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Laser-based cell printing techniques for additive biomanufacturing

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Abstract

Additive manufacturing guided by computer-aided technologies has enabled new possibilities in tissue engineering. Laser-based cell printing techniques are at the forefront due to the ability to deposit single cells with high accuracy and reproducibility (1 cell, +/–2 μm, 500 cells/sec). Engineered tissue constructs can now be fabricated by layered manufacturing with single cell precision and complete heterogeneous fidelity. As such, researchers are taking aim at fundamental challenges within tissue engineering, including vascularization. Laser direct write techniques are being utilized to fabricate vasculature and investigate vascular interactions with the goal to produce larger tissue substitutes that to this point have been restricted by nutrient flow (<500 μm). This review discusses the recent advancements in laser-based cell printing techniques, their applications, and how they seek to address the vascularization issue.

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Introduction

The application of additive manufacturing (AM) techniques to address challenges in tissue engineering (TE) represents one of the most rapidly advancing areas in biomedical science. The rapid development of new TE strategies, based on AM principles, aspires to produce biological substitutes of human tissues for two primary functions: (1) for use in *in vitro* research applications (drug screening, test beds) to improve the reliability of experimental results and (2) for use in *in vivo* research applications to mitigate the organ shortage and transplantation need [1–3]. The development of cell-laden constructs or tissues often involves layer-by-layer deposition. The deposition of scaffolding materials, living cells, nutrients, growth factors, drugs, and other required chemicals with precise control over deposition time, position, and volume, allows fabrication of tightly controlled microenvironments for the development of customized, living tissue-engineered constructs [4–6].

Additive biomanufacturing techniques can be classified by fabrication mechanism: direct-contact or direct-write. Direct-contact printing is analogous to stamping, in which biomaterials are transferred, from topographically patterned surfaces laden with the species of interest, to a receiving substrate all at once by physical contact. For example, the topographical plateaus of molded “stamps” cast in microcontact printing techniques replicate the positive image at imprint. Biomaterials in the negative space of the stamp do not contact the substrate surface and thus are not transferred. Direct-write printing is the controlled and localized unit-delivery of biomaterials to create self-assembled constructs as specified by computer aided design (CAD) protocols. For example, inkjet-based bioprinting delivers volumetric equivalent droplets of cell suspension, actuated by piezo-pressure pulses on the syringe cartridge [7–9].

Despite their biocompatibility and ability to be seeded with the desired cells, many tissue-engineered constructs are restricted in size and shape due to diffusion limitations on receiving nutrients and transporting wastes [10–12]. Such limits highlight the necessity and challenge of vasculature in TE. To date very few engineered tissue constructs have demonstrated the ability to incorporate functioning vasculature [12–14]. This impediment highlights the value of precise spatial patterning of diverse cell types; having control over individual cell location in addition to biological and synthetic scaffolding would allow the building of a cellular construct, on a cell-by-cell basis, from the bottom-up. When coupled with the ability to use multiple cell types, this precise control makes incorporation of secondary structures, such as vasculature, feasible [15].

Direct-write processes are being used with increasing frequency to deposit biomaterials on diverse types of substrates in TE and regenerative medicine. In general,

direct-write processes rely on the dispensing, transfer or printing of discrete voxels (volume-pixels) at predetermined locations on a substrate [16,17]. These voxels serve as the building blocks for the lines, sheets, and 3D structures required to fabricate the scaffolds and constructs. Direct-write technologies, such as ink-jet printing [18], extrusion-based bioprinting [19], or laser direct-write (LDW) [20], integrate computer-aided design/computer-aided manufacturing (CAD/CAM) for high-level precision in spatial positioning of voxels of bioink within a co-fabricated 3D hydrogel matrix [21,22].

