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3D PRINTING AND 3D BIOPRINTING TO USE FOR MEDICAL APPLICATIONS

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Abstract: The Additive manufacturing 3D printing is a process of creating a three dimensional solid objects or rapid prototyping of 3D models from a digital file, which builds layer by layer. The 3D bioprinting is a form sophisticated of 3D printing technology involving cells and tissues for the production of tissue for regenerative medicine, which is also built layer by layer into the area of human tissue or organ. This paper defines the modern methods and materials of the AM, which are used for the development of physical models and individually adjusted implants for 3D printing for medical purposes. The main classification of 3D printing and 3D bioprinting technologies are also defined by typical materials and a field of application. It is proven that 3D printing and 3D bioprinting techniques have a huge potential and a possibility to revolutionize the field of medicine.

Keywords: additive manufacturing, 3D printing, 3D bioprinting, tissue engineering, regenerative medicine.

1. INTRODUCTION

Additive Manufacturing (AM) 3D printing is defined by American Society for Testing and Materials (ASTM) Committee F42 on Additive Manufacturing Technologies, which are grouped under seven categories, as shown in Table 1 [1−16]. The main classification of Additive Manufacturing 3D printing process and examples of a Research Company of 3D printers are in the description of each process according to typical materials and a field of application given in the table.

In this review, we will present the most important 3D printing techniques and materials, with the basic characteristics and possibilities, which are used in medical applications.

3D Bioprinting is an advanced technology for tissue engineering processes that can be used for a wide range of medical applications. The bioprinting process is based on the classic Inkjet 2D printing technology. Here, instead of inks, conglomerates are using cell-spheroids, which are placed in the hydrogel. Depending on the type of tissue, the corresponding spheroids, which are filled in the cartridge and through the piston nozzle, are printed on the artificial structure - the scaffold. Spheroids are poured on the scaffold and form the tissues of the future organ. The Scaffold structure is very important because it should support the formation of three-dimensional tissue, enable cell association and migration, retain cells and biochemical factors, and enable the integration of layer by layer [1−3].

The four main categories of Bioprinting process and a few examples of Research Company of 3D bioprinters according to typical materials and field of application are given in Table 2.

Behind the mentioned 3D printing processes, (Table 1 and Table 2) are the well-known Research Company launched on the market alongside professional and low cost - consumer grade 3D printers. Our research has shown that low-cost 3D printers cannot be successfully fabricated on the geometrically complex models [3].

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Table 1. The main classification of Additive Manufacturing 3D printing process and example a Research Company of 3D printers according to typical materials and a field of application

PROCESS / Examples	TYPICAL MATERIALS	APPLICATION
Material Extrusion: Fused Deposition Modeling (FDM); -Stratasys, 3D Systems, RepRap, Prusa i3, Ultimaker, etc.	Polymer (ABS, PP, PC, PPS, PLA, ASA), Composite, Wax, WPC, Gels	Prototypes, Casting Paterns, Soft Tooling, Functional Parts
Material Jetting: Multi-jet modeling (MJM) – Object PolyJet, 3D Systems Projet, etc.	Polymer (ABS, PP, Acrylic, Rubber), Wax	Prototypes, Casting Patterns, Soft Tooling
Binder Jetting: Powder bed and inkjet head, plaster based 3D printing; - Zcorp, Voxleljet, ProMetal/ExOne, etc.	Composite Gypsum, Ceramic, Sand, Metal, Polymer	Functional Parts, Prototypes, Casting Paterns, Soft Tooling
Sheet Lamination: Laminated object manufacturing (LOM), Ultrasonic (UAM); - mCor Technologies Iris, Fabrisonic UAM, etc.	Paper, Metal (Steel, Aluminium, Titanium, Cooper)	Functional Parts, Prototypes, Casting Paterns, Soft Tooling
Vat Photopolymerization: Stereolitography (SLA); - Digital Light Procesing (DLP), Micro-SLA, Stereolitography (SLA)-Stratasys, etc.	Polymer (Epoxy, ABS, PP), Compostie Gypsum, Ceramic, Wax	Prototypes, Casting Paterns, Soft Tooling
Powder Bed Fusion: Selective Laser Sintering (SLS), Electron beam melting (EBM), Direct metal laser sintering (DMLS), *EOSINT*, etc.	Metal (Alloy Steel, Aluminium, Titanium), Ceramic, Polymer, Composite, Rubber, Silicate	Functional Parts, Prototypes, Casting Paterns
Directed Energy Deposition: Focused thermal energy is used to fuse materials, Laser metal deposition (LMD), (LENS), Trumpf, etc.	Metal (Alloy Steel, Aluminium, Titanium)	Prototypes, Functional Parts

