workforce and high material costs, such as ECM and growth factors	Automation Scaling up production and synthetic alternatives to ECM 323 307,318
	Scaling production batches, yield, and throughput	Shortening production cycles and increasing number of organoids	Reduce growth factors use with autocrine factors and supporting cells co-cultures Parallelized multi-well cultures High throughput microfluidics 3D cell culture platforms Large suspension cultures and continuous production systems 305,306 55 329 326
	Quality control and regulations	Higher reproducibility and simpler characterization	Sensors and image processing for quality control Standardize batch release tests and regulatory compliance protocols 330 320
Logistics and supply chain	Cell sources, specialized media or ECM, and cold chain logistics	Cell banks, organoid cryopreservation, proximity with hospitals	331
		Existing supply and cold chains	

Addressing production rates and biological constraints

Growing biological materials is generally slower than producing their synthetic counterparts. For instance, Nephila spider MA silk is produced 30 times slower than Kevlar, *i.e.* 5 µm diameter at 10 cm/s for silk³³² and 10 µm diameter at 80 cm/s³³³. However, spiders use liquid silk preliminary stored in the ampulla. Accounting for protein synthesis rates would likely reveal an even smaller production rate than synthetic polymers, as observed in other species³³⁴. Although essential, this comparison is somewhat inequitable since industrial polymer synthesis has already gone through decades of optimization. Synthetic biology can also accelerate cell cycle and optimize the growth and metabolism of tissues³³⁵. Indeed, modeling growth rates⁵⁶ and gene regulation³³⁶ highlight potential improvements³³⁷ and trade-offs³³⁸. To compensate growth limitations, material-producing organoids may produce in parallel to increase the throughput. Organ production units are self-organized and compact, potentially enabling their large proliferation in number, facilitating their parallelization⁵⁶.

Since biological materials aim to improve sustainability compared to fossil-based solutions¹⁷⁷, the environmental impact of biotechnologies should be considered³³⁹. Large scale self-microfabrication may also eventually compete for arable land to produce biomass, as already observed for biofuels³⁴⁰. Potential solutions include polycultures, yield optimization³⁴¹ and circular economies with the valorization of wastes³⁴².

Challenges in developing material-producing organoids are mostly addressed in Section 6. Beforehand, we present a theoretical framework for self-microfabrication to examine key concepts.

5. Theoretical considerations

5.1. How organs are made and maintained

Multiple developmental trajectories

Extensive studies have detailed the formation of organs^{343,344}; here, we focus on the plasticity of developmental trajectories. Given the challenges in developing material-producing tissues, it is important to note that organoids can often be cultivated using multiple methods, providing alternatives if one approach

fails. For instance, intestinal organoids can be derived either from adult stem cells (ASC)²⁴⁹, or from embryonic pluripotent stem cells (PSC) and iPSC³⁴⁵, each using different developmental trajectories. The organoid's maturity is affected by its cellular origin²³⁴, but can be partly compensated by long-term cultures³⁴⁶ and co-culture interactions³¹⁴. Organoids can still be grown in tissues lacking ASCs *in vivo*, such as the heart or brain^{347,348}, by leveraging cellular plasticity³⁴⁹. Many culture methods have been developed but the field needs standardized protocols and unified representations³²¹. For instance, signaling pathways, cell differentiation trajectories³⁵⁰ and other biological processes can be formalized into workflows with step-by-step descriptions³⁵¹. We suggest that similarly, a systematic definition of organoid developmental trajectories in standardized workflows would help future discoveries. Such workflow description is generally useful for computational approaches and may eventually contribute to developmental trajectory inference, as it is currently the case with signaling pathways³⁵².

Organoid protocols only use a few signaling factors to trigger stem cell self-organization³⁵³. Developmental workflows should emphasize key induction events, such as differentiation signals, symmetry breaking, or pattern formation³⁵⁴. The triggers for these events can be transcription factors, chemical gradients, or bioelectric fields³⁵⁵. Specific to material-producing organs, workflows can also describe biomolecule synthesis and assembly.

Tissue maintenance strategy

Once an organ is formed, it is maintained by multiple mechanisms that may be exploited for self-microfabrication. Under normal physiological conditions, also called steady-state homeostasis, tissues use specific maintenance strategies to function throughout the lifetime of an organism³⁵⁶ (Table 3). Other strategies may be activated following a perturbation, such as regeneration in injuries, dysfunctions, pathologies or aging³⁵⁷. This diversity of available tissue maintenance strategies, often within a single organ, can be exploited to grow organoids of interest. For instance, many organoids rely on ASC-mediated tissue renewal⁵⁰, such as the hair bulge, basal keratinocytes or intestinal crypts³⁵⁶.

Table 3: Tissue maintenance strategies under physiological and pathological conditions

Some organs combine multiple strategies upon specific signaling, such as steady state homeostasis or regeneration; examples are grouped as follows; green: liver, yellow: pancreas, orange: cartilage, red: blood vessels, blue: zebrafish heart.

