Bio-manufacturing in Medical Devices

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The Promise of Additive Manufacturing in Biotechnology: A New Era of Biomanufacturing in the Medical Device Industry

The latest advances in biomanufacturing are creating new exciting avenues in research and developments in modern biotechnology for applications in next generation implantable organs and medical device industry. 3D printing or additive manufacturing (AM) is one such initiative in biomanufacturing. AM comprises of a versatile, growing array of technologies for generating 2D or 3D materials that are synthesized layer-by-layer, which deposits, fuses or builds layers of materials [1]. AM has come a long way from being a prototype builder to a thriving manufacturing technique that has the potential to take over the future medical device industry (Figure 1). Currently, there are many US Food and Drug Administration 'FDA' approved 3D printed medical devices including surgical instrumentations (e.g., guides to assist with proper surgical placement of a device), implants (e.g., cranial plates or hip joints), and external prostheses (e.g., hands) [2]. To this end, industrial and lab scientists are working together to push the envelope to develop fully functional organs with all necessary tissues and subcellular entities embedded in it. Few of them have reported success in building a prototype [3, 4].

Recently, researchers reported the first 3D printed heart with vascularized tissues and chambers. In this work, researchers demonstrated manufacturing of the artificial organ with human cells and patient-specific biomaterials containing sugar and proteins as bio inks. It was mentioned that this 3D printed heart had similar biochemical, mechanical and topographical properties of the patient's own tissues (Figure 2) [1]. However, the 3D printed heart has yet to overcome the limitations of pumping and functioning mechanically like a normal heart [3]. In a related work, another research group reported prototype fully functional heart. The prototyping phase of organ 3D printing was reported with the potential to transition to clinical trials and practical applications with further research and developments of such 3D printed heart. Researchers are working to address the challenges that are associated with the development, manufacturing, sterility and packaging and regulatory approval.

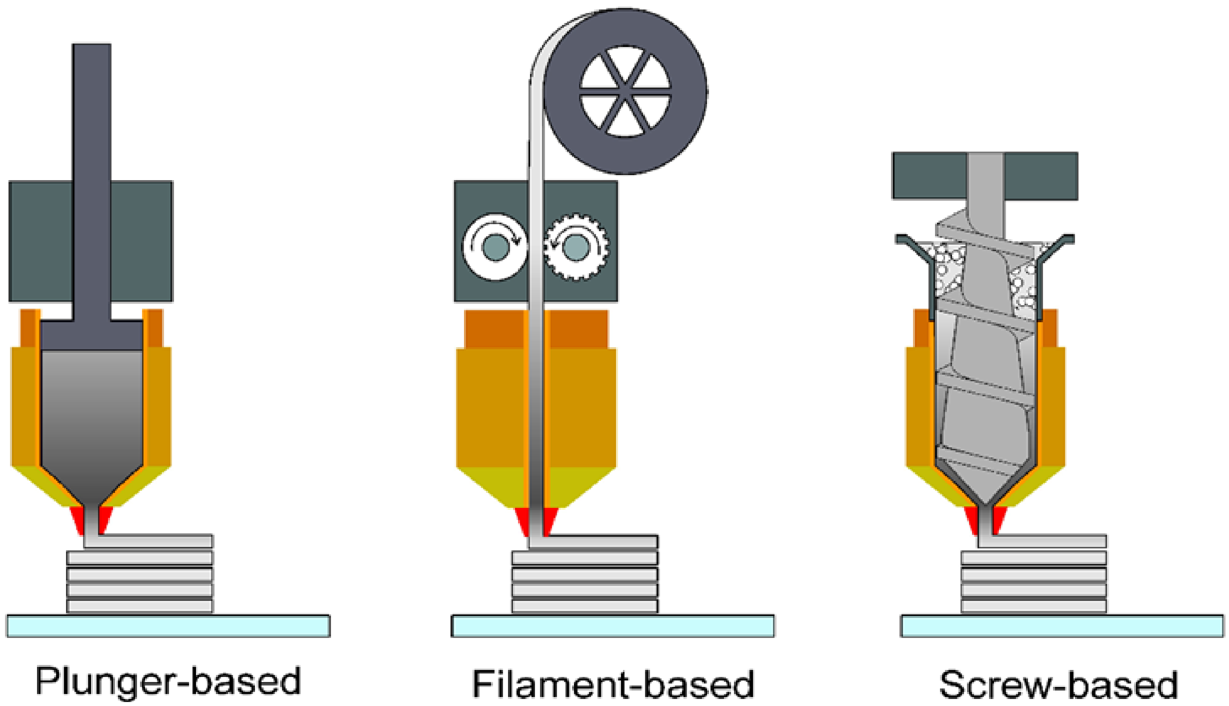

*Figure 1. The Additive Manufacturing Process. (**Source:** Materials* 11(5), 840, 2018*].*

Despite the challenges, AM based biomanufacturing is believed to impact the field of biotechnology quite significantly in the future. The main reason is that there are no major regulations that are required in general, in adapting 3D printing for biotechnological applications. We will describe here the major applications for AM in this field that are related to bioprinting of complex cellular co-culture constructs, advanced bioprocess engineering and development of task-specific AM-enabled microfluidic systems [5].