Table 2. The main classification of 3D bioprinting process

PROCESS / Examples	MATERIALS	APPLICATIONS
Fused deposition modeling (FDM): Stratasys 3D printer, Ultimaker 2+, BigRep One, Dimension Elite-Stratasys, etc.	Polymer (ABS, PP, PC, PPS, PLA, ASA), Composite, Wax, WPC, Gels	Precision Healthcare Solutions, Medical Device Design and Manufacturing of RP medical models, Surgical planning, etc.
Vat photopolymerization Stereolitography (SLA): Z-Rapid SLA500, 3D Systems, Envisiontec, RapidShape C30, Wiiboox, etc.	Plastics and Polymers: UV-curable Photopolymer resin, Silver nanoparticles, Nanocomposite	3D Printing for Good, 3D-printed prosthetics, Manufacturing of tissue scaffolds, Specific medical devices, RP medical models, etc.
Selective laser sintering: 3D Systems' Selective Laser Sintering (SLS), 3D Nylon Printers, Cellink GelMa, EOS GmbH.	Nylon, (Duraform PA), Glass Filled Nylon (Duraform GF), Fiber-filled Nylon, Metal, Ceramic	Medical and Healthcare Design Evaluation Models (Form, Fit & Function), Fabrication of tissue scaffolds, RP medical models, etc.
Inkjet 3D biprinting: EnvisionTEC's 3D Bioplotter system, Organovo sytems, 3D Bioprinting Solutions-Moscow, CELLINK Inkredible, etc.	Liquids, Hydrogels, Cell-laden, silicone, hydroxipatite, titanium, chitosan	Regenerative medicine, Inkjet printing for pharmaceutical applications, 3D printed tablets, Bioprinting organ transplants, etc.

2. 3D PRINTING APPROACHES IN MEDICINE

Application of AM 3D printing and 3D bioprinting are based on the 4 steps of the 3D printing system: (1) Image Acquisition of 3D imaging data with Computed tomography (CT) or Magnetic Resonance Imaging (MRI), with Digital Imaging and Communications in Medicine (DICOM) medical file format, (2) Image processing, including segmentation steps and surface modeling, (3) Manufacturing with 3D printer or 3D bioprinter and (4) Post-processing techniques, Figure 1.