Mechanism	Hypothesized Function	Hypothesized Advantages	Hypothesized Disadvantages	Examples	Refs	
Proliferation-based mechanisms	Stem cell mediated renewal (single-cell/population asymmetry, TA, progenitors)	Continuous replacement of cells in tissues with high turnover or exposure to damage.	Allows rapid regeneration; minimizes wear on stem cells via transit-amplifying cells.	Risk of stem cell exhaustion or mutations; high turnover increases cancer risk.	Mesenchymal stem cells (MSCs) in bone and cartilage repair (mammals)	358
					Vascular endothelial stem cells (CD157) residing in large blood vessel for homeostasis and regeneration (mammals)	359
					Intestinal crypt stem cells maintaining gut epithelium (mammals)	360
					Hair follicle stem cells driving hair regeneration (mammals)	361
					Limbal stem cells in corneal epithelium (mammals)	362
					Basal keratinocytes in the epidermis of skin (mammals)	361
					Hematopoietic stem cells (HSCs) in bone marrow (mammals)	363
					Neural stem cells in the ventricular-subventricular zone of the lateral ventricles and the subgranular zones of the hippocampal formation (mammals); ventricular zone of zebrafish brain	364,365
					Germline stem cells in <i>Drosophila</i> ovaries	366
					Planarian neoblast lineage	367
					Sponge archaeocytes (sponges)	368
					Hydra head regeneration through epimorphosis after a mid-gastric cut	369
Non-proliferative mechanisms	Intermediate levels of potency (such as progenitor cells with limited self-renewal and restricted potency)	Provides regeneration in tissues where stem cells are absent or inactive.	Efficient for tissues with low stem cell density; simplifies regeneration by directly producing needed cells.	Limited to tissues with specific progenitors; may have a lower regenerative capacity compared to stem-cell-mediated renewal.	Hepatic oval cells in liver regeneration upon certain injuries (mammals)	370
					Pancreatic ductal cells for β -cell regeneration upon injury (mammals)	371
					Chondrocyte progenitors in cartilage regeneration following injury (mammals)	372
					Endothelial progenitor cells (CD34) in blood vessel regeneration (mammals)	373
	Proliferation of terminally differentiated cells (quiescent or post-mitotic cells)	Allows regeneration in tissues with few or no stem cells.	Avoids reliance on a dedicated stem cell niche; efficient for low-turnover tissues.	Limited regenerative capacity; proliferating differentiated cells may accumulate mutations.	Hepatocytes during liver homeostasis (mammals)	370
					Endothelial cells responding to angiogenic signals (mammals)	375
					Cardiomyocyte proliferation in zebrafish heart from injury-induced factors and hypoxia; rare in adult mammals	376
					Chondrocytes dedifferentiating during cartilage repair (mammals)	377
					Zebrafish heart regeneration via cardiomyocytes	376
					Zebrafish fin regeneration	378
Non-proliferative mechanisms	Dedifferentiation, redifferentiation	Plasticity: reverts differentiated cells to progenitor-like states for regeneration; robustness: distributed regeneration potential sources	Efficient and bypasses need for stem cells; enables full regeneration in some organisms.	Rare in mammals; may not fully restore function in humans.	Vascular Smooth Muscle Cells during vascular remodeling following injury (mammals)	379
					Skeletal muscle regeneration via satellite cells (mammals)	380
					Myofibroblasts dedifferentiating during wound healing (mammals)	381
					Axolotl limb regeneration	382
					Hepatocytes transdifferentiating into cholangiocytes upon injuries, such as toxins and bile duct ligation (mammals)	370,383
					Pancreatic acinar cells transdifferentiating into insulin-producing β -cells and duct cells (mammals)	384
	Transdifferentiation	Rapid regeneration by converting one differentiated cell type directly into another without passing through a dedifferentiated state	Efficient and avoids intermediate states; reduces repair time and energy costs.	Rare in mammals; risk of incomplete or incorrect transdifferentiation.	Zebrafish heart regeneration: atrial cardiomyocytes migrate and transdifferentiate ventricular myocardium upon extensive loss	376
					Pigmented epithelial cells transdifferentiating to lens cells in Newts	385
					Myofibroblasts transdifferentiating into many cell types during ocular wound healing (mammals)	386
					Hydra morphallactic regeneration from epithelial cells upon amputation (away from mid-gastric region)	369
Non-proliferative mechanisms	Cell migration (distant cell source)	Supplies new cells to damaged areas by migrating from other tissue regions	Rapid response to injury, using existing cell reserves	Dependent on source availability; may not fully replace all lost cell types	Cnidarian choanocytes converting into multiple cell types during regeneration	387
					Keratinocytes migrating to wound edges (mammals)	388
					Planarian neoblast migration	367,389
	Cell lifespan compensation (highly specialized, post-mitotic cells in minimal cell turnover; increased intracellular repair)	Maintains highly specialized, non-dividing cells over an organism's lifetime	Preserves complex and specialized cells; minimizes dysregulated proliferation	Limited regenerative capacity; damage results in permanent functional loss	Hair cells in the cochlea (inner ear of mammals)	390
					Long-lived neurons : cortical pyramidal neurons, hippocampal neurons critical for memory and motor neurons controlling voluntary muscle movements (mammals)	391
					Podocytes in kidney glomeruli (mammals)	392
	Cell size compensation (compensatory hypertrophy)	Restores organ function by increasing cell size or tissue mass without heavy cell division, notably through multinucleation	Avois excessive cell division, reducing cancer risk; restores functionality	Does not restore original cell numbers; hypertrophic cells may become overburdened	Hepatocytes upon surgical injury by 30% partial hepatectomy (mammals)	370
					Retinal pigment epithelial cells in aging retina (mammals)	393
					Skeletal muscle cells enlarging during strength training (mammals)	394
Cell shape and structure remodeling ³⁹⁷ (cytoskeleton, ECM and forces compensations)	Adapts cellular structures to maintain or restore tissue integrity	Maintains mechanical stability and functionality under stress; versatile response	May not address cell loss; remodeling can lead to suboptimal tissue organization over time	Cardiomyocytes during cardiac hypertrophy upon physiological and pathological stimuli (mammals); post-prandial python heart hypertrophy, cardiac remodeling in fishes for cold temperatures, birds for high altitude flights and mammals during endurance training	395,396	
					Fibroblasts cytoskeletal remodeling in connective tissue repair (mammals)	398
					Podocytes adjusting their foot processes in kidneys (mammals)	399
					Sponge mesohyl cells' cytoskeletal rearrangement during regeneration	400
					Hydra epithelial cells adapting to stress (hydras)	369
Cell metabolism plasticity (functional compensations in gene regulation and metabolism)	Enhances tissue function without requiring cell proliferation	Increases functional capacity without increasing cell numbers; lowers cancer risk	Does not restore lost cells; tissue function may still decline with severe damage	Hepatocytes in liver adapting to fasting or alcohol metabolism (mammals)	401	
					Type I alveolar epithelial cells compensating for lung damage (mammals)	402
					Adaptive physiological changes in hibernating bears (mammals)	403
					Physiological adaptations in fasting penguins (birds)	404

Other organs are maintained by progenitor cells with restricted self-renewal, or terminally differentiated cells that revert to proliferation⁴⁰⁵. Others leverage dedifferentiation or transdifferentiation, such as hepatocytes upon chronic injuries⁴⁰⁶. A few tissues have little to no cell turnover, such as most post-mitotic neurons or the inner ear hair cells³⁹⁰, and may rely on increased intracellular repair mechanisms to maintain their function³⁹¹. Other non-proliferative strategies, such as cell compensations for metabolism, size or shape help maintain the organ function⁴⁰⁷; for instance, physical exercise induces skeletal muscle cell hypertrophy³⁹⁴.

Some organs use more than one tissue maintenance strategy, the liver being a prime example. Hepatocytes use cell proliferation during steady-state homeostasis. Following the surgical removal of 30% of the liver, hepatocytes activate compensatory hypertrophy, and following other injuries like toxin exposure, they can transdifferentiate or recruit progenitor cells³⁷⁰. Switching from one mechanism to the next can be either preprogrammed within cells, or triggered by external signals, such as apoptosis⁴⁰⁵, phagocytosis, ECM remodeling, and inflammation. Surrounding cells can also signal what tissue maintenance strategy to use, such as macrophages⁴⁰⁸, adipocytes⁴⁰⁹, or microbes⁴¹⁰. These signals can be induced in culture and engineered to enable tissue growth in non-

regenerative organs^{411,412}. Thus, self-microfabrication is conceivable even in non-regenerative organs.

5.2. Dealing with complex organs

A simple representation for hierarchical tissues

We have seen how multiple developmental trajectories and tissue homeostasis strategies enable organoid growth. These mechanisms are complex, interconnected, and operate at multiple biological scales, making them challenging to apprehend. This section examines how to simplify and better understand essential mechanisms of self-microfabrication.

Waddington introduced simple representations of complex biological systems, named epigenetic landscapes⁴¹³. We propose to extend the idea into hierarchical landscapes, describing organ formation across biological scales (Fig. 5A). For instance, at the cellular scale, cell types are viewed as balls rolling down a hilly landscape, where valleys are differentiation trajectories, from stem cells at the top to lower specialized cells at the bottom. These simple diagrams allow researchers to depict and share diverse phenomena, such as cell-cell communication (Fig. 5B). Each layer may be built by integrating experimental data from various sources, such as gene sequences, cell's gene expression profiles or tissues' spatial omics (Fig. 5C). Since tissues are made of cells,

