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Review article

Additive Biotech—Chances, challenges, and recent applications of additive manufacturing technologies in biotechnology

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ABSTRACT

The diversity and complexity of biotechnological applications are constantly increasing, with ever expanding ranges of production hosts, cultivation conditions and measurement tasks. Consequently, many analytical and cultivation systems for biotechnology and bioprocess engineering, such as microfluidic devices or bioreactors, are tailor-made to precisely satisfy the requirements of specific measurements or cultivation tasks. Additive manufacturing (AM) technologies offer the possibility of fabricating tailor-made 3D laboratory equipment directly from CAD designs with previously inaccessible levels of freedom in terms of structural complexity. This review discusses the historical background of these technologies, their most promising current implementations and the associated workflows, fabrication processes and material specifications, together with some of the major challenges associated with using AM in biotechnology/bioprocess engineering. To illustrate the great potential of AM, selected examples in microfluidic devices, 3D-bioprinting/biofabrication and bioprocess engineering are highlighted.

Introduction

Terminology

The term additive manufacturing (AM) refers to a very wide range of technologies: in 2010, it was defined by the American standardization organization ASTM as "…a process of joining materials to make objects from three-dimensional (3D) model data, usually layer upon layer, as opposed to subtractive manufacturing methodologies…" [1]. It is largely synonymous with several other terms that have been used in the literature, including 3D-printing, rapid prototyping (RP), rapid manufacturing (RM), direct digital manufacturing, solid freeform techniques and layer manufacturing. Despite the very similar meanings of these terms, it is important to differentiate between rapid prototyping (defined as "… a process for rapidly creating a system or part representation before final release or commercialization…") and rapid manufacturing, which involves "…the use of AM to produce parts which will be used as an end-product…" [2].

Historical development

The history of 3D printing begins in 1983 in California, when the American engineer Charles "Chuck" Hull developed and patented the first AM device, which was used to manufacture 3D products by using UV light to cure photopolymers. This technology and the corresponding device were patented as "stereolithography" [3]. In 1986, Hull founded the company 3D-Systems, which launched the first commercial available 3D Printer: the SLA-1. Over the last two decades, several companies have followed in the footsteps of 3D-Systems, including Stratasis from the US, Arcam from Sweden, and EOS from Germany. These companies have developed innovative AM technologies and devices that can work with a great variety of materials including ceramics, composites and metals. While the first AM systems were better suited for RP-type applications, advancements made by these firms and others have driven a transition towards RM in research and industry.

Abbreviations: AM, additive manufacturing; PDMS, polydimethylsiloxane; CAD, computer-aided design; RP, rapid prototyping; RM, rapid manufacturing; NIR, near-infrared; LOC, lab-on-chip; FPA, flat-panel-airlift; PBR, photobioreactor; OLED, organic light emitting diode; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

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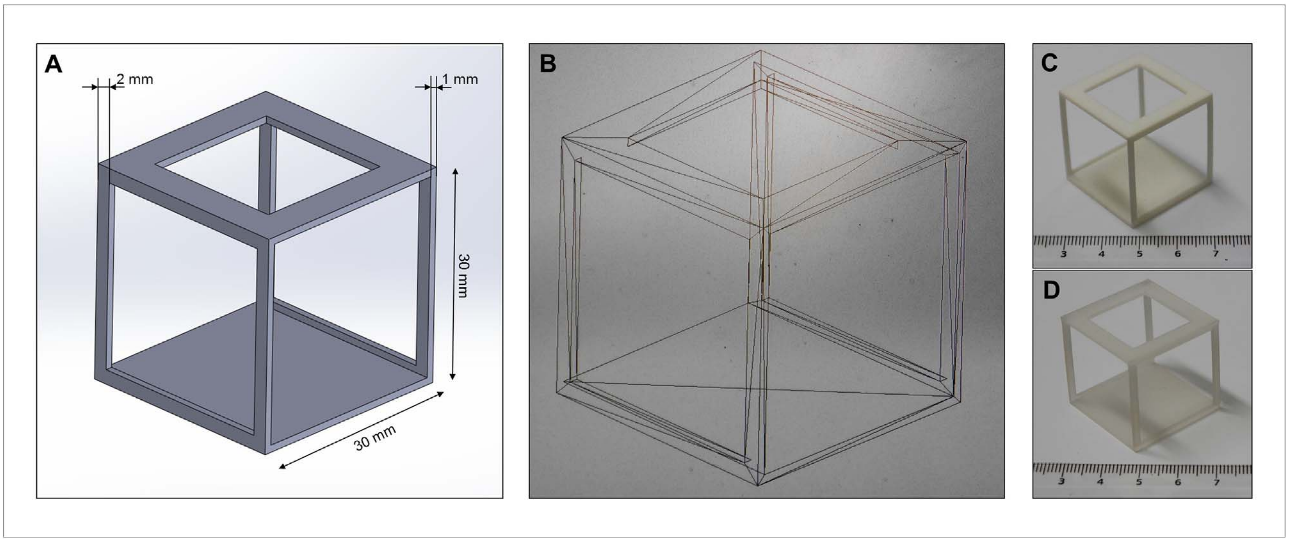

Fig. 1. (A) CAD-model of a test structure; (B) surface geometry of the CAD-model expressed by 92 triangles (.stl-file, binary file of 4684 bytes); (C) fabricated test structures from polyamide using the selective laser sintering technology and (D) from Accura Si60 using stereolithography.