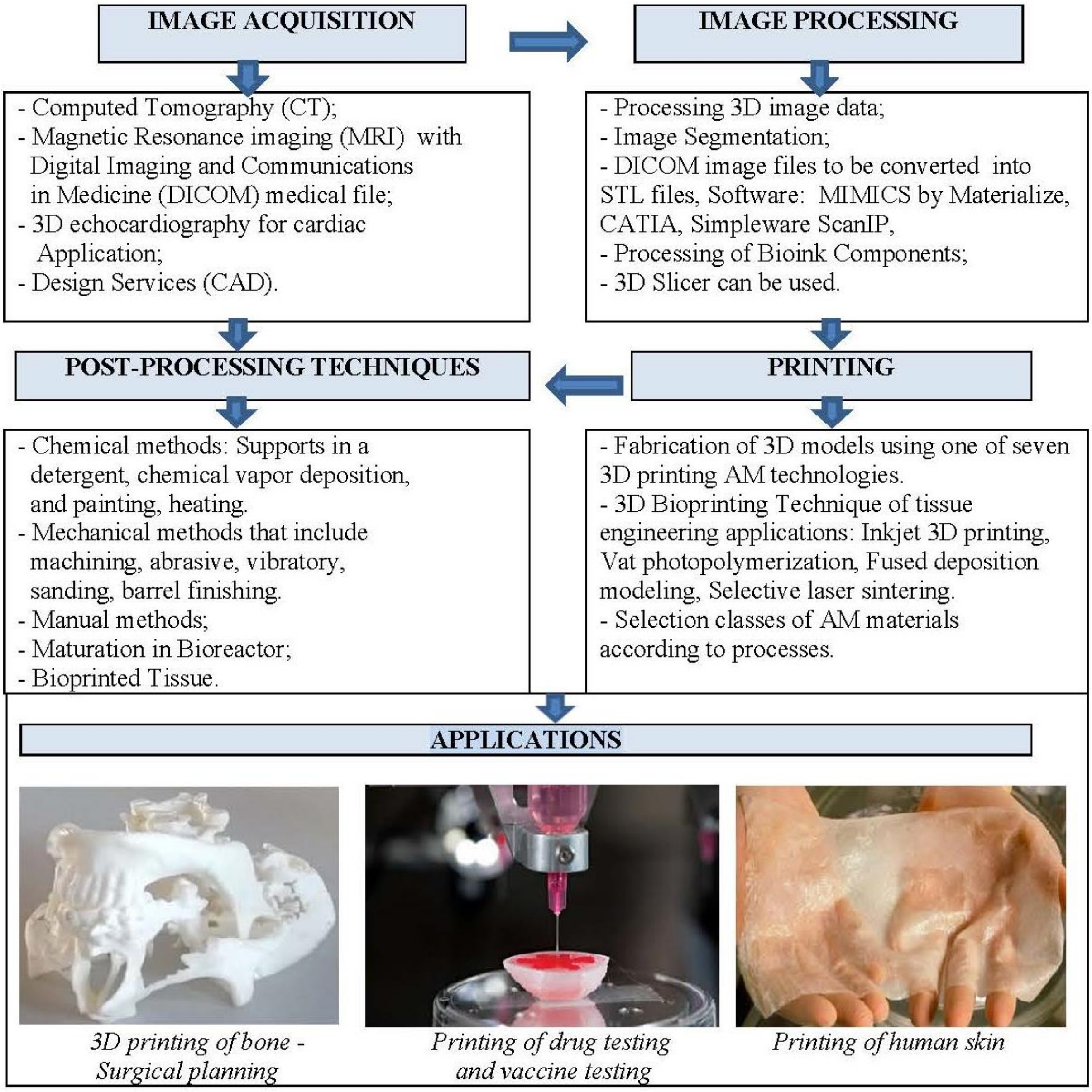
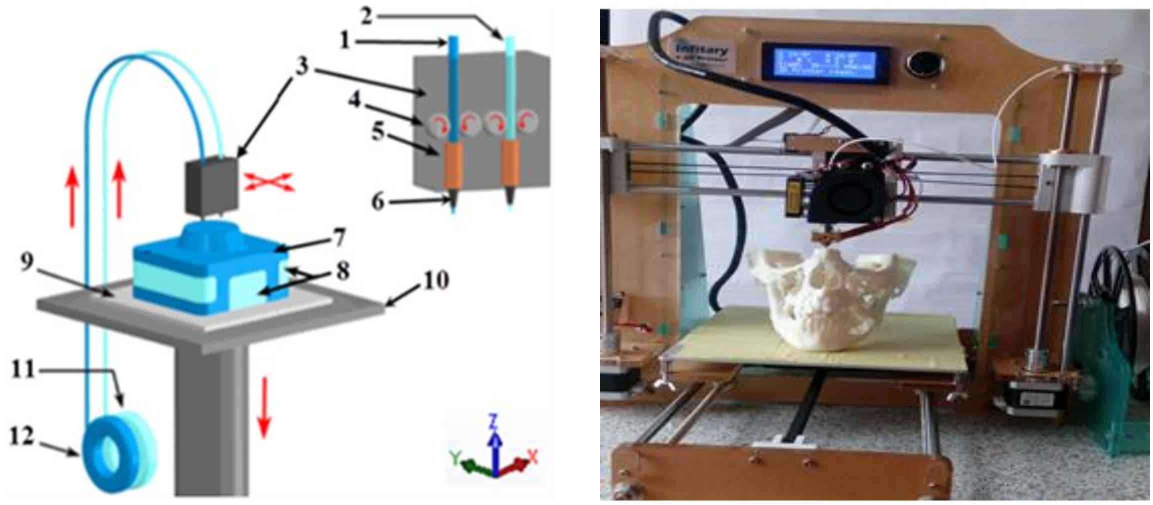


Figure 1. Basic steps in the fabrication of 3D medical models using 3D printing and 3D bioprinting Additive Manufacturing (AM) technologies

2.1. Fused deposition modeling (FDM) process

In the process of Fused Deposition Modeling (FDM), plastics of wax are extruded through a nozzle that follows a component's cross section forming the geometry of a body, layer by layer. The nozzle contains resistant heaters which heat and keep the material above the melting point, thus enabling the flow of material and forming of layers. Various types of materials are used including ABS plastics, polyamides, polycarbonates, polyethylene, polypropylene and melted wax. The schematic showing the forming of layers using FDM methods is presented in Figure 2 (a), and (b) shows Picture of the FDM Infitary i3 3D printer based on FDM.