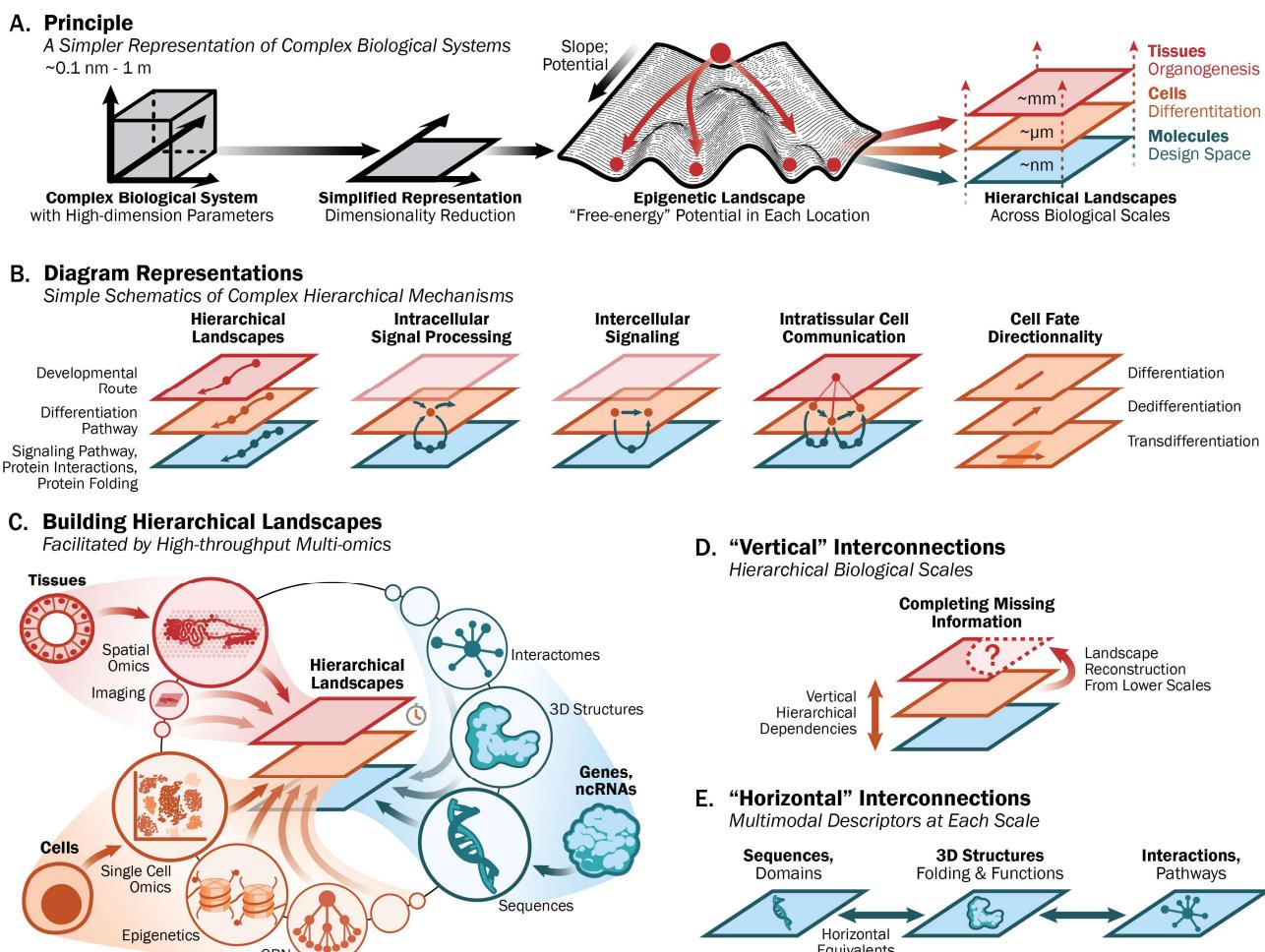


Figure 5: Modeling Complex Biological Systems with Hierarchical Landscape Diagrams

A. Construction of an epigenetic landscape, biological system represented as a hilly landscape, the valleys are trajectories, and the pits are stable attractors. Landscapes can be hierarchical and interconnected between each biological scale. **B.** Simple diagrammatic representations of hierarchical phenomena. **C.** Multimodal modeling of biological systems, notably data-driven using high-throughput multi-omics experiments. Tissues: architecture and composition; cellular: cell types and gene regulation; molecular: sequences, 3D folding and pathways. **D.** Transferring information across biological scales. Red: tissular landscapes, orange: cellular landscapes, blue: molecular landscapes. **E.** Transferring information across modalities.

themselves composed of biomolecules, we suggest that this formalism may allow a “vertical” flow of information across scales (Fig. 5D). Similarly, “horizontal” information transfer may be envisioned within a layer (Fig. 5E). The purpose is to offer a simple mental image of complex organs and eventually generalize their principles to new material-producing organoids.

As diagrams may be abstract, Figure 6 provides a more detailed representation of hierarchical landscapes. At the tissular scale, valleys represent the multiple developmental routes discussed in the previous section (Fig. 6A). The width of a valley, or canalization, indicates how robust development is to perturbations. For example, the “Picasso frog” can self-correct significant embryonic defects⁴¹⁴. Each location represents an organ state, composed of multiple cell types structured together and linking this tissular scale to the next.

The cellular scale showcases basins of attraction, where a region canalizes cells to an attractor. ASC are metastable attractors, differentiating in multiple specialized cell types⁴¹⁵ (Fig. 6B). Landscapes are useful to find genes guiding differentiation⁴¹⁶ or reprogramming factors⁴¹⁷.

At the molecular scale, a free-energy landscape models biomolecules conformation and self-assembly⁴¹⁸, it supports discoveries⁴¹⁹ and enables microstructure engineering⁴²⁰ (Fig. 6C). This representation should not be seen as static, some hills and valleys can dynamically change, influenced by GRNs and surrounding microenvironments⁴²¹. For instance, cell reprogramming factors may “invert the slope” during dedifferentiation⁴¹⁷ (Fig. 5B). Such hierarchical landscapes offer a simple and generalizable representation of complex self-microfabrication systems.