Workflow of additive manufacturing

The first step in the fabrication of a 3D-object is to design a CAD-based model, which is then converted into a .stl (*standard tessellation language* or *stereolithography*) file. The .stl format describes the unstructured surface geometry of the 3D-object in terms of the unit normal and vertices of triangles using a 3D Cartesian coordinate system. This file format was developed by Chuck Hull and some coworkers at 3D-Systems during the late 80′s and remains one of the most important interfaces between CAD software and AM devices today. The .stl file is processed with a so-called "slicer software" that converts the geometrical object into thousands of 2D-layer data [4], which are translated by the AM device to build up the 3D-object layer by layer (Fig. 1). Several factors must be considered to identify the most suitable AM technology for a given application, including the required object accuracy, the object's size, the material requirements and the cost of the material [5]. Once the 3D-object has been fabricated, final finishing is generally necessary. This may involve removing excess material or supporting structures, polishing, lacquering, coloring, or infiltrating.

Materials & processes

AM technologies have the potential to create a new industrial revolution [6] while providing new degrees of freedom in terms of structural complexity for (biotechnological) fabrication. Today, many different plastics, metals, ceramics, polymer plasters and resins can be processed using a wide range of technologies. The following section focuses on widely used AM technologies that have the greatest potential for use in biotechnological applications yet. Table 1 provides a detailed overview of the materials used in these technologies as well as their fabrication parameters and properties. From a bioprocess engineer's point of view, there are two particularly important parameters to consider: the material's heat stability in case heat sterilization is necessary and the required object accuracy (Table 1).

The 3DP/binder jetting (Fig. 2A) uses a powdery polymer plaster that is distributed as a thin layer on a carrier plate using a roller system [7]. The powder material is then hardened by integrating a binding material via inkjet-print heads. The carrier plate is then lowered by around 0.1 mm and the next layer of powder is distributed and fabricated with the inkjet and so on until the complete 3D-object has been built up. Finally, excess powder is removed and recycled for use in the next fabrication process. In contrast, the Fused Deposition Modeling (FDM) approach, also denoted Fused Filament Fabrication (FFF) in the literature, developed by Stratasys, uses plastic materials, usually filamentous acrylonitrile-butadiene-styrene (ABS), which is heated until the material's flow characteristics become suitable for extrusion through a dosing nozzle (Fig. 2B). In addition to the building material, FDM uses a second plastic to fabricate supporting structures, which must be removed at the end of the fabrication process. Because of the low heat stability of the fabricated materials and their currently limited object accuracy, 3DP/binder jetting and FDM are typically used for RP-applications.

The transition from RP (i.e. the creation of models) to RM (the creation of practical components) was, for example, enabled by the development of laser-based AM technologies such as Selective Laser Sintering (SLS). SLS processes use plastics such as polyamides, elastomers, nylon, or alumide that offer high mechanical stability, biocompatibility, high processing precision and low material costs [8]. The SLS manufacturing process uses a powdery starting material that is heated at elevated pressure on a carrier platform (Fig. 2E). The local sintering of the material layers is induced with a focused laser beam, typically a CO_2 or Nd:YAG laser, and the carrier is lowered in a stepwise fashion to enable the layer-by-layer construction of the object [9]. As with 3DP, the final step in the manufacturing process is to remove excess powder.

Selective Laser Melting (SLM) and Electron Beam Melting (EBM) permit fabrication with metallic powder materials such as tool steel, stainless steel, titanium or aluminum [10,11]. To prevent corrosion, SLM and EBM are performed under a protective atmosphere (Fig. 2C, D). The metallic source materials and the requirements of the fabrication process make metallic AM comparable expensive. However, SLM and EBM enable the production of highly complex, non-porous and sterilizable 3D-objects with excellent heat stability and mechanical properties [12,13].

The stereolithography (SLA) process uses UV-curable photopolymers, elastomers, epoxies or acrylates [14]. The liquid photopolymer is placed into a bath with a retractable carrier plate and is then locally hardened by means of a mirror-controlled UV-laser (Fig. 2F). The carrier plate is then lowered in a stepwise fashion to build up the 3D-object layer-by-layer. The use of a liquid source material necessitates the use of additional supporting structures to fix the component within the water bath, which must be removed after the fabrication step. SLA-fabricated components have high levels of detail accuracy and very favorable mechanical properties. In addition, the SLA process enables the production of (semi)-transparent components.

The PolyJet™ (PJ) process closely resembles the MultiJet Modelling