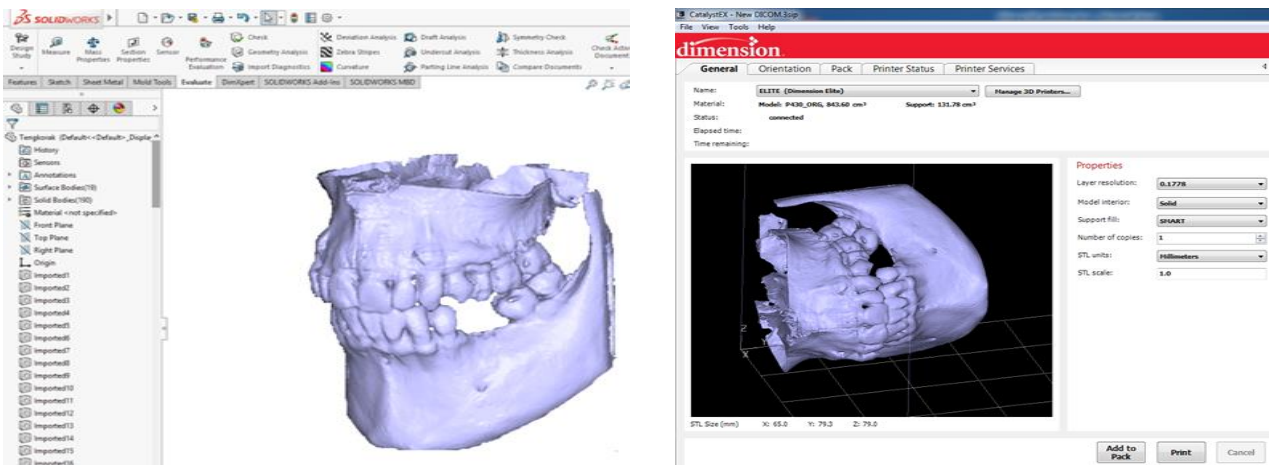


(a) (b)

Figure 2. (a) The schematics of the Fused deposition modeling (FDM) process: 1-Build material filament, 2- Support material filament, 3-Extrusion head, 4-Drive wheels,5-Liquifiers,6-Extrusion nozzles, 7-Part, 8-Part supports, 9-Foam base,10-Build platform, 11-Support material spool, 12- Build material spool and (b) Picture of the FDM Infitary i3 3D printer during a process of making a physical model of the skull.

2.1.1. FDM applications in Biomedical Engineering

FDM is often the go-to method for fabricating rapid prototyping mainly non-functional three-dimensional prototypes for the preparation of applications in multiple branches of medicine. These are models for medical applications where several iterations are needed and they are quick and cost-effective. Here is presented surgery planning using FDM Process of a case study of a jaw of that anonymous patient, it was carried out on the Laboratory for Technology of Plasticity, Faculty of Mechanical Engineering of the University of Banja Luka [3,22−25]. All the steps for creating a model on FDM printer went according to the next procedure: (i) Scanning of data (using CT, MRI, etc.), (ii) Measuring, (iii) Designing, (iv) Modeling. The processing of the jaw was imported in SolidWorks, Figure 3 (a), with a choice of STL Orientation, Orient Selected Surface and STL scale, was carried out in the CatalistEx, Figure 3 (b). The production of a physical model of the human jaw has been performed on Dimension Elite 3D printer. The post processing of the jaw model, namely, the removal of support material, which has provided support for the successful achievement of dimensional accuracy, was conducted in the SCA (Support Cleaning Apparatus) -1200 Stratasys. This model is now ready to go to a clinic for a surgical assessment and testing in order to determine the irregularities and damage. Printed out model of the jaw, otherwise made according to the requirements of the medical team, was delivered to the team for further analysis and processing, in order to be prepared for a specific medical procedure.

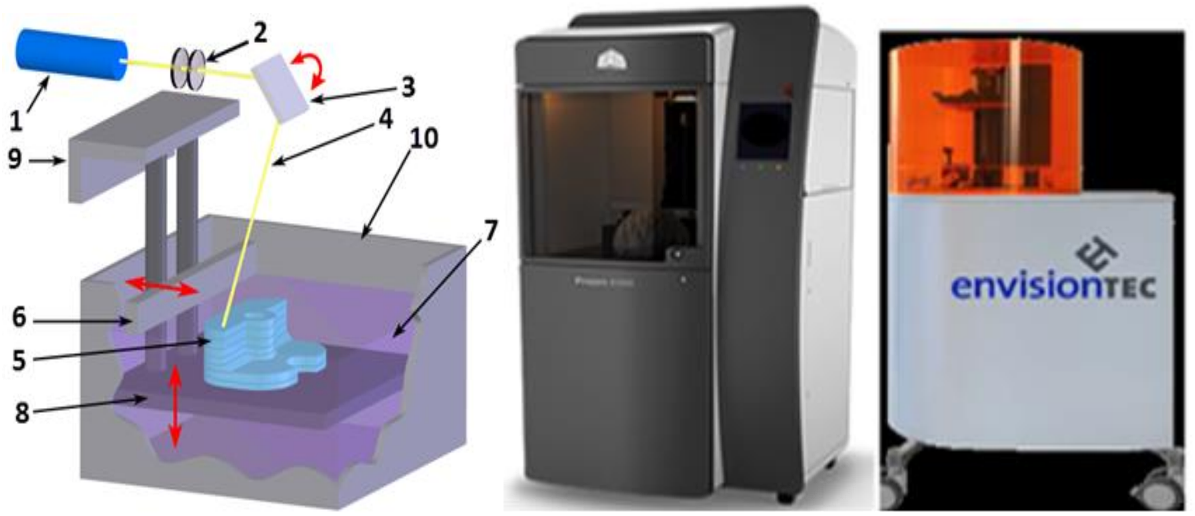


(a) (b)