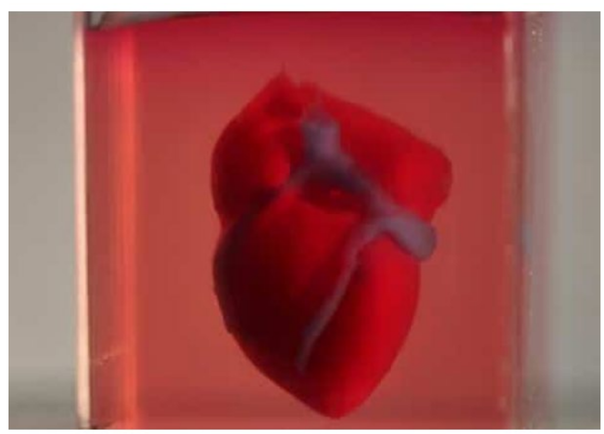

*Figure 2. 3D printed heart by additive manufacturing [**Source:** Advanced Science 2019].*

3D Bioprinting for Printed Tissues and Organs and a Whole Host of New Applications in Modern Biotechnology

Bioprinting involves controlled deposition of acellular functional scaffolds incorporating biological components or deposition of cell-laden constructs recapitulating *in-vivo* process. In addition to the development of printable tissues and organs, there are a number of other possible applications of 3D printing that include(i) printed tissue mimics that can function as disease models, (ii) acellular constructs functioning as structured scaffolding for bone grafting materials, (iii) development of high throughput assays and drug discoveries, (iv) pattern drugs and factors toward the development of printable medicines, (v) bioactive coatings, (vi) affinity membranes and (vi) high throughput screenings. A recent research has reported a technique known as 'Green Bioprinting' in which patterned human/algal co-culture scaffolds are fabricated by multichannel- plotting. This co-culture has been suggested to serve as the basis for new therapeutic approach to overcome the lack of oxygen in human cell-lines during *in-vitro* tissue engineering. This technique could also be extended to plants *in-vitro* cultures for cascaded bioprocesses using the metabolic properties of different cell types, or to establish model systems for studying biofilms or symbiotically living species [5, 6].

Additive Manufacturing Brings Hope in Advanced Bioprocess Engineering

AM can play an important role in the bioprocess engineering. The latest developments are summarized here. Mainly, there has been several studies, which have reported possibilities of making multifunctional bioreactors through different 3D printing techniques. Selective laser sintering (SLS) fabricated microwell plates made from polyamide, which could cultivate *S. cerevisiae* and adherent/suspended human cells. A smart 3D designed shake flask caps known as "shake flask pH controller unit" (SFC) was fabricated by SLS technique. The SFC included materials-integrated channels, membranes and valves as well as controlling electronics and piezoelectric micropumps, to close the control loop by pumping sodium hydroxide (NaOH) or hydrochloric acid (HCl) into the culture broth. The SFC was successfully used in a controlled shake flask cultivation of E. coli K12, during which it maintained a narrow pH range in the culture medium. A novel rocking bioreactor for fermentative hydrogen production that features internal AM-fabricated porous cartridges made from polylactic acid with REPRAP 3D printing platform. The cartridges were filled with immobilized microbial communities and were designed to increase the cells' exposure to the culture medium by acting as baffles and facilitating mixing. The tailor-made reactor system exhibited a higher peak hydrogen production than a conventional production system. A modular reactor setup consisting of porous monolithic enzyme carriers made from VeroClear RGD810 (PolyJet®) and an AM-fabricated housing with integrated fluid distributors. The 3D-fabrication of porous columns and monolithic structures could be also useful as an analytical system in biotechnology. The MicrOLED-PBR is a miniaturized flat-panel airlift-PBR (FPA-PBR) with an overall volume of 15 mL and several useful features. The FPA-PBR was made from polyamide using the SLS technology and includes a sensor board containing optical elements (LEDs, photodiodes and control electronics) for non-invasively monitoring cell-specific process parameters such as the cell density and chlorophyll fluorescence. The MicrOLED-PBR enables rapid strain screening and small-scale bioprocess development for photobiotechnological processes. This represents the first step towards a new generation of tailor-made AM fabricated bioreactors [5].

