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Three-dimensional tissue fabrication

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Abstract

In recent years, advances in fabrication technologies have brought a new dimension to the field of tissue engineering. Using manufacturing-based methods and hydrogel chemistries, researchers have been able to fabricate tissue engineering scaffolds with complex 3-D architectures and customized chemistries that mimic the in vivo tissue environment. These techniques may be useful in developing therapies for replacing lost tissue function, as in vitro models of living tissue, and also for further enabling fundamental studies of structure/function relationships in three dimensional contexts. Here, we present an overview of 3-D tissue fabrication techniques based on methods for: scaffold fabrication, cellular assembly, and hybrid hydrogel/cell methods and review their potential utility for tissue engineering.

Keywords: Tissue engineering; Scaffolds; Hydrogels; Micropatterning; Poly(ethylene glycol)

Contents

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1. Introduction

Tissue engineering typically involves the assembly of tissue structures by combining cells and biomaterials with the ultimate goal of replacing or restoring physiological functions lost in diseased or damaged organs. The biomaterial scaffolds are designed to provide mechanical support for the cells which can then perform the appropriate tissue functions; however, in practice, the simple addition of cells to porous scaffolds is often inadequate for reproducing sufficient tissue function. One approach to increasing the functionality of these tissue-engineered constructs relies on attempts to mimic both the microarchitecture of tissues and the microenvironment around cells within the body. In vivo, tissues consist of smaller repeating units on the scale of hundreds of microns (e.g. islet, nephron) [1]. The three-dimensional architecture of these repeating tissue units underlies the coordination of multicellular processes, emergent mechanical properties, and integration with other organ systems via the microcirculation. Furthermore, the local cellular 'microenvironment' (~ 10 μm) presents biochemical, cellular, and physical stimuli that orchestrate cellular fate processes such as proliferation, differentiation, migration, and apoptosis. Thus, successful fabrication of a fully functional tissue must include both an appropriate environment for cell viability and function at the microscale level, as well as macroscale-level properties that allow sufficient transport of nutrients, provide adequate mechanical properties, and facilitate coordination of multicellular processes.

Tissue engineering scaffolds have traditionally been composed of porous polymer scaffolds that act as substrates for cell attachment [2]; however, more complex architectures that mimic tissue structures have been more difficult to produce. In recent years, CAD-based manufacturing technologies have been applied toward the fabrication of three-dimensional scaffolds with tunable micro- and macro- scale features. Tissue engineering may benefit from potential opportunities offered by these additive 3-D fabrication approaches. For example, independent control of micro- and macro-scale features may enable the fabrication of multicellular structures that are required for complex tissue function. In addition, fabrication of vascular beds would allow the construction of larger tissue constructs than could be supported in scaffolds limited by diffusion. Furthermore, the combination of clinical imaging data with CAD-based freeform fabrication techniques may offer the capability to form constructs that are customized to the shape of the defect or injury. Finally, such fabrication technology may provide a means for large-scale production of multiple identical tissue constructs for use in drug discovery or fundamental scientific studies. Fabrication approaches have been previously used in two-dimensional micropatterned model systems and have led to insights on the effect of cell–cell and cell–matrix interactions on hepatocyte and endothelial cell fate [1]. Extending upon these studies, the application of three-dimensional fabrication techniques may also prove useful for studying structure/function relationships in model tissues.

In this review, we describe various three-dimensional tissue fabrication methods and compare their structural resolution, developmental progress, and potential utility for tissue engineering. Fig. 1 depicts three general approaches to tissue engineering that we will discuss in further detail throughout this review: (1) fabrication of acellular polymer scaffolds, (2) techniques for cellular assembly, and (3) hybrid cell/scaffold systems.

2. Additive acellular scaffold fabrication

Early scaffolds fabricated by methods such as solvent casting/particulate leaching contain pores that reflect the shape and size of the particulates used, but do not allow for the predetermination of the internal scaffold architecture or pore connectivity. In contrast, rapid prototyping technologies, originally developed for the manufacturing industry, provide exceptional spatial control over polymer architecture. As a result, in recent years various CAD-based techniques have been adapted to fabricate three-dimensional polymer scaffolds for tissue engineering applications. We have classified the various scaffold fabrication techniques by their modes of assembly as seen in Fig. 1: fabrication using heat, fabrication using light, fabrication using adhesives, and fabrication by molding. A summary of these techniques is presented below, and detailed reviews of solid freeform fabrication are available elsewhere [3–5].