Figure 3. (a) The jaw presented in SolidWorks, (b) Conversion of the STL format of the jaw in the CatalistEx for printing on Dimension Elite 3D printer

2.2. Vat photopolymerization

Vat Photopolymerization is the AM process in which liquid photopolymer in a vat is selectively cured by light-activated polymerization. It is also defined as Stereolithography – SLA. Produces parts are directly maid from 3D CAD model by solidifying the surface of a liquid photo polymer layer by layer with the help of a laser beam. Stereolithography is the first RP technique commercially used and the most common RP technique that has become standard for industrial and medical prototypes. The operation principle of the most commonly used system is shown in Figure 4 (a), (b) shows Picture 3D Printer of the Company 3D Systems ProJet 6000 HD Printer and (c) Picture of the Company Envisiontec: Perfactory4 DPP 3D Printer [18,20].



(a) (b) (c)

Figure 4. (a) The schematics of the Vat photopolymerization 3D printing process: 1-Laser, 2-Lenses, 3-X-Y scanning mirror, 4-Laser beam, 5-Layered part, 6 -Sweeper, 7-Liquid photopolymer, 8-Build platform, 9-Elevator, 10-Vat; (b) Picture of the 3D Systems ProJet 6000 HD Printer, and (c) Picture of the Envisiontec: Perfactory4 DPP 3D Printer (Source: Picture of the 3D Systems and Envisiontec)

2.2.1. Vat photopolymerization aplications in Medicine

Vat photopolymerization in medical applications are using the creation of medical models, applied in dental medicine, used to prototype products in development, to create a casting pattern for casting of metals, low-run injection mold, for the fabrication of tissue scaffolds for use in regenerative medicine and patient specific medical devices. The fabricating tissue scaffolds using vat photopolymerization is very important because that can support cell proliferation and encourage the formation of developed tissue [14,17].

2.3 Selective laser sintering (SLS)

Selective laser sintering (SLS) is an additive manufacturing process that builds three dimensional parts by using a laser to selectively sinter (heat and fuse) a powdered material, as shown in Figure 5 (a) and (b) shows Picture of 3D printer Company 3D Systems. SLS is used to produce, layer by layer, both metallic and non-metallic parts. SLS uses fine powder that is equally distributed over a work platform using rollers and selectively scanned by a laser when powder is heated up to melting temperature, and during cooling they physically connect. SLS is an advanced universal rapid prototyping technology which can be used to create metal, plastic, and ceramic objects [18−20].