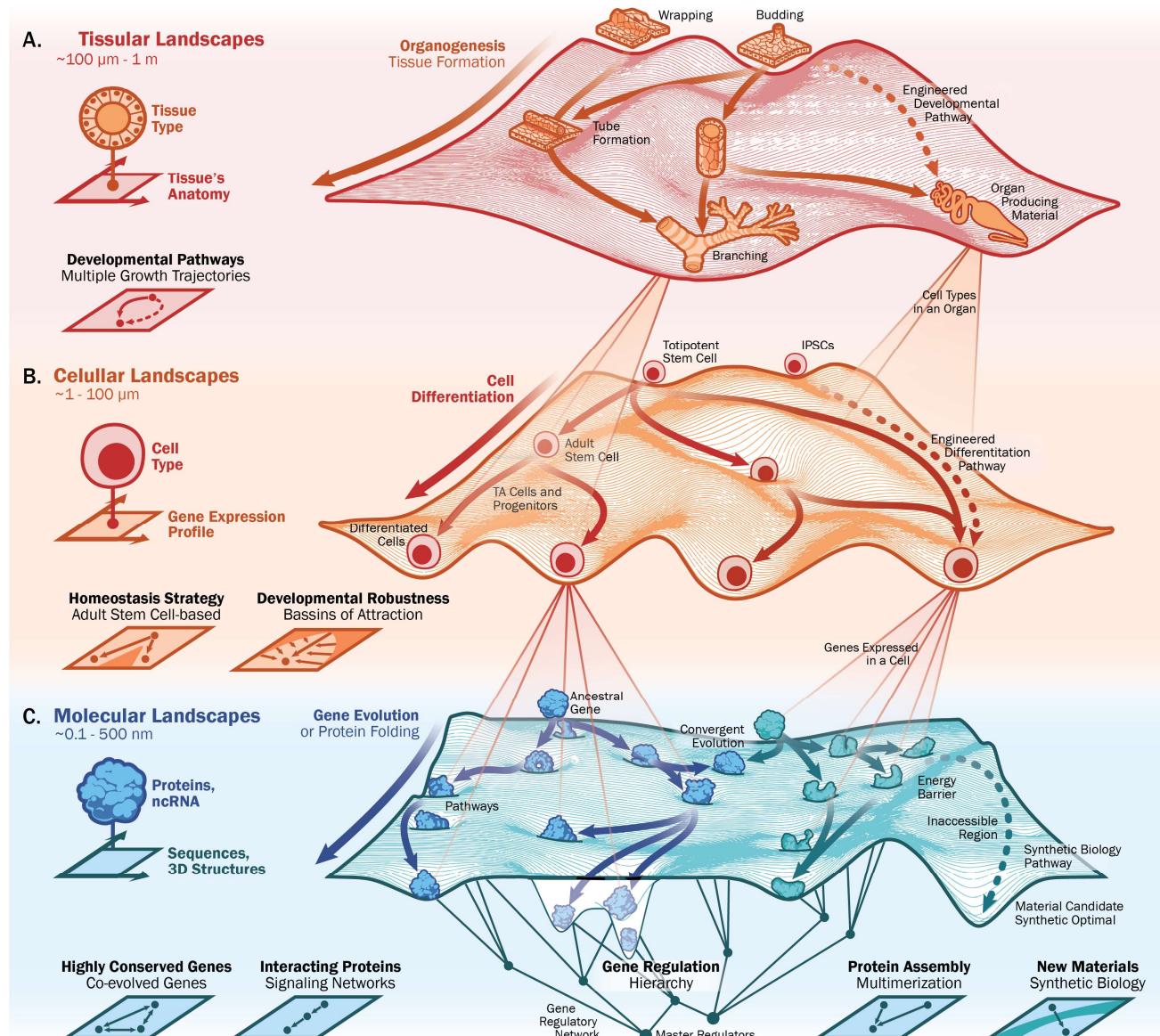


Figure 6: Hierarchical Epigenetic Landscapes

A. Tissular scale: each location is an organ, valleys are developmental routes, and the slope represents organogenesis. Red: landscape, orange: tissues. **B. Cellular scale:** each location is a cell type, or state, valleys are differentiation trajectories, and the slope is cellular commitment. Totipotent stem cells are at the top, while terminally differentiated cells are at the bottom; ASC are in middle metastable attractors. Red: cells, orange: landscape. **C. Molecular scale:** multiple landscapes are possible at this scale. In a first, each location is a biomolecule, valleys represent protein folding and interactions, and the slope is the free energy. In a second model, each location is a DNA sequence; valleys represent phylogenetic relationships, and the slope is evolutionary conservation. Both views are complementary. The branching structure at the bottom represents GRNs influencing the landscapes. Blue: landscape and molecules with different colors for different molecular ancestry.

Modeling complex tissues

Beyond a conceptual tool, an epigenetic landscape enables computational modeling⁴¹⁵, using General Systems Theory⁴²². For instance, at the cellular scale a cell type's unique gene expression profile can be viewed as a point in multidimensional space, with each coordinate corresponding the expression level of each particular gene⁴²³ (Fig. 5A). It is commonly used in single-cell sequencing, with the gene expression matrix containing all information and dimensionality reduction techniques enabling clustering and other data processing⁴²⁴.

Different biological processes can be modeled depending on how the coordinates, or parameters, are defined. For instance, at the molecular scale, using chromatin modifications as variables for the landscape give insights about epigenetics⁴²⁵. If the topography is built using DNA sequences, it may represent GRNs^{426,427}, protein conformations⁴²⁸, chromosome interaction⁴²⁹ or phylogenetic relations⁴³⁰. Similarities between these modalities may help to interconnect landscapes (Fig. 5E). Landscapes have been defined at many biological scales⁴³¹, including the tissular layer describing developmental trajectories during morphogenesis³⁵⁵. We suggest that interconnecting them can allow the flow of information across scales (Fig. 5D). As cells are easier to characterize than organs, tissular landscapes may be inferred from more accessible cell measurements, such as single-cell transcriptomics used in cellular landscapes^{432,433}, even in non-model species⁴³⁴. To support the idea of vertical interconnections, we propose a theoretical demonstration of its feasibility. Consider a space X representing a molecular landscape with biomolecules x, Y as the cellular landscape, and Z tissular. $P(x)$ is the probability of a molecule x to be in a particular state, the same applies to $P(y)$ for a cell, and $P(z)$ for a tissue. Using experimental data, the density distributions of $P(x)$, $P(y)$ and $P(z)$ can be computed (e.g. gaussian mixture models, normalization flows, variational autoencoders or other methods⁴³⁵). Similarly, conditional probabilities can be derived from empirical data, such as $P(y|z)$, the probability of a cell type y being in a tissue z, and $P(z|y)$ that a tissue z contains a given cell y. To carry the contribution from one scale to the next, we need to connect them hierarchically ($X \rightarrow Y \rightarrow Z$). As an example, we focus solely on two scales ($Y \rightarrow Z$). Equation 1 expresses $P(z)$, the probability of a tissue state, as a marginal distribution derived from $P(y,z)$, the joint probability of a cell state y and a tissue state z:

$$P(z) = \int P(y, z) dy = \int P(y | z) P(z) dy \quad (1)$$

Using Bayes' theorem (Equation 2), we can further decompose $P(z)$ in terms of $P(y)$, the cell state probability, and $P(z|y)$, the probability that a tissue state contains a specific cell state. This highlights the dependence of tissues on the lower cellular level.

$$P(z) = \int P(y) P(z | y) dy \quad (2)$$

To create the landscape's topography (Fig. 5A), we use a potential (V), analogous to energy landscapes used in physics and biology:

$$V_z(z) = -\ln(P(z)) \text{ and } V_y(y) = -\ln(P(y)) \quad (3)$$

Finally, the potential at the tissue scale (V_z) is derived from the cell-scale landscape (V_y) and the conditional probability $P(z|y)$, creating a bridge between these scales:

$$V_z(z) = -\ln \left(\int e^{-V_y(y)} P(z | y) dy \right) \quad (4)$$

It is currently challenging to estimate the probability $P(z)$ of a tissue to be in a specific state as it would require extensive measurements from numerous tissues and samples. Instead, we show that interconnected landscapes can potentially derive $P(z)$

using only a few observations of cells within a tissue $P(z|y)$, along with the more readily available probability $P(y)$ of a cell being in a specific state. This development illustrates one way to bridge landscapes across biological scales.

While the proposed framework provides a theoretical basis for bridging scales, more applied approaches are available⁴³⁶ (e.g. coarse grained⁴³⁷, agent-based⁴³⁸, cell-cell communication models⁴³⁹, or virtual cells⁴⁴⁰). *In silico* representations aim to complement experimental evidence and facilitate the understanding, prediction, simulation, and optimization of biological tissues over time²²⁶. In the meantime, valuable insights can be gained from the models themselves. For instance, how cellular collectives, or decentralized multi-agent systems, are programmed to reach specific outcomes⁴⁴¹. Improved modeling, prediction and simulation approaches could accelerate the development of new organoids.

Guiding development with cellular microenvironments

Since CellμEnvs control tissue behaviors, we can guide development by engineering these microenvironments. This paragraph discusses key aspects: characterization, modeling, understanding the effects of CellμEnvs, and engineering.

Characterization techniques have improved in throughput and sensitivity in the past decade, reaching single-cell resolution with spatial omics⁴⁴², measurements of key regulators⁴⁴³, functional perturbations using CRISPR⁴⁴⁴, and mechanical tests⁴⁴⁵. Moreover, versatile data-driven approaches help uncover cellular communication pathways⁴⁴⁶ and their downstream effects⁴⁴⁷.