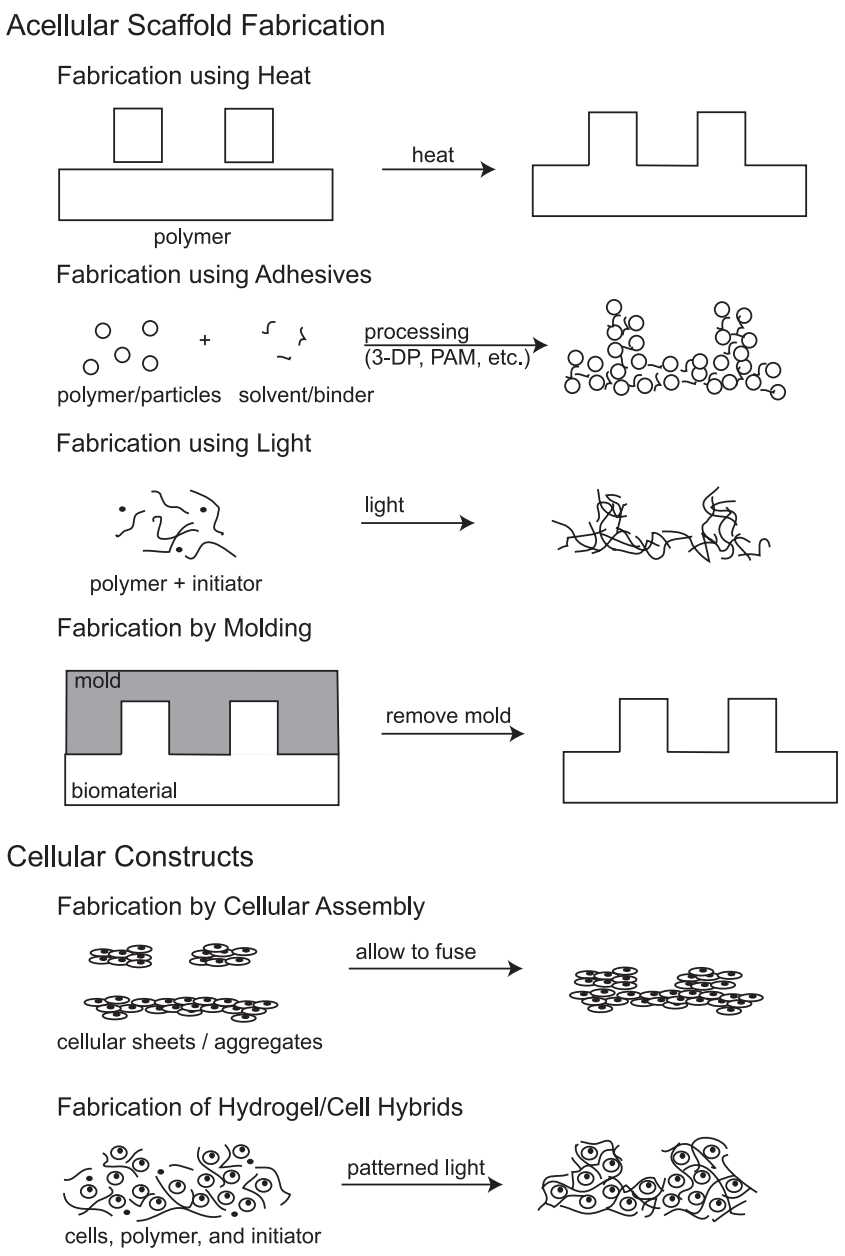


Fig. 1. Methods of 3-D tissue fabrication. Acellular scaffolds can be fabricated using various techniques, such as heat (FDM), adhesives (3-DP), light (SLA), and molding. Cells can also be manipulated in the fabrication process by cellular assembly or by photopatterning of cell/hydrogel hybrid constructs.

2.1. Fabrication using heat

Most heat-based fabrication techniques involve the application of heat energy to fuse layers of material to each other by raising the biopolymer above its glass transition temperature and applying pressure. A simple example of this is sheet lamination, a technique in which a laser is used to cut shapes out of polymer sheets which are then sequentially fused together by applying heat and pressure [5]. In its current stage of

development, the resulting prototype from sheet lamination is extremely dense (i.e. low void volume) and may not be practical for construction of highly cellular tissues.

More intricate scaffolds that contain small pores and features can also be fabricated using lamination techniques. For example, Borenstein et al. cast thin films of poly(DL-lactic-*co*-gycolic) acid (PLGA) onto microfabricated silicon wafers to create biodegradable membranes containing small trenches that are the inverse of the silicon masters (Fig. 2c) [6]. By laminating the patterned PLGA membranes to each other, channels (20 μm diameter) were formed between the layers to create a scaffold for vascular tissue engineering. Bhatia et al. used a similar method to create porous tissue engineering scaffolds using soft lithography techniques (Fig. 2b) [7]. A mold consisting of the elastomer polydimethylsiloxane (PDMS) is cast from a microfabricated silicon master [8]. A solution of PLGA is cast onto the PDMS mold and then heated, forming a solid PLGA layer containing microstructures equivalent to those on the silicon master (20–30 μm resolution). A 3-D scaffold is then be constructed by lamination of the patterned PLGA membranes. Micropores can also be incorporated into the PLGA by solvent casting and particulate leaching to increase the surface area for cell attachment and proliferation.