Due to the flexibility of CAD/CAM, virtually any histologically relevant tissue geometry can be reconstructed, though at different resolutions. Inkjet printing utilizes piezoelectric-pressure [23] or heat [24] to deposit droplets of biological "inks" on demand, and can form meso-scale constructs from micro-scale subunits [4,25]. However, the technique, and the similar extrusion-based techniques, are limited by bioink viscosity. Nozzle-clogging is a constant problem when printing viscous hydrogel solutions, and variability in droplet-to-droplet cell density, as cells in suspension may settle over the duration of printing. In addition, variability in droplet-to-droplet composition does not allow inkjet printing to consistently deposit single subunits or cells from a prepared suspension [22,26].

LDW provides an attractive alternative for bioprinting multicellular constructs in spatially ordered patterns at near single cell resolution. It is a non-contact, orifice-free group of techniques that offers the ability to deposit biological materials with micro-scale precision (±5 μm) [15,27]. And deposit objects over two magnitudes of voxel size (up to 600 μm) via expansion of the laser cross-sectional area [28]. Thus, CAD/CAM laser direct-write additive biomanufacturing techniques offer a powerful set of tools for fabricating microscale structures for tissue engineering and regenerative medicine applications.

In this review, we discuss the most recent and important examples of laser-based additive biomanufacturing modalities and their applications in biomedical engineering. While there are other non-laser-based modalities and other key components to the 3D bioprinting process (cell source and biomaterials), we will focus on laser-based 3D bioprinting platforms and their end products to present state-of-the-art 3D laser bioprinting capability. We first introduce the current prevailing LDW cell printing techniques, including laser-induced forward transfer (LIFT), absorbing film-assisted laser-induced forward transfer (AFA-LIFT), and matrix-assisted pulsed laser evaporation direct writing (MAPLE-DW). Examples of current applications of each technique are presented to demonstrate the capabilities and limitations of the modality. Then we will specifically address the role of laser-based cell printing in tissue vascularization as it represents one of the most fundamental challenges in tissue engineering. Lastly, we will summarize the challenges and future directions of laser-based additive biomanufacturing for tissue engineering.

Overview

Laser direct writing was first used to write patterns of metals for fabrication of mesoscopic conformal passive electronic devices [29–33]. Thick films of Ag, $BaTiO3$, and NiCr have been printed to construct conductors, capacitors and resistors, respectively, with a spatial resolution between 1 and 3 μm using laser-based additive direct writing [33]. It was this resolution and reproducibility that made laser direct-write techniques desirable for adaptation to biomedical applications, such as cell printing [34]. A typical LDW set-up is generally composed of three elements: a pulsed laser source, beam delivery optics, and a target coated with the material to be printed (the ribbon) opposite to the receiving substrate. The ribbon is a multilayer component: a support, which is transparent to the laser radiation wavelength, is coated with a transfer layer (bioink) composed of the biological material to be printed (e.g., biomaterials, cells, biomolecules).

LIFT, AFA-LIFT, and MAPLE-DW share similarities in methodology for the direct writing of cells. These direct-write techniques utilize laser transparent print ribbons on which one side is coated with cells that are either adhered to a biological polymer through initial cellular attachment or uniformly suspended in a thin layer of liquid (usually cell culture medium mixed with glycerol) or a hydrogel. A receiving substrate is coated with a biopolymer or cell culture medium to maintain cellular adhesion and sustain growth. The receiving substrate is mounted on motorized stages and positioned facing the cell-coated side of the ribbon. A pulsed laser beam is transmitted through the ribbon and is used to propel cells from the ribbon to the receiving substrate. The rapid volatilization and subsequent expansion of the cellular support layer on the ribbon creates the force necessary to allow the cells to cross the small (700–2000 μm [35]) gap between the ribbon and receiving substrate.

LIFT [29,36–41] utilizes a high power density, typically a femtosecond laser pulses to directly write and physically transfer biomaterials from a source platform onto a receiving substrate. In this process, the laser transparent quartz ribbon is coated with a thin film of metal, or other laser-absorbing biocompatible material, to protect from potentially damaging effects of the high-power laser pulses. The cells of interest are suspended in culture medium or hydrogel on the underside of the ribbon. The laser pulse heats the interface of the film at the source substrate, resulting in a melt front that propagates through the film until it reaches the free surface, at

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