To model spatiotemporal CellμEnvs, biosignaling fields can be developed³⁵⁵; using scalar values (e.g. temperature, diffusing chemicals or electric potentials), vectors (e.g. velocities⁴⁴⁸), and tensors (e.g. mechanical stresses^{449,450}). As each cells emits and receives signals, their individual contribution can be added or subtracted to the field. For instance, such "sources" and "sinks" can be localized in 3D⁴⁴⁶ and modeled with diffusion-consumption mechanisms⁴⁵¹ using secreted signaling factors⁴⁵² and expressed membrane receptors from spatial single-cell transcriptomes⁴⁵³. Maps can be established for each signal, representing gradients of diffusing chemicals⁴⁵⁴. Biosignaling fields may even be simulated over time, notably using Fick's second law with C as the concentration and D the diffusion coefficient:

$$\frac{\partial C}{\partial t} = D \nabla^2 C \quad (5)$$

Once a biosignaling field description is established, we may investigate its effect on cell behavior. Local microenvironment can be estimated in each location, notably what signals a given cell receive⁴⁵⁵. From this, the cell reaction can be deduced⁴⁵⁶, such as gene expression changes, using cell-specific membrane receptors, signaling pathways⁴⁵⁷ and GRN⁴⁵⁸. In principle, by updating cells' expression profile, notably newly secreted signals, the cycle may be repeated to simulate the dynamics of multicellular tissues⁴⁵⁹. Such computational approach can be simplified to accommodate large amount of cells⁴⁶⁰, notably using graph representations of interconnected cells, instead of 3D coordinates⁴⁶¹. Such biosignaling field reconstruction and modeling from spatial omics data face challenges, including anatomical variability⁴⁶², dependence on sections orientation⁴⁶³, and destructive experiments⁴⁶⁴. Improved experimental repeatability and data integration already support time series measurements, encouraging future cellular communication models and simulations⁴⁶⁵. Once signaling factors guiding development are identified, their spatiotemporal implementation may use various techniques⁴⁶⁶, notably

synthetic ECM⁴⁶⁷ and signal patterning devices^{229,468}. 3D cultures are influenced by their scaffold's composition⁴⁶⁹, porosity, topography³¹⁰, functionalization, degradation and release of signals⁴⁷⁰. CellμEnv engineering use techniques such as coated beads, soft lithography⁴⁷¹, gradients⁴⁷², bioprinting⁴⁷³, optogenetics⁴⁷⁴ and magnetic fields⁴⁷⁵. To grow larger tissues, bioreactors⁴⁷⁶ and microfluidic channels help oxygen and nutrients supply, as well as waste and dead cells removal⁴⁷⁷. Finally, mechanical signals can be tuned by materials stiffness and viscoelasticity or using pressure chambers and shear forces⁴⁷⁸. Using these techniques, tissue engineering can control the biosignaling field to regulate organoid long-term cultures⁴⁷⁹. Self-microfabrication benefits from continuous improvements in CellμEnvs characterization, modeling and engineering to support future material-producing organoid development.

6. Future outlook to address challenges

6.1. Growing new organoids

Exploring non-model species

Many biological materials of interest come from less-studied species compared to model organisms (Table 1). The development of new model species is supported by versatile research tools⁴⁸⁰, notably single-cell multi-omics^{481,482}. Adult stem cells are identified across kingdoms^{483–485} and for many species, cells can be dedifferentiated into iPSC⁴⁸⁶ owing to greater insights into reprogramming factors⁴⁸⁷ since Takahashi and Yamanaka's discovery in 2006²⁴⁸. Similarly, the achievement of organoid development by Sato *et al.* in 2009²⁴⁹ has reached many new tissues and organisms^{275,488,489} (Table 4). Expanding organoids to lesser-studied species, notably for material production, is challenging due to the difficulty to transferring biological knowledge from one species to another^{490,491}. Computational approaches help to generalize information across species, such as the inference of gene annotations, sets, pathways, GRN⁴⁹², phenotypes or cell types. Many algorithms often use conserved molecular components (*e.g.* orthologs) to find similarities between organisms⁴⁹³. Similarly, cross-species knowledge transfer can be viewed as “horizontal” connections between the landscapes of different organisms (Fig. 7A). As hierarchical landscapes can also link biological scales (Fig. 5D), we suggest their use to infer cell types⁴⁹⁴ and organogenesis mechanisms from known species to non-model organisms (Fig. 7B). Transferring landscape topography across species could and guide experiments by highlighting regions of interest, likely to contain cell types or molecular components, such as promoter, growth factors or “missing links” in signaling pathways. Such cross-species knowledge transfers could help accelerate the current expansion of organoid technologies to non-model species that produce biological materials.

The “missing body problem”: cellular microenvironment

When an organ is removed, or grown outside its native body, it requires specific signals to support its survival. Developing material-producing organoids encourages the study of CellμEnvs in non-model species, which can lead to unexpected breakthroughs⁴⁹⁵. Key signals from the “missing body” can already be studied, independently from other self-microfabrication challenges, using transplants⁴⁹⁶ and *ex vivo* explant cultures⁴⁹⁷. Before growing material-producing organs, explants serve as effective *in vitro* models to examine their physiology and characterize essential CellμEnv factors for survival⁴⁹⁸. To demonstrate this principle, we have developed a spider silk gland explant that spins fibers *in vitro*. The MA

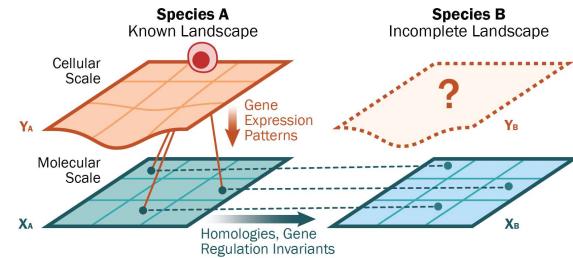
glands are extracted and cultured in a dish, preserving all structures intact, *i.e.* tail, ampulla, duct, spigot and the 2 μm diameter threads. Pulling the hanging fibers (the spinning trigger) produces new native spider silk. This explant first demonstrates that spider silk gland may produce material autonomously from the rest of the body and serves as *in vitro* model for this organ. Other material producing tissues could be studied with explants. As an example, developing a byssus-producing mussel foot explant could leverage existing culture media^{499,500}, growth factors^{501,502}, cell lines⁵⁰³ and *in vitro* expression protocols⁵⁰⁴.

Other approaches can be considered to circumvent the “missing body problem”. A material may be produced in a different organ with similar characteristics (*e.g.* ChemμEnv). For instance, growth factors and gene editing tools are available in silkworms but not in spiders. Thus, silkworms glands can be edited to produce a spider silk analogue¹⁸³. Although the silk glands of spiders and silkworms have different phylogenies and embryogenic origins^{46,505}, their convergent evolution demonstrates material-processing similarities⁴⁵, enabling transgenic silkworms to produce exogenous materials¹⁸⁵. Edited spidroin, combined with a silkworm silk promoter, can be transfected in *Bombyx mori*'s genome and sustained through generations, aiming to produce spider-silkworm hybrid fibers at industrial scales¹⁸³. We call this approach “environmental transfer”, for producing an exogenous material in an already similar organ.

Rather than adapting a material to match a similar tissue, the opposite could be considered by editing an organ to produce the desired material. We refer to this as “environment morphism”. This principle of changing the CellμEnv to affect a tissue's physiology is used in transplants⁵⁰⁶, tissue rejuvenation²⁴⁴ and humanized mice⁵⁰⁷. A tissue can even change its anatomy following the addition of a single cell type, such as thickening skins following volar fibroblast transplantation²⁴⁷. Similarly, we suggest that self- microfabrication could eventually affect an organ's physiology to improve material processing.