Selective laser sintering (SLS) is a manufacturing technology that uses heat to fuse polymer particles into desired shapes and layers. A laser beam rasters across a powder bed and raises the local surface temperature, causing fusion of polymer particles and forming patterned structures within each layer. The resolution of SLS is limited by the laser beam diameter used in this system, which currently is in the range of approximately 400 μm [5]. The unfused powders within the structures may be an advantage by increasing the porosity of the scaffold and therefore increasing surface area. Lee and Barlow have used this method with polymer-coated calcium phosphate powders to fabricate scaffolds, and have demonstrated bone tissue ingrowth over several weeks in dog models [9]. In addition to ceramic/polymer blends, others are also working on ways to improve the SLS process for biopolymer applications [4].

Fused deposition modeling (FDM) is another heat-based manufacturing technology that has been applied toward 3-D scaffold construction. A 3-D scaffold is deposited layer by layer as molten plastics or ceramics are extruded through a nozzle, merging with the biomaterial that was deposited in the previous layer. Hutmacher et al. have used this technique to fabricate bioresorbable scaffolds of poly(ε-caprolactone) (PCL) with feature sizes of approximately 250–700 μm [10]. Their group has also demonstrated primary human fibroblast proliferation and extracellular matrix production when seeded and cultured in these scaffolds [3]. Other groups have also explored the use of FDM for scaffold production using bioceramic or polymer materials (Fig. 2a) [4]. While FDM allows exceptional control in the *xy* plane, this method is however limited in the *z*-direction in that the height of the pores is predetermined by the size of the polymer filament extruded through the nozzle. In addition, the available

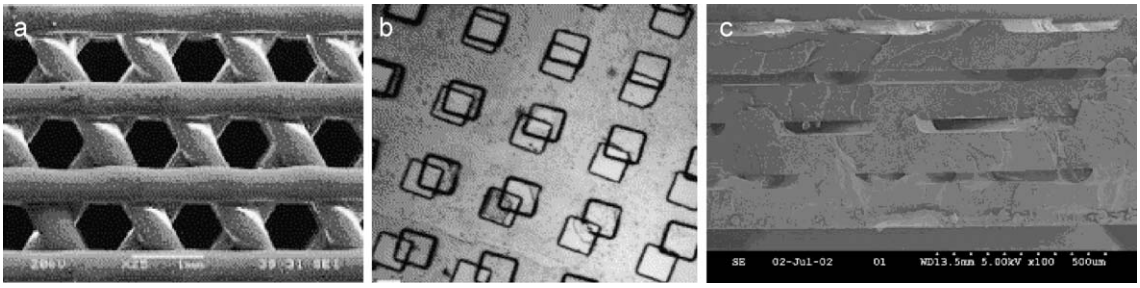


Fig. 2. Fabrication using heat. (a) Fused Deposition Modeling. Molten biomaterials are extruded through a nozzle to build 3-D scaffolds layer by layer (from Ref. [4], reprinted with permission of Elsevier). (b–c) Molded Lamination. Membranes of the biodegradable polymer PLGA are cast from PDMS (from Ref. [7], reprinted with permission of Elsevier) (b) or silicon (c) molds and then laminated to create 3-D scaffolds. In (c), layers of PLGA are fused together to form microfluidic channels for vascular tissue engineering (photo courtesy of Jeff Borenstein and Kevin King, Draper Laboratory).

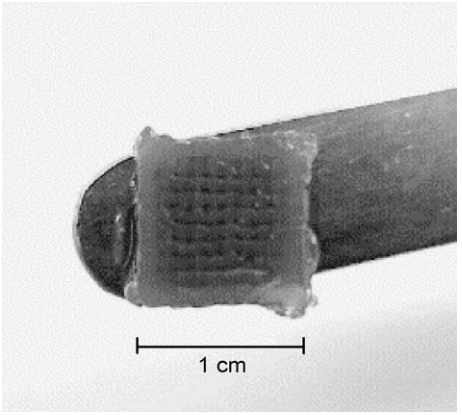


Fig. 3. 3-D plotting. Heated liquid agar solidifies into a 3-D hydrogel scaffold when deposited into a cooled medium (from Ref. [11], reprinted with permission of Elsevier).

materials for FDM are limited by the melting points and processing conditions involved.

Most materials used in heat-based fabrication are synthetic polymers that can withstand high temperatures while retaining their desired properties such as degradation and biocompatibility. Other temperature dependent fabrication methods that rely on phase transitions at lower temperatures have been used with some natural hydrogel biomaterials. Mulhaupt et al. used 3-D plotting technology to deposit heated agar and gelatin solutions (90 °C) into a cooled plotting medium (10–15 °C), resulting in 3-D hydrogel scaffolds (Fig. 3) [11]. They then demonstrated the adhesion of human osteosarcoma cells or mouse fibroblasts to fibrin coated scaffolds that were created using this method.

2.2. Fabrication using light

In addition to heat-based fabrication, light can also be used to create polymer structures. Photopolymerization involves the use of light energy to initiate a chain reaction, resulting in the solidification of a liquid polymer solution. Stereolithography is a photopolymerization technique used in manufacturing that can be applied to fabrication of tissue engineering scaffolds. Light from a laser beam is directed onto preprogrammed regions of a layer of liquid polymer, causing solidification in the exposed areas. The stage is then lowered, covered with a new layer of polymer solution, and the process repeated. The application of stereolithography for generating biodegradable 3-D polymer scaffolds was demonstrated by Cooke et al., who used diethyl fumarate, poly(propylene fumarate), and the photoinitiator bisacylphosphine oxide (Fig. 4) [12]. Structures generated using stereolithography typically have features as small as 250 μm, but certain systems have been shown to produce 70 μm features using small-spot lasers [5].