Additive Manufacturing Assisted 3D Printed Microfluidic Devices in Biotechnology

Microfluidic devices are miniaturized structure, which facilitated the analyses of fluid in the microliter (μL) to milliliter (mL) range. They were used as lab-on-a-chip and micro total analysis system (μTAS) with multiple application in the field of biomedical engineering, biotechnology, environmental sensing and analytical techniques. Fabrication of microfluidic systems has been performed by lithography and soft lithography techniques using glass and silicone as the materials of interest in building these systems. However, this particular fabrication procedure is time consuming and expensive. AM can be employed to enable the microfluidic based fabrication technology to overcome the shortcomings in three different ways. They are as follows: (i) In general, soft lithography technique involves development of a mold which is later used to make the microfluidic system of choice. AM has the capability to eliminate the need for the mold preparation as it can create a structure with micro-channels. Not to forget the fact that AM itself can be employed to fabricate molds with more precision compared to traditional manufacturing techniques. (ii) AM-assisted 3D printed microfluidic process allows one-time fabrication capability to complete the whole structure of the system over a single manufacturing process and an equipment. However, the exception is with the lithographic techniques where additional steps are required, for example, an extra step is required for the development of molds in the process of soft lithography. (iii) AM-assisted process also allows the possibility of including device specific active components such as pumps and microlense, and passive components such as droplet generators, microcapillary emulsion generators, functional microfluidic valves, chip interconnectors or flow meters [5].

Researchers developed an immunomagnetic flow assay based on antibody-functionalized magnetic nanoparticles for capturing and quantifying Salmonella bacteria in water samples and E. coli from milk, respectively (Figure 3). Separately, a Czech group used the FDM/FFF process with ABS or polylactic acid to fabricate a number of similar bio-analytical microfluidic devices for detecting the influenza virus, methicillin-resistant Staphylococcus aureus, and nucleobases in hydrolyzed samples. Recently, Dolomite Microfluidics launched the Fluidic Factory, which became the first commercial available AM device for fabricating tailor-made microfluidics from a cyclic olefin co-polymer.[5]

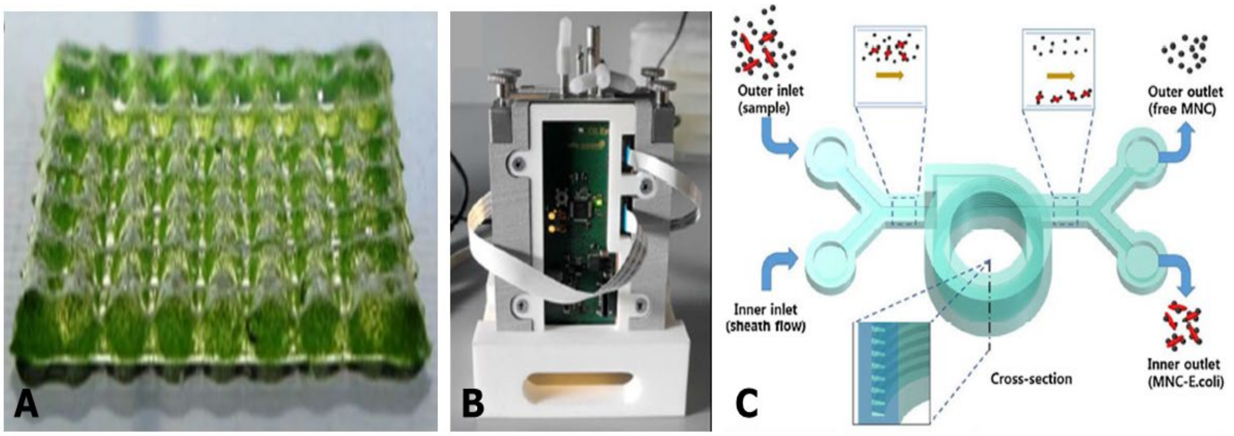

*Figure 3. AM-assisted microfluidic biomanufacturing (A-C): (A) Photosynthetic active cell clusters are visible within the 3D extruded hydrogel environment; (B) MicrOLED-PBR with combined electronic and structural design; (C) 3D-designed microfluidic device for capturing bacteria by inertial focusing (MNC = magnet nanoparticle clusters) [**Source:** N Biotechnol. 2017].*

Conclusion

This article gave a brief overview into the possibilities of leveraging AM for biotechnological applications in developing next generation medical devices and printed organs. Even though most of these reported applications are still in their research phase, commercialization of these techniques will be significantly easier and it is believed that organs can be developed with lesser risk with respect to their end use. The ability of AM to cut down fabrication cost, labor, develop multifunctional microfluidic systems and bioreactors, and create complicated co-cultures will be invaluable in providing a new impetus to the field of biotechnology in the future.

Author's Biography

Dr. Sathyanarayanan Sridhar holds a PhD in Bioengineering from the University of Texas at Dallas. He has more than five years of experience in the medical devices space. As a part of his PhD dissertation, he has developed novel testing protocols to understand the material performance of commercial titanium and zirconia dental implants. In addition to his research expertise, he is a passionate science communicator. He has authored/co-authored a number of peer-reviewed publications and a book chapter. He has been invited to present his research outcomes at prestigious international conferences organized by National Association of Corrosion Engineers (NACE), Society for Biomaterials (SFB), International Association of Dental Research (IADR) and American Society for Microbiology (ASM). He runs a newsletter titled "Medtech Outtakes" which provides snippets of recent trends in the medical device industry. Currently, he is part of a "Medical Innovation Fellowship" program offered by WORLDiscoveries at the University of Western Ontario in Canada. In his free time, he loves to hit the trails and enjoys learning music. Dr. Sridhar can be reached at sathya.sridhar1389@gmail.com

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