A. Similarities Between Species

Interconnecting the Landscapes



B. Knowledge Transfer to Non-model Species

Predictions from Model Species

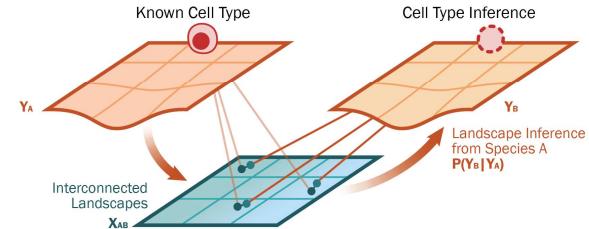


Figure 7: Cross-species Knowledge Transfer

A. Similarities help connect epigenetic landscapes across species and scales using space transformations. **B.** Information from a model organism is transferred to a lesser-studied species. Orange: cellular landscapes, blue: molecular landscapes.

Table 4: Organoids across different species

Mainly developed in mammals, with some organoids in birds, reptiles, amphibians and fishes. They are studied for zoonotic diseases, veterinary studies, livestock medicine, model systems for human diseases or comparative evolution. Modified from the Table 1 of Gabriel et al.²⁷⁵. Other reviews cover humans and mice extensively⁵⁰⁸, only the first reported organoids in these species are included here.

Taxonomy	Animal	Species	Date	Organ Types	Model Significance	Ref
Mammals (Primates)	Human*	<i>Homo sapiens</i>	2010	Intestine	First human organoid	509
	Monkey	<i>Macaca fascicularis</i> (cynomolgus macaque)	2021	Colon	Drug permeability and toxicology	510
		<i>Macaca mulatta</i> (rhesus macaque)	2021	Full intestine	Intestinal model, closer to humans for chemosensory cells physiology	511
Mammals (Rodentia)	Mouse*	<i>Mus musculus</i>	2009	Small intestine	First organoid	249
	Prairie voles	<i>Microtus ochrogaster</i>	2022	Mammary gland	Mammary gland cancer	512
	Hamster	<i>Mesocricetus auratus</i>	2024	Mammary gland	Mammary gland cancer	488
Mammals (Lagomorpha)	Rabbit	<i>Oryctolagus cuniculus</i> (European rabbit)	2020	Cecum	Intestinal model relevant to humans, pathogen-host interactions	513
			2021	Full intestine		514
			2022	Mammary gland	Mammary gland cancer	512
Mammals (Chiroptera)	Bat	<i>Rhinolophus sinicus</i> (Chinese rufous horseshoe bat)	2020	Small intestine	Zoonotic diseases, viral transmission to humans, notably SARS-CoV-2	515
	Rousette	<i>Rousettus leschenaultia</i> (Leschenault's Rousette)	2021	Intestine		516
Mammals (Carnivora)	Cat	<i>Felis catus</i>	2017	Liver	Drug testing, toxicology and disease model	517
			2017	Ileum	Zoonotic pathogens, disease model, drug testing	518
			2020	Colon	Zoonotic pathogens, disease model, drug testing	519
			2022	Mammary gland	Mammary gland cancer	512
	Dog	<i>Canis lupus familiaris</i>	2022	Cornea	Comparative ophthalmology, veterinary application	520
			2015	Liver	Drug testing, toxicology and disease model	521
			2017	Ileum	Zoonotic pathogens, disease model, drug testing	518
			2018	Skin	Cutaneous disorders	522
Ferret			2019	Kidney	Drug testing, toxicology and disease model	523
			2019	Intestine	Gastrointestinal disease model	524
Mammals (Perissodactyla)	Horse	<i>Equus ferus caballus</i>	2022	Urinary bladder	Urinary Bladder Cancer	525
			2022	Cornea	Comparative ophthalmology, veterinary application	520
			2024	Mammary gland	Mammary gland cancer	488
Rhinoceros		<i>Equus ferus przewalski</i> (Przewalski's horse)	2017	Ileum	Zoonotic model, medicine of equine for agriculture	518
		<i>Dicerorhinus sumatrensis</i> (Sumatran rhinoceros)	2017	Jejunum		526
			2020	Endometrium	Equine health and reproduction	527
Mammals (Artiodactyla)	Pig	<i>Sus scrofa domesticus</i> (bama miniature pigs)	2022	Mammary gland	Mammary gland cancer	512
			2013	Jejunum	Zoonotic model, health of livestock for agriculture; gastrointestinal model relevant to human physiology, transplantation therapy models	529
			2016	Duodenum		530
			2017	Ileum		518
			2017	Anus, rectum	Crohn's disease and stem cell regeneration	531
			2017	Esophageal glands	Esophageal model of squamous & columnar cells	532
			2019	Colon	Pathogen-Host Interaction	533
Cattle			2022	Mammary gland	Mammary gland cancer	512
		<i>Bos taurus</i> (cow)	2017	Ileum		518
			2018	Jejunum	Zoonotic model, health of livestock for agriculture, pathogen-host interactions	534
			2019	Colon		535
			2021	Abomasum		536
Sheep			2024	Mammary gland	Mammary gland cancer in dairy animals	488
		<i>Ovis aries</i>	2017	Ileum	Zoonotic model, health of livestock for agriculture	518
			2020	Pancreas	Copper influence on pancreas development	537
Goat		<i>Capra hircus</i>	2024	Mammary gland	Mammary gland cancer in dairy animals	488
	Deer	<i>Odocoileus virginianus</i> (white-tailed deer)	2022	Mammary gland	Mammary gland cancer	512
Alpaca		<i>Vicugna pacos</i>	2024	Nasal turbinates	Zoonotic diseases, notably SARS-CoV-2	538
	Opossum	<i>Monodelphis domestica</i> (gray short-tailed opossum)	2024	Mammary gland	Asynchronous concurrent lactation in marsupials, milk regulation model for nutritional adaptations	488
Birds (Aves)	Chicken	<i>Gallus gallus domesticus</i>	2017	Cecum	Gastrointestinal models for poultry health and agriculture, insights in specific avian physiology and development	518
			2018	Jejunum		539
			2020	Full intestine		540
Reptiles	Snake	5 cobras, 1 elapid, 2 vipers, 2 pit vipers	2020	Venom gland	Venom production for antivenom studies	223
	Lizard	<i>Anolis carolinensis</i> (green anole)	2022	Tail blastema	Epimorphic regeneration model	541
Amphibian	Frog	<i>Xenopus laevis</i> (African clawed frog)	2020	Mucociliary epidermis	Barrier and mucus production similar to humans	542
	Turtle	<i>Apalone spinifera</i> (softshell turtles) <i>Chelydra serpentina</i> (juvenile snapping turtles) <i>Chrysemys picta</i> (adult painted turtles)	2024	Liver	Hypoxia, anoxia and oxidative stress research mimicking ischemia-reperfusion injuries during organ transplants; organ cryopreservation	543
Ray-finned fishes (Actinopterygii)	Zebrafish	<i>Danio rerio</i>	2017	Retina	Nonal lamination mechanisms	544
	Medaka	<i>Oryzias latipes</i> (indian ricefish)	2020	Endothelial embryoid	Endothelial and vascular research	545
			2023	Testicular aggregate	Spermatogenesis, germ-somatic cell interactions	546

6.2. Overcoming biological limitations

Synthetic and hybrid routes

Although natural selection led to optimal biological systems, synthetic approaches can go beyond²²². Biological machinery provides key insights to improve biological materials production, though it also has limitations that can eventually be overcome. For instance, spider silk properties can be improved with highly hydrophobic domains, but cells are incapable of synthesizing them as their increased hydrophobicity prevents the engineered proteins from passing the endoplasmic reticulum membrane⁵⁴⁷. Synthetic routes can reach normal inaccessible regions of the molecular epigenetic landscapes and create new optimal materials^{548–551} (Fig. 8).