Light energy can be used not only to solidify rigid polymers such as in stereolithography, but also to fabricate hydrogel polymer scaffolds using photolithographic techniques. Hydrogels are crosslinked networks of insoluble hydrophilic polymers that swell with water. Their high water content and tissue-like mechanical properties have led to their increasing popularity as a tissue engineering biomaterial. Yu et al. reported a photolithographic method of patterning

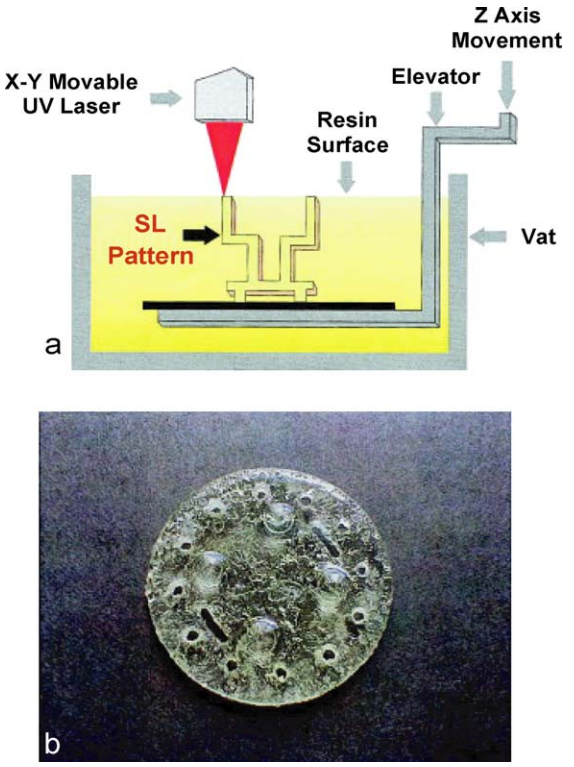


Fig. 4. Stereolithography. (a) UV light is used to crosslink the material in specific regions of a layer. The elevator is then lowered to reveal a new layer of polymer, and the process is repeated to create the desired shape. (b) A prototype scaffold designed using SLA (from Ref. [12], reprinted by permission of John Wiley & Sons, Inc.).

dried 2-hydroxyethyl methacrylate which is later rehydrated before cell seeding [13]. Their group has demonstrated fabrication of single layer structures, although this method could potentially be adapted for multilayer fabrication. However, some patterning resolution may be lost during rehydration. Photopatterning of hybrid constructs of cells and hydrogels will be discussed in a later section.

2.3. Fabrication using adhesives

Another approach to fabricating scaffolds is to bind polymers by using solvents or adhesives rather than heat or light, eliminating any biomaterial limitations such as heat compatibility or photoinitiator dependence. An example of this type of fabrication is three-dimensional printing (3-DP), in which a binder solution is deposited onto a biomaterial powder bed using an ink jet printer. 3-D structures of approximately 200–500 μm are thusly fabricated one layer at a time (Fig. 5) [14]. Griffith et al. combined 3-DP with particulate leaching to fabricate porous PLGA scaffolds, and demonstrated attachment rat hepatocyte and nonparenchymal cell cocultures [15]. Zeltinger et al. expanded upon this work and explored its limitations by examining cell attachment, growth, and matrix deposition on 3-D printed scaffolds with various pore sizes and cell types [16].

Like 3-D printing, pressure assisted microsyringe (PAM) fabrication also involves layer by layer deposition with the solvent acting as a binding agent. Unlike 3-DP in which binder is printed onto a bed of powder, the microsyringe method involves the deposition of polymer dissolved in solvent through a syringe fitted with a 10–20 μm glass capillary needle [7]. The thickness of the polymer stream can be varied by changing the syringe pressure, solution viscosity, syringe tip diameter, and motor speed. This deposition method is similar to FDM, but can produce structures with greater resolution and is not require the addition of heat. While the resolution of PAM is greater than most of the other fabrication methods, micropores cannot be incorporated using particulate leaching due to the syringe dimensions.

2.4. Fabrication by molding

In addition to the techniques described above in which scaffolds are directly fabricated, the same methods can also be used to indirectly fabricate scaffolds by using the prototypes as molds. Indirect fabrication expands the range of biomaterials that can be used to include many of those that are not compatible with the fabrication processing conditions. For example, Orton et al. created a negative epoxy mold of the desired scaffold design using stereolithography (Fig. 5a) [17]. A hydroxyapatite/acrylate suspension was then cast onto the mold and cured with heat, and the 3-D hydroxyapatite scaffold was formed by incinerating the mold and acrylate binder in a furnace. Implantation into the mandibles of minipigs resulted in bone ingrowth after 9 weeks [18]. Three-dimensional ink jet printing can also be used to fabricate molds by depositing wax or other low melting point compounds which can be removed by melting and washing with solvents (Solidscape). Hollister et al.