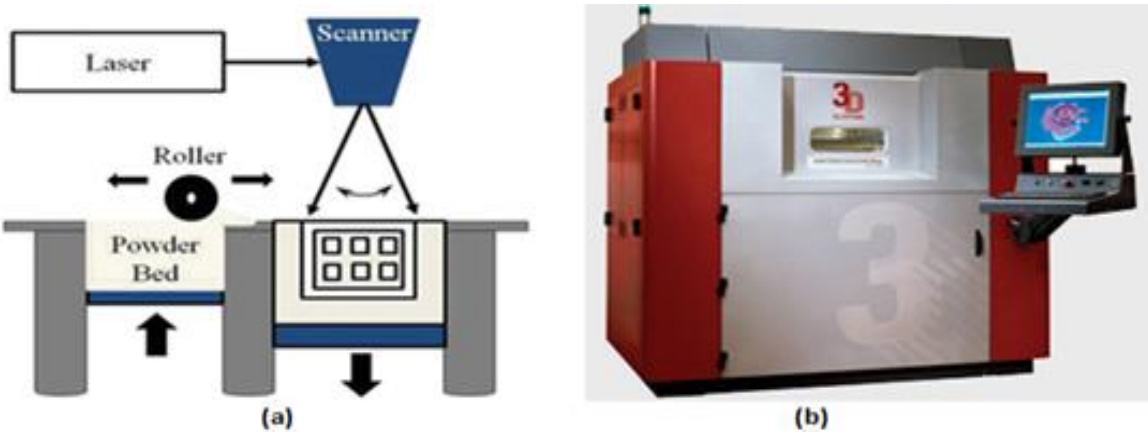


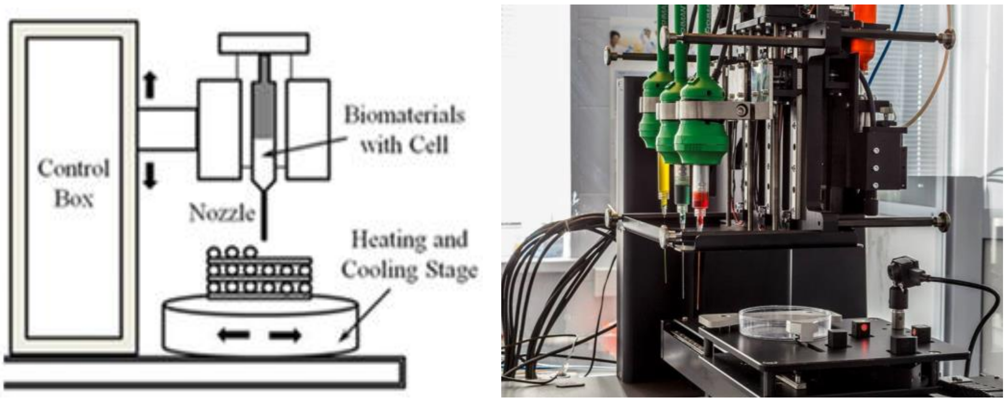
*Figure 5. **(a)** The schematics of Process Selective laser sintering, and **(b)** Picture of Selective laser sintering 3D printer Company 3D Systems [18−20].*

2.3.1. SLS applications in Biomedical Engineering

Selective laser sintering (SLS) applications of biomedical and clinical applications are focus on polymer and composite powders. The article [18] presents a comprehensive literature review of biomedical and clinical applications of selective laser sintering (SLS) with a focus on polymer and composite powders. These are next medical application: (i) Surgical planning and simulation using medical models built with Rapid prototyping (RP) technologies, which give the surgeon a realistic impact of research body structures before a surgical intervention; (ii) Various of skull implants to produce patient specific implants; (iii) Patient-specific prosthetics and orthotics (iv) Tissue engineering scaffolds to fabricate biocompatible, which bone cells can grow normally.

2.4. Inkjet 3D bioprinting process

Inkjet-based 3D bioprinting process is of Company “Organovo sytems” USA has created the world’s first commercial 3D bioprinter to print human tissues and organ engineering [21]. The schematics of the Inkjet 3D printing process is shown in Figure 6 (a). An Inkjet 3D printer consist of one or several ink chambers with different nozzles. The Ink chambers are activated with a short pulse of electrical current in functionality of structural designing organ onto the platform of printer through the piezoelectric, thermal, or acoustic actuating nozzles, shown in Figure 6 (b). The starting materials (Liquids, Hidrogels, Cell-laden, Silicone, Hydroxyapatites, etc.) need to be printed onto a solid platform. Inkjet 3D bioprinting process can by successfully used for printed: (i) engineering porous scaffolds, (ii) homogeneous tissues, (iii) cell/biomaterial composites, (iv) multiple tissue contained organs, (v) 3D printed metal hip joints with the go-through channels, (vi), based on the MRI and CT image of the patient, it is possible to print the contours of some tissues and organs (e.g., ear, nose, jaw, etc.) with all channels to use of reconstruction purposes. Inkjet bioprinting technique is a technique for the future that can be successfully used for bioprinting of 3D human tissue and organs, which will be able to replace donor transplant organs.



(a) (b)

Figure 6. (a) The schematics of the Inkjet 3D printing process, and (b) Picture of the Inkjet 3D bioprinter from 3D Bioprinting Solutions’ Printer - Moscow [2]

3. ORGAN BIOPRINTING TECHNOLOGY

With the help of "Organ bioprinting technology" – The technology of futures, the organs of the human body will be printed and reconstructed in the near future. Moscow scientists have opened the first bioprinting laboratory "3D Bioprinting Solutions" - Moscow, on the whole with prof. Vladimir Mironov started with the project of bioprinting human organs [2, 23-29]. The aim is to replace the donor organs with bio print organs that are grown from the patient's own cells, which will be completely biologically compatible with his organism. Previous research shows that it will be easier to adapt to the body and that organ rejection will not occur, as opposed to donor organs that the organism often rejects [1,2,23-30]. The procedure goes so that the first 3D model of the future organ is created with all external and internal forms, including the blood vessels. The next stage is to extract the stem cells from the fat tissue of the patient to obtain the cell spheroid, the materials needed for the construction of the organ. The printed organ structure with 3D bioprinters is then placed in a bioreactor, where under the action of the simulator there is an accelerated tissue ripening. Main steps in organ printing technology are: (i) Preprocessing, (ii) Processing and (iii) Postprocessing [1,2,23-30].