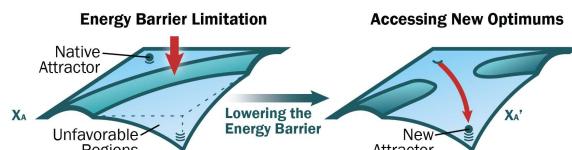


Figure 8: Overcoming Biological Limitations

Lowering energy barriers to reach new optimal attractors for tissues and material using synthetic biology and microenvironment engineering. Blue: molecular landscape.

Biohybrids can capture the best of both worlds, by overcoming biological limitations while being self-organized⁵⁵². For instance, neurons grown on microelectrodes arrays (MEAs)⁵⁵³ can regulate digital systems⁵⁵⁴, such as a flight simulation⁵⁵⁵, and help brain-computer interfaces⁵⁵⁶. Biohybrids can connect tissues digitally⁵⁵⁷ through long distances⁵⁵⁸, perform cell-based computation⁵⁵⁹, and develop biosensors⁵⁶⁰, artificial pancreas⁵⁶¹ and robots⁵⁶².

Synthetic biology helps to design materials⁶⁵, developmental routes⁵⁶³, tissues⁵⁶⁴, and cell regulation⁵⁶⁵. Artificial cells⁵⁶⁶ can even perform multicellular communication⁵⁶⁷ and induce cell differentiation⁵⁶⁸. “Anatomical compilers”⁵⁶⁹ may help design novel tissues⁵⁷⁰ to perform a targeted function²²⁶ and self-replication⁵⁷¹. Self-microfabrication has much to learn from biological self-organization but can go beyond current biological constraints.

Beyond materials: self-organized devices

The recyclability of biological materials may also expose them to degradation by other organisms and environmental conditions⁵⁷², eventually requiring protection layers to meet industrial standards. Interestingly, spiders create a natural coating on their silk⁵⁷³, limiting protease digestion⁵⁷⁴. Aquatic species even keep their silk dry with hydrophobic motifs⁵⁷⁵, inspiring self-assembled composite materials.

Biological systems not only grow materials but also composite structures and living machinery. This opens new avenues for self-organized devices, such as insulin-producing organoids transplants for pancreatic applications⁵⁷⁶ or high specific surface electrodes for batteries⁵⁷⁷. Taking inspiration from the electrocytes in electric eels, high density batteries^{578,579} may eventually be self-organized using an organoid approach.

Devices could also be grown by synthesizing multiple materials at different locations simultaneously. For instance, existing anatomies may be edited to express exogenous materials in specific tissues using cell-specific promoters^{580,581}. Biohybrid solar cells⁵⁸² may eventually be grown to harvest electricity from photosynthesis^{583,584}. Synthetic biology can also improve the carbon capture in algae⁵⁸⁵ and could be applied to trees⁵⁸⁶ for bioenergy and carbons storage⁵⁸⁷. These advancements raise ethical questions explored in the next section⁵⁸⁸.

7. Ethical, societal and technological implications

7.1. Societal and technological impact

Microfabrication revolution

Material-producing organoids can not only produce better materials, but also improve manufacturing techniques. Bringing fabrication to microscopic scales has enabled pattern-driven material microstructures⁵⁸⁹ and miniaturized devices, revolutionizing everyday lives⁵⁹⁰. For instance, photolithography has supported the semiconductor industry, telecommunication, modern computing⁵⁹⁰, and brought microelectromechanical systems (MEMS)⁵⁹¹, sensors⁵⁹² and implants⁵⁹³. However, both manufacturing costs⁵⁹⁴ and production volumes⁵⁹⁵ are constrained by available technologies. In contrast, nature achieves complex self-microfabrication in large sizes and at low costs⁵⁹⁶ through self-organization²¹ (Fig. 9).

Engineering material microstructure in bulk materials can enhance their mechanical properties, as demonstrated in hierarchical materials⁵⁹⁷. For instance, while chemically similar to chalk⁵⁹⁸, bivalve shells are up to 100 times tougher (3.3 to 9

MPam^{1/2} of fracture toughness), thanks to their microstructure⁹⁷. At the nanoscale, CaCO₃ crystal grains form microscopic tiles⁵⁹⁸, blocking fracture propagation and enhancing material properties⁵⁹⁹. Organic bridges measuring 1-5 nm highlight the competitive feature size of self-organized biological materials⁵⁹⁹ compared to photolithography's limits⁶⁰⁰. Self-microfabrication has the potential to improve existing achievements, and introduce innovative manufacturing methods⁶⁰¹, such as pattern-driven materials self-assembly. Applications of this approach⁶⁰² promise biological materials combining sustainability with high mechanical performance⁵⁹².

Self-organized microfabrication

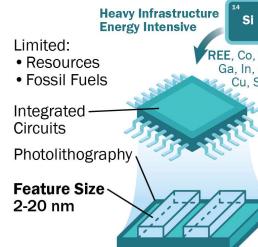
Polymers have shaped modern products, with copolymers diversifying applications by increasing the complexity of their components⁶⁰³. However, copolymers are typically limited to 2-5 monomers with simple assembly patterns, such as random and alternating blocks, or graft. Biology achieves higher complexity by freely assembling twenty monomers, along with non-canonical amino acids⁶⁰⁴, post-translational modifications and multimerization⁶⁰⁵. This combinatorial genetic code generates all proteins and biological materials, of the molecular landscape⁶⁰⁶ (Fig. 5). Biomimicry first explores naturally selected optima, or peaks on a molecular landscape, and applies them to engineer superior materials²²² using existing biological machinery and synthetic approaches⁶⁰². Spatiotemporal control over chemical reactions and materials processing conditions is precisely regulated in biological systems, using nanoscale bioreactors, including membrane-less organelles²³².

More than materials, the biological machinery itself is self-organized from the bottom-up, maintained through homeostasis and self-repaired²²⁹. Using existing developmental trajectories, complex production units can emerge from lower scales of organization²¹⁵. For instance, only a few genes in Drosophila initiate the complex development of a limb, while altering

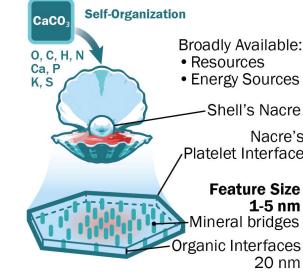
A. Microfabrication Approaches

Resources and Processes

Conventional Microfabrication



Self-Microfabrication



B. Economic Potential

Microfabrication at Scale and Lower Cost

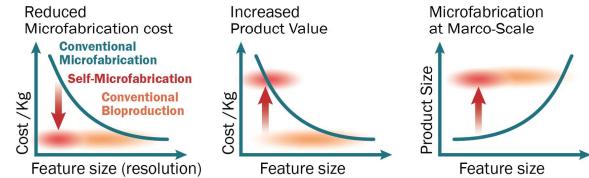


Figure 9: Comparison of Self-Microfabrication with Conventional Microfabrication

A. Key resources needed and minimal feature sizes achievable in the semiconductor industry versus self-microfabrication. Red: biological system or proteins, blue: other materials.

B. Schematic representation of the economic opportunities offered by self-microfabrication when looking at current bioproduction. Blue: schematic tendency in the semiconductor industry, orange: conventional biofabrication (including biological materials) and its achievable manufacturing scales, red: future potential of self-microfabrication.

solely the bioelectric field in flatworms affects their whole body plan²⁴¹. A single seed encodes the blueprint for complex plant development. Similarly, self-microfabrication seeks to grow intricate systems from minimal inputs²¹, blending high-tech development with low-tech implementation ('high-dev low-tech'). By engineering the conditions of emergence^{466,607}, living machines self-organize and produce hierarchical biological materials² differently than conventional machines⁶⁰⁸.