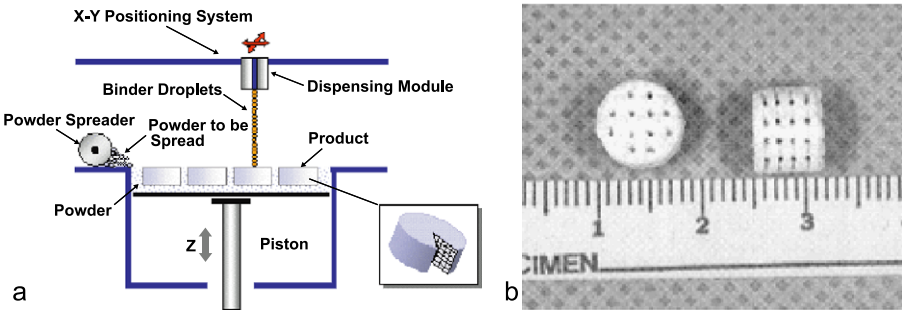


Fig. 5. 3-D printing. Ink jet technology is used to print a binder solution onto a bed of polymer powder. An additional layer of powder is then deposited, and the process is repeated to form 3-D scaffolds. (a) from Therics, website, with permission; (b) from Ref. [15], reprinted with permission of Leppincott Williams & Wilkins.

have used this technique to create molds for casting hypoxyapatite, poly(L)lactide, and polyglycolide scaffolds [19,20], and combined this technique with particulate leaching to create micropores within the scaffolds. Sachlos et al. also used ink jet printing to create molds dissolvable by ethanol for casting of the extracellular matrix component collagen with features on the order of 200 μm (Fig. 6b) [21]. The use of extracellular matrix as a building material presents special cellular adhesion properties; however, it is limited in that regions of adhesivity and nonadhesivity cannot be designated, and there may be non-specific adhesion many cell types, which may be problematic upon implantation.

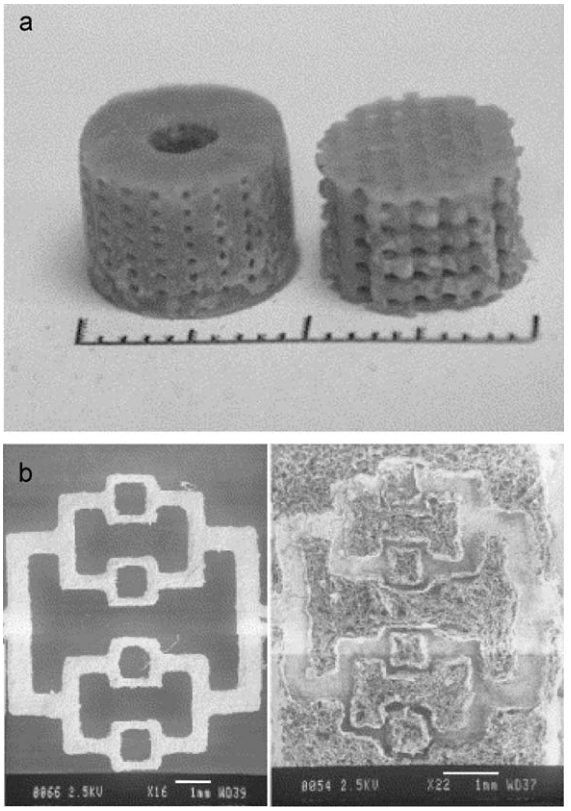


Fig. 6. Molded scaffolds. (a) Hydroxyapatite was cast into a negative epoxy mold (manufactured using stereolithography) and then cured by heat. The scaffold was then placed in a furnace to burn out the mold (from Ref. [18], reprinted with permission of Elsevier). (b) The extracellular matrix compound collagen was cast onto a negative mold that was printed using ink jet technology. The mold was then dissolved away with ethanol, leaving a patterned collagen scaffold (from Ref. [21], reprinted with permission of Elsevier).

3. Fabrication by cellular assembly

Acellular scaffolds fabricated by the tissue engineering techniques described above may be limited by inefficient and heterogeneous cell engraftment. A contrary approach to tissue engineering is being undertaken by some groups by directly constructing layers of live cells. Yamoto et al. have proposed the construction of 3-D tissues by assembling layers of cultured cell sheets [22]. Cardiomyocytes cultured on temperature-responsive culture surfaces (dishes grafted with poly(*N*-iso-propylacrylamide)) were released as a layer by lowering the temperature to hydrate the grafted polymer. Multiple sheets of cardiomyocytes can then be layered to create an in vitro myocardial tissue construct. However, this cell layering method does not allow the creation of complex three-dimensional patterned structures.

Auger et al. have used cultured cell layers for vascular tissue engineering. Sheets of smooth muscle cells were 'rolled' around a tubular support to form a cylinder, and endothelial cells were seeded within the lumen. These engineered blood vessels were then cultured with pulsatile flow to condition and strengthen the constructs [23]. After culture, the tissue engineered blood vessels demonstrated excellent mechanical properties and the cells exhibited key markers of native vessels.