3.1. Preprocessing

The preprocessing is a very important first step in the development of bioprinting of 3D human tissue and organs. Those are:

(i) Acquisition of 3D patient model by Imaging of X-ray, MRI or CT;

(ii) Design approach: CAD-design by FreeCAD, CATIA, Solidworks, Inventor, etc, BioCAD-design by MIMICS -Materialize, CATIA, Simpleware ScanIP, etc ;

(iii) Blueprints: The development of BioCAD design of organ;

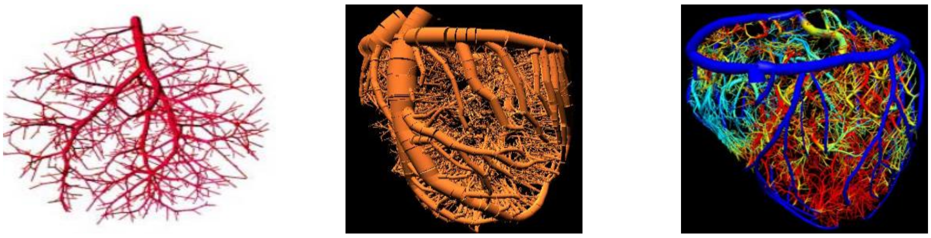
(iv) Preconditioning: Simulation step-up models, preprocessing assemblies and material selection.

The steps in the preprocessing are as shown in Figure 7 (a), (b), (c) and (d).

The Blueprint as an important step in the preprocessing phase is shown for several vasculatures in Figure 8 (a), (b) and (c).

(a) (b) (c) (d)

Figure 7. Preprocessing: (a) MRI scan machine: MRI or CT, (b) BioCAD-design of heart (c) Rapid prototyping 3D heart patient design, (d) Blueprint of heart [2]



(a) (b) (c)

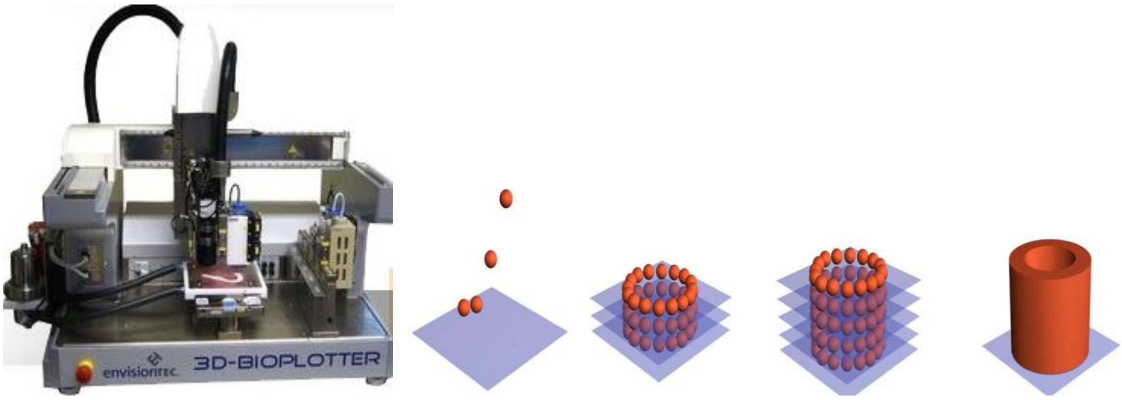
Figure 8. Preprocessing: (a), (b) and (c) Blueprint for a few Vasculatures [2]

3.2. Processing

The processing is, in fact, the 3D bioprinting process performed by 3D bioprinters on the basic biofabrication of inkjet, micro-extrusion or laser-assisted 3D-printed of relevant materials such as biopolymers and cells. According to [2,19,25] today has developed several world-renowned 3D bioprinters, namely: (i) Organovo Holdings Inc., San Diego, CA, USA; (ii) 3D bioprinter designed by 3D Bioprinting Solutions Printer - Moscow, Russia; (iii) 3D Organ Printer designed by the Wake Forest Institute for Regenerative Medicine; (iv) 3D Bioplotter designed by Envisiontec, Germany; (v)

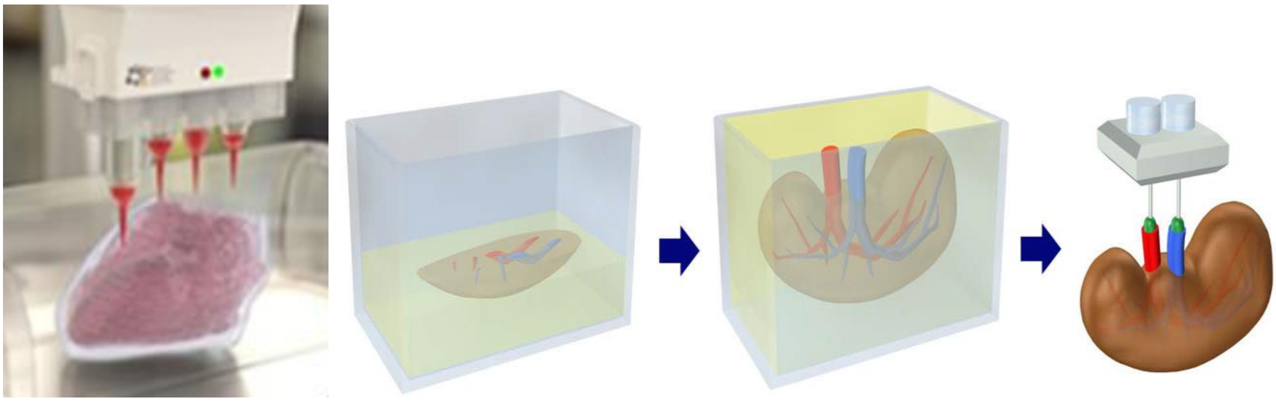
Commercialized Novogen MMX Bioprinter TM, designed by Organo Inc, etc. One of 3D bioprinter from Envisiontec for Tissue engineering process is shown in Figure 9 (a), shows methods of dispensing bioinc spheroid printing with bio-paper support (b), and (c) steplessly printing layers in place of the object, (d) by connecting bioinc spheroids and dispensing of bio paper and (e) the final living tissue.