7.2. Ethical considerations and contrary views

The complexity objection

A key concern of self-microfabrication is its complexity, notably its need for developmental knowledge in non-model species. Some complex problems require equally complex solutions and may justify why material-producing organoids challenge the "Keep It Simple, Stupid" principle. Even with a simple example, Ashby's law of requisite variety demonstrates that a certain level of complexity is required to regulate a variety of disturbances⁶⁰⁹. Interest in biological materials stems from their capacity to collectively optimize multiple criteria that simpler synthetic methods struggle to solve³³; including recyclability, raw material abundance, high mechanical performance, use of aqueous solvents, non-harmful chemicals and room temperature synthesis²⁶. Organoids could even simplify the manufacturing of complex systems by leveraging emergence and self-organization⁶⁰⁷, as discussed in the previous section with the high-dev low-tech approach.

Ethical considerations

Most ethical concerns regarding organoids pertain to human medical applications and are not relevant for material production⁶¹⁰. Concerns about consciousness do not apply to material-producing organoids lacking a central nervous system, but remain valid for brain-computer hybrids with advanced cognitive functions⁵⁵⁴. Animal experimentation should follow the 3R rule ("replace", "reduce", "refine") and self-microfabrication could eventually reduce the need for animals in some conventional farming, as intended for cultured meat⁶¹¹.

8. Summary and Conclusion

Summary

We explore the idea of growing biological organs for material production. Resource scarcity and global warming present challenges in balancing sustainability with the demand for high-performance materials. Biological materials bridge this gap with versatile properties, available resources and biodegradability. We describe the spider silk gland to illustrate how organs regulate the self-assembly of hierarchical materials, giving rise to their properties. Similar organ production units can be cultured *in vitro* and self-organized from pluripotent stem cells, such as hair-bearing organoids. Growing tissues for material production, helps to approach organoid challenges from a new angle, notably the generalization of knowledge acquired from well-studied species to non-model organisms, such as arachnids. We propose a theoretical framework to help transfer information across biological scales and species. Finally, we discuss research opportunities to overcome biological limitations and produce optimal materials, using synthetic biology and biohybrids.

Conclusion

Organoids can expand beyond medicine toward new applications, notably improving material microfabrication. Viewing organoids as living machines, and developmental biology as a manufacturing process, opens new avenues for

self-microfabrication of next generation materials, such as spider silk. Self-organized organ production units, which can generate complex biological materials, have the potential to revolutionize the microfabrication industry by enabling the scalable production of large microstructured materials with unique properties. The prospect of achieving lower marginal costs for producing sustainable, high-value-added products creates opportunities for multidisciplinary collaborations among material scientists, tissue engineers, and developmental biologists, paving the way for innovative research trajectories and applications.

9. Glossary and Definitions

Glossary

(PSCs)	Pluripotent Stem Cells
(iPSCs)	Induced Pluripotent Stem Cells
(ASCs)	Adult Stem Cells
(ECM)	Extracellular Matrix
(Chem μ Env)	Cellular Microenvironment
(Cell μ Env)	Cellular Microenvironment
(GRN)	Gene Regulatory Networks
(BMP)	Bone Morphogenetic Protein
(TGF β)	Transforming Growth Factor Beta
(M-CELS)	MultiCellular Engineered Living Systems
(MA)	Major Ampullate
(SpiCE)	Spider Silk-Constituting Elements
(NT, CT)	N-Terminus or C-Terminus domains
(LLPS)	Liquid-Liquid Phase Separation
(DOPA)	Dihydroxyphenylalanine
(DP)	Dermal Papilla
(MEMS)	MicroElectroMechanical Systems
(MEAs)	MicroElectrodes Arrays
(PDMS)	Polydimethylsiloxane

Definitions

Organoid

A tissue self-organized from cells, notably stem cells, displaying some physiological behavior; often a miniaturized version recapitulating the organ of origin.

Biological material

Material produced by living organisms, such as proteins or polysaccharides, often referencing hierarchically microstructured materials like spider silk.

Self-microfabrication

Self-organized production units regulate the self-assembly of microscale structures from the bottom-up. Material-producing organoids such as the hair-bearing organoid², are great examples. This self-organized organoid regulates the self-assembly of the hair shaft.

Conventional microfabrication

Top-down manufacturing processes used to create precise microscale structures, typically for semiconductors, electronics, and MEMS. It relies on techniques such as photolithography, etching, or thin-film deposition.

Chemical self-assembly

Molecules spontaneously forming ordered structures under certain conditions (the chemical microenvironment) without explicit guidance.

Chemical microenvironment

The local chemical and physical conditions like pH, salt concentration, temperature, etc.

Biological self-organization

Spontaneous formation of structured patterns and tissues in biological systems, under certain conditions (the cellular microenvironment) without explicit guidance.

Cellular microenvironment

The immediate surroundings of a cell, influencing its behavior, like growth factors, other diffusing biosignals, gradients, ECM composition, surrounding cells, mechanical stresses, bioelectric fields, etc.

Biosignaling fields

Field representation a CellμEnv's subset (e.g. scalar, vector, matrix or tensor in one or more dimensions).

Homeostasis

Tendency of a system toward a state of equilibrium, notably during the physiological or pathological maintenance of an organ.

Stem cell

A cell that can self-renew and differentiate into other cell types.

Potency

Potency refers to a stem cell's ability to differentiate into different cell types. The more potent a cell is, the more types of cells it can become.

Quiescence

A dormant, non-dividing state of cells.

Senescence

Permanent cell growth arrest due to aging or damage.

HOX genes

HOX genes are a group of genes that determine the body plan and the identity of structures during embryonic development

Simplicity

A system with few components.

Complexity

A system with many interconnected parts.

Emergence

Complex patterns arising at a higher order (or scale) from simpler interactions from a lower order.

Missing body problem

When a tissue is dissected from an organism, grown *in vitro*, the new CellμEnv might not replicate the one of origin, “missing” the surrounding tissue or the rest of the body.

Environment morphism

Editing an existing microenvironment into another.

Developmental routes

Spontaneous sequential steps during organogenesis or any self-organizing biological development. Differentiation of stem cells is an example.

Inductive events

External signaling events that direct cells or tissues toward a specific developmental fate.

Developmental disruption

When a developmental route deviates from its trajectory or fails to reach an expected outcome, like a normal embryogenic development.

Epigenetic landscape

Metaphor introduced by Waddington to describe how gene regulation influence cell differentiation and development. It represents cells as balls rolling downhill, valleys in the landscape guide achievable cell states and represent genetic and environmental factors.

Hierarchical epigenetic landscapes

The epigenetic landscape metaphor is extended to multiple scales of biology, stacking them up, including molecular, cellular and tissular scales (Fig. 5-6); they may be referred to as “episystemic landscapes”. At the tissular level the same concept can represent not cell differentiation trajectories but developmental routes and organogenesis. A location on such “epi-tissular landscape” represents a particular tissue, typically composed of multiple cell types, connecting the tissular layer to the cellular layer and so on (Fig. 5D).

High-dev low-tech

Concept combining a high-tech, or cutting-edge, technological research and development, with a simple, low-tech implementation. Low-tech implies simpler technologies requiring minimal tools or techniques. Self-microfabrication requires a complex development (e.g. studying organogenesis) but may eventually offer a simpler implementation by leveraging self-organization (e.g. planting a seed).

Single-cell and multi-omics techniques

Techniques integrating multiple types of molecular data at the single-cell resolution (such as genomics, transcriptomics, proteomics, and metabolomics).

Spatial-omics techniques

Techniques mapping molecular data to their specific locations in tissues or cells, preserving the spatial context.

Spidroins

Spider silk proteins.

Spider silk dope

Precursor solution of spider silk, notably containing spidroins, peptides, lipids, lubricants and glycoproteins.

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