Cellular assembly by manipulating layers of cells is limited in the complexity of architectures that can be formed. Some groups are attempting to develop methods to directly 'plot' living cells into 3-D structures by depositing cells and allowing them to fuse spontaneously [24–26]. Mironov et al. demonstrated that the printing of cell aggregates and embryonic heart mesenchymal fragments resulted in fusion into a tube-like structure when placed in a three-dimensional collagen or thermosensitive gel [25]. If successful, this type of technology could allow for cells to be placed into precise locations within a three-dimensional tissue construct. Odde et al. have also developed methods to directly plot cells using laser guidance. A stream of cells is 'written' onto a surface in a specified pattern using optical trapping forces to guide cells [27]. While this technique allows for specific placement of individual cells, scaling up may become limiting due to the serial nature of the technique. Because these technologies rely, to some extent, on the emerging field of

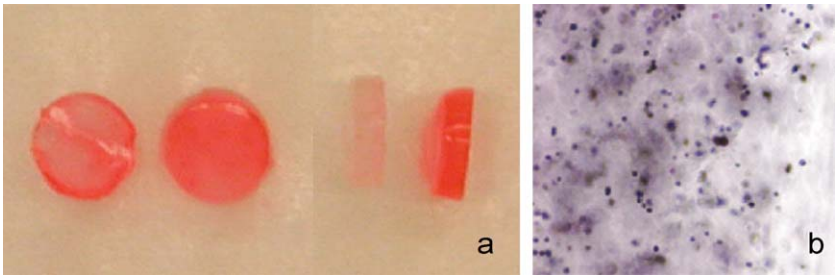


Fig. 7. PEG-based hydrogels containing cells. (a) PEG-based hydrogels are crosslinked to form the shape of the container (dye added for clarity). (b) Living cells are suspended within the crosslinked hydrogel (MTT stain for viability) (photos courtesy of Jennifer Elisseeff, Johns Hopkins University).

cellular assembly, future studies will be required to determine which tissues will be amenable to assembly by this approach.

4. Fabrication of cell/scaffold hybrid constructs

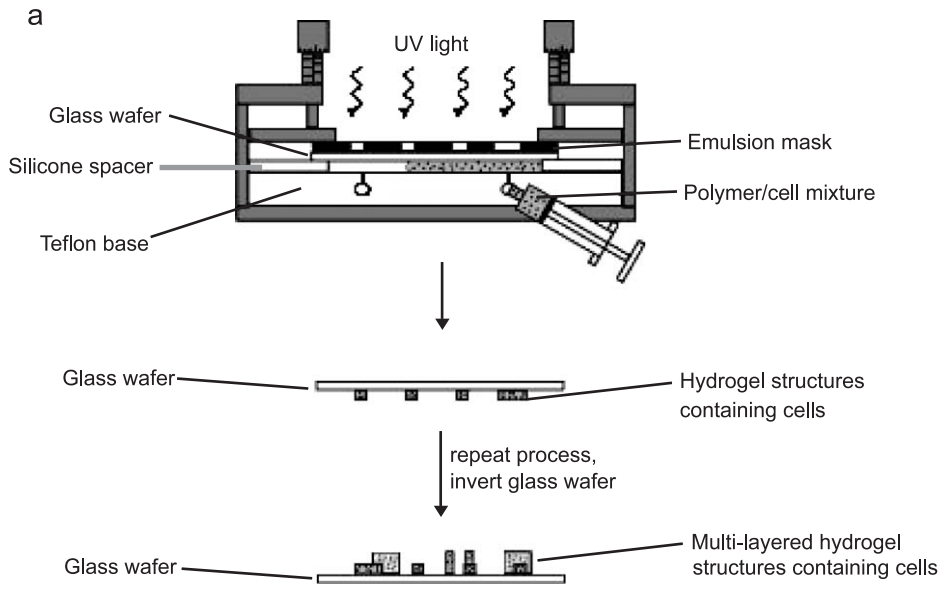
Acellular scaffolds possess excellent mechanical integrity on the whole, but may be difficult to populate with cells. In contrast, cellular constructs provide high tissue density but may be mechanically unstable. Hydrogel polymers have therefore become increasingly popular because of their ability to provide both structural support and high tissue density while maintaining an in vivo-like environment for cells [28]. Many of these water-swollen polymers can also be formed in mild conditions, and in some cases in the presence of cells. Their shape can be determined either by the mold or container used during crosslinking or by spatial patterning using light.

4.1. Molded cell-laden hydrogels

An advantage of many hydrogel systems is that they can be used to entrap cells during the gelling process, allowing a more uniform distribution of cells throughout a construct. Biological hydrogels such as fibrin and collagen have been explored to encapsulate cells. Hubbell and colleagues have functionalized fibrin gels by incorporating genetically engineered bioactive sites to allow cell adhesion and proteolytic remodeling [29–31]. Desai et al. have used microfluidic molding methods to deposit patterned structures of collagen gels containing cells [32]. This method would be useful to fabricate certain model tissues; however, it may be difficult to generalize to 3-D architectures due to the constraints of the microfluidic network on a flat surface.