The Printing of living organs is pioneering step in Organ printing technology for 3D printing applications in medicine. The process of bioprinting of a human body, a kidney is shown in Figure 10. (a), (b), (c) and (d) [26, 27, 28].



(a) (b) (c) (d) (e)

Figure 9 (a) 3D-BIOPLOTER-Envisiontec for Tissue engineering process. Methods of Dispensing: (b) Beginning of bioinc spheroid printing with bio paper support; (c) Printing and other layers in place the object; (d) Connecting of bioinc spheroids and dispensing of bio paper; (e) The final living tissue [27].



(a) (b) (c) (d)

Figure 10. Processing: The process of bioprinting of a kidney. (a) 3D bioprinter; (b), (c) and (d) A schematic presentation of the kidney bioprinting process. [28]

3.2 Postprocessing

The postprocessing is to create a stable structure of printed tissues and organs from biological material to channel through perfusion, postconditioning or accelerated tissue maturation. For postprocessing of printed tissues and organs, bioreactors with integrated capacities for various forms conditioning and monitoring of the tissue and organ are mainly used. The schematics representation of any Bioreactor is given in Figure 11 (a) [28], and one Premium bench-top bioreactor system from FerMac 310/60 Cell Culture Bioreactor -Electrolab, Biotech UK, Figure 11 (b).

(a) (b)

Figure 11. (a) The schematics of any Bioreactor, (b) Premium bench-top bioreactor system (FerMac 310/60 Cell Culture Bioreactor –Electrolab, Biotech UK) [28]

Otherwise, for the purpose of a successful postprocessing, the research institutes work on the development of more powerful bioreactor for 3D bioprinted tissue and organs.

4. CONCLUSION

Techniques of AM 3D printing and 3D bioprinting are giving a variety of possibilities for application in medicine where they are used for: creating models for planning complex surgical interventions; craniofacial implants to hip, knee and spinal implants; production of various medical tools used for cutting and drilling in surgery; prosthetic dentistry; bioprinting of human tissues and organs and others. The choice of suitable materials is a key for the successful application of 3D printing and 3D bioprinting techniques. World-renowned researchers are working on the use of stem cells for bioprinting, which can be obtained from the fat tissue of the patient. Stem cells are then transformed into a laboratory cell conglomerate and filled into bioprinter cartridge, to process biofabrication-formed corresponding tissues and organs [1,2,23-30]. According to the same sources, in the next decade, it is expected to come to the point where full biofabrication could be: (i) human skin, (ii) complete human organs: kidney, heart, liver, pancreas, etc., (iii) biofabrication of bones, (iv) bio-prosthetic lamination, (v) biofabrication of body parts. We can conclude that the possibilities of applying AM 3D printing and 3D bioprinting in medicine are limitless and that they represent a revolutionary future in the whole field of modern medicine.

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3Д ШТАМПАЊЕ И 3Д БИОШТАМПАЊЕ ЗА УПОТРЕБУ У МЕДИЦИНСКИМ АПЛИКАЦИЈАМА

Сажетак 3Д штампање је процес адитивне производње тродимензионалних чврстих тијела или брзе израде прототипова 3Д модела из дигиталног фајла и то градећи слој по слој. 3Д биоштампање је софистициранија форма 3Д штампања, која укључује ћелије и ткива за производњу ткива за регенеративну медицину, а такође се изводи слој по слој у подручје ткива или органа. У овом раду су дефинисане савремене методе и материјали адитивне технологије, који се користе за развој физичких модела и индивидуално прилагођених имплантата за 3Д штампање у медицинске сврхе. Главна класификација 3Д штампања и 3Д биоштампања дефинисана је према типичним материјалима и области примјене. Доказано је да технике 3Д штампања и 3Д биоштампања имају огромне потенцијалне могућности за револуционизирају медицину.

Кључне ријечи: адитивна производња, 3Д штампање, 3Д биоштампање, инжењеринг ткива, регенеративна медицина.

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