Cells can also be encapsulated homogeneously within synthetic polymer hydrogels, many of which are crosslinked in the presence of light. Poly(ethylene glycol) (PEG)-based hydrogels are particularly intriguing because of their biocompatibility, hydrophilicity, and ability to be customized by changing the chain length to tune transport properties or by incorporating biologically relevant molecules [33]. They have been used to immobilize various cell types including chondrocytes [34,35], vascular smooth muscle cells [36], osteoblasts [37],and fibroblasts [38,39] that can attach, grow, and produce matrix. PEG-based hydrogels can be customized by incorporation of adhesion domains of extracellular matrix proteins to promote cell adhesion, growth factors to modulate cell function, and degradable linkages [36,39–45]. Photopolymerization of hydrogels for tissue engineering is a rapidly growing field because of its chemical flexibility to be customized and the resulting tissue-like physical properties.

Fig. 8. 3-D photopatterning of hydrogels. (a) Photopatterning Method. Polymer solution and cells are introduced into a chamber. The unit is exposed to 365 nm light through an emulsion mask, causing crosslinking of the polymer in the exposed areas and trapping the cells within these regions. The uncrosslinked polymer solution and cells are then washed away, and the process is repeated with thicker spacers and a new mask to create 3-D cellular hydrogel structures. Each layer may contain the same type of polymer/cell mixture, or can be composed of different polymer properties or different cell types. (b) Schematic and images of three-layered hybrid tissue consisting of PEG hydrogel containing mammalian cells (from Ref. [49]).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UV light
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Silicone spacer
Teflon base
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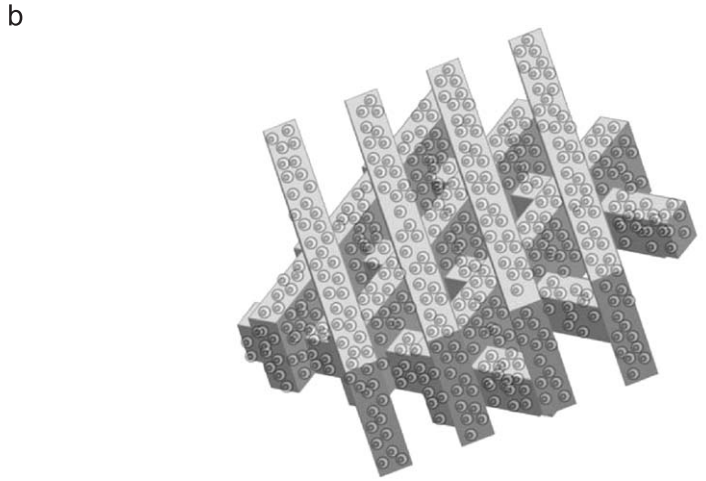
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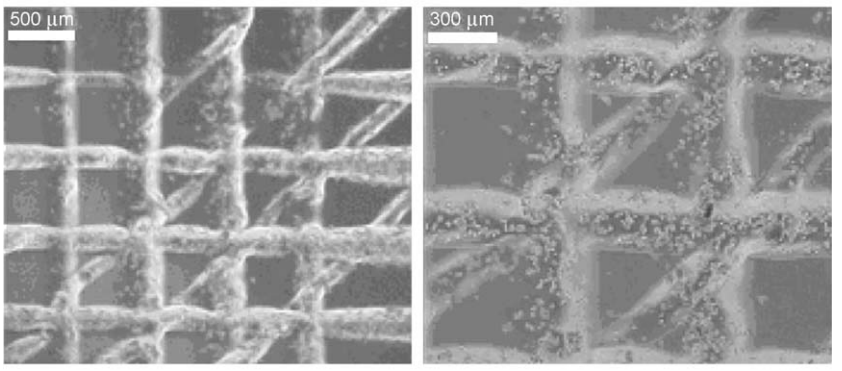
500 µm
300 µm

4.2. Photopatterned cell-laden hydrogels

The shape of cell-containing hydrogels is typically determined by the container used for photocrosslinking, as in the examples above. For example, the disc-like structures shown in Fig. 7 depicts were cast in a cylindrical vial. One property of photosensitive hydrogel systems that until recently had not been exploited was the ability to localize photocrosslinking by controlling areas of light exposure, thereby forming defined hydrogel features containing living cells. In other non-med-

Table 1
Comparison of 3-D scaffolding methods

	Resolution (μm)	Advantages	Disadvantages
Acellular 3-D Scaffolds			
		use of well-established fabrication methods, usually automated	must seed cells post-processing, less control in cell placement and distribution
Fabrication using Heat			
Micro Molding [6,7]	20–30	simple; reusable molds	limited to thin membranes, each layer must be contiguous structure, manual alignment required
Selective Laser Sintering [4,5,9]	400	high porosity, automated	high temperatures during process, powder may be trapped
Fused Deposition Modeling [3,4,10]	250–700	no trapped particles or solvents, automated	high temperatures during processing
3-D Plotting [11]	1000	use of hydrogel materials (agar, gelatin), automated	limited resolution
Fabrication using Light			
Stereolithography [5,12]	70–250	ease of use, easy to achieve small features, automated	limited choice of materials must be photosensitive and biocompatible; exposure of material to laser
Fabrication using Chemicals			
3-D Printing [14–16]	200–500	versatile; high porosity, automated	limited choice of materials (e.g. organic solvents as binders); difficult to reduce resolution below polymer particle size
Pressure Assisted Microsyringe [7]	10	high resolution, not subject to heat, automated	viscosity dependent, no inclusion of particles
Fabrication by Molding			
Matrix Molding [21]	200	use of biological matrix materials (collagen), mold fabrication can use automated methods (above)	features must be interconnected, weaker mechanical properties
Cell-Laden 3-D Scaffolds			
		precise placement of cells throughout construct, ability to place multiple cell types arbitrarily	limited fabrication conditions (sterility, temperature, pH), still in earlier phases of development
Cellular Assembly			
Organ Printing [24–26]	100	incorporation of cell aggregates or tissue explants, precise cell placement, automated	lack of structural support, dependence on self assembly
Laser-Guided Deposition [27]	<1	precise single cell placement, automated	has yet to be extended to 3-D structures, lack of structural support
Cell/Biopolymer Hybrids			
Hydrogel Photopatterning [50]	100	incorporation of living cells within scaffold, leverages existing hydrogel chemistry (incorporation of peptides, degradation domains), versatile	not yet automated, exposure of cells to ultraviolet light, diffusion of large molecules limited by hydrogel pore size

ical fields, photolithographic patterning has been applied to pattern hydrogel microstructures [46], valves within microfluidic systems [47], and single-layer cell-laden microstructures on silicon [48].

The application of photolithography-based methods toward hydrogel tissue engineering may enable the construction of complex three-dimensional tissues. We have recently combined photolithographic techniques with existing PEG-based cell encapsulation chemistries to build structural features within a 3-D cell/hydrogel network (Fig. 8) [49]. Using this method, live cells suspended in polymer solution are photoimmobilized locally in multiple cellular domains in a controlled hydrogel architecture. The uncrosslinked polymer and cells are then rinsed away and the process can be repeated in the same layer or in additional layers with similar or different cell types and concentrations or different polymer mixtures. By increasing the height of the photocrosslinking chamber in between steps, additional layers can be added to create a 3-D cellular hydrogel tissue construct. Fig. 8 demonstrates the fabrication of a tissue layer that has raised protrusions containing a high cell concentration, simulating, for example, an engineered skin tissue and glands. Thus far, hydrogel features as small as 50 μm containing cells have been achieved, and structures up to three layers have been fabricated. In complementary experiments, we have also developed a tool to specify cellular location within the prepolymer solution (as opposed to random dispersal) using electromagnetic fields [50]. In conjunction with hydrogel technologies being explored by other groups (bioactive materials, incorporation of adhesion peptides and growth factors, biodegradable linkages), photopatterning of hydrogels containing cells may lead to the development of improved tissue engineered constructs that can be customized spatially, physically, and chemically. The flexibility of these hydrogel systems shows great promise for tissue engineering by allowing researchers to address the structural, multicellular, and biochemical complexity found in many organs in the body.

5. Summary

Recent advances in scaffold fabrication methods, many stemming from adaptations of manufacturing-based technologies, have led to the development of complex 3-D tissue engineering constructs. In general, approaches to implantable cellular therapies include the farication of acellular, cellular, or hybrid constructs. Various techniques that have been developed for three-dimensional tissue fabrication are summarized in Table 1. The technologies listed are compared with regard to their spatial resolution and relative advantages and limitations. The utility of each technique for engineering of specific tissues will ultimately depend upon several design criteria including mechanical stability, chemical composition, degradation, cellular organization, and nutrient requirements. In the future, fundamental studies of structure/function relationships may also help to determine the most appropriate approach for fabricating a particular tissue.

6. Future directions in 3-D tissue fabrication

The field of tissue engineering has come a long way from the early examples of populating synthetic polymer scaffolds with living cells to the development of more physically and biochemically complex tissue constructs. As researchers develop a greater understanding of the biology underlying fundamental structure-function relationships, factors that influence cell fate (proliferation, differentiation, apoptosis) and function (migration, gene expression, morphogenesis) can be incorporated into the design of tissue engineering strategies. These factors include signals from the in vivo microenvironment such as cell–cell interactions, cell–ECM interactions, soluble signals, and mechanical forces—all in a three-dimensional context. The ability to control the presentation of such microenvironmental cues on the level of individual cells (10 μm) and functional subunits (100 μm) will be enabled by leveraging emerging three-dimensional fabrication technologies. While the goal of engineering complex tissues such as liver and kidney remains a lofty goal, interdisciplinary interactions between medicine, cell and molecular biology, biomaterials, and chemistry will ensure timely progress towards tangible improvements in human health.

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