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VYUŽITÍ 3D TISKÁREN V MEDICÍNĚ
THE USE OF 3D PRINTERS IN MEDICINE

BAKALÁŘSKÁ PRÁCE
BACHELOR'S THESIS

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Využití 3D tiskáren v medicíně

POKYNY PRO VYPRACOVÁNÍ:

Cílem práce je představit technologii 3D tiskáren a varianty jejich využití pro lékařské účely.

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Abstrakt

Text se zabývá rychlým rozvojem trojrozměrných tiskáren popsání jejich obecných komponent a využití 3D tiskáren v medicíně. V našem současném světě se v poslední době objevily trojrozměrné tiskárny a byly okamžitě použity v různých oborech a průmyslech. 3D tisk je inovační a perspektivní technologie, která nepředstavitelně mění lidské životy a zkrátí obrovské množství času a zdrojů, které se vynakládají na vytváření určitých produktů. V této semestrální práce jsou uvedené příležitosti využití těchto technologií v různých oblastech především v medicíně, stejně jako rozdíly mezi jednotlivými technologiemi a jejich výhody a nevýhody.

Klíčová slova

Trojrozměrná tiskárna, technologie 3D tisku, provoz, průmysl, zdroje, medicína.

Abstract

The text deals with a rapid development of three-dimensional printers, description of their general components, and the utilization of 3D printers in medicine. In our contemporary world, three-dimensional printers have appeared more recently and immediately were applied in various fields and industries. 3D printing is innovative and forward-looking technology that will unimaginably change people's lives and will reduce an enormous amount of time and resources, that is spent on creating certain products. The opportunity of using such technology in different areas particularly in medicine are described in this bachelor thesis, as well as the differences between individual technologies and their advantages and disadvantages.

Keywords

Three-dimensional printer, 3D printing technology, operation, industry, resources, medicine.

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V Brně dne: …………………………

Vladislav Shchennikov

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1 INTRODUCTION

Three-dimensional printing is one of the latest innovative technologies that made a breakthrough in engineering, manufacturing and information technology and has every chance to revolutionize medicine incredibly. What a decade ago seemed impossible and beyond our understanding now is getting in common practice. The 3D printing revolution transforms our life. While traditional printers operate only with paper, 3D printers construct objects from plastic, metal, glass and even from cells. An example of visual representation of three-dimensional printer “Makerbot Replicator (5th generation)” is shown on the Figure 1.

A jeweler could print rings, earrings, medallions to utilize it as layers for future products. An inventor could use a 3D printer to create an inexpensive prototype of a handle for a new screwdriver, testing it in plastic first to ensure himself that the design feels appropriate. A robotics hobbyist might find a 3D printer helpful for producing small gears or wheels unique in size or shape, that can’t be offered in usual markets.

What about medicine? Nowadays, right before our eyes there is a revolution in the field of medicine. Scientists from all over the world use 3D printers to print organs, tissues and implants for people with various diseases and injuries. Printing in medicine is a more reliable, cheaper and faster solution than traditional outdated methods. With each passing day, progress is being made, research is being conducted and trials are being conducted to provide a wider range of services to patients seeking of treatment and organ transplants.

And it is just a beginning, it is hard to imagine what 3D printer will “build” in the next decades.

Figure 1 An example of 3D printer "Makerbot Replicator 5th generation" (retrieved from https://www.3dhubs.com/3d-printers/makerbot-replicator-5th-gen)

2 OPERATION OF 3D PRINTER

2.1 Definition of 3D printing

Dr. Kalaskar from Institute of Orthopaedics and Musculoskeletal Science defines 3D printing as:

"Additive manufacturing or rapid prototyping or layered manufacturing. Conversely, 3D printing is a generic term that describes various methods of constructing objects in a layer-by-layer fashion. The object to be printed is created using computer-aided- design software package which is then exported as a file to be printed. The exported file splits the 3D object into a series of layers—the object is then printed layer by layer. The technology involves printing a single material or a combination of multiple materials in a layer-by-layer manner, regulating the shape of every individual layer, eventually resulting in a complex 3D structure with limited restrictions on its spatial arrangement" (1).

2.2 Process of operation

The personal 3D printers people use at present often construct things from plastic using an approach called fused filament fabrication. Brian Evans describes this process as follows: *"Plastic filament is heated and extruded from a nozzle like a tiny and precise hot glue gun while the machine draws out 3D objects layer by layer. As one layer of plastic is laid on top of another, they fuse together, and, when cooled, form a solid and durable plastic part."* (1). This innovation is utilized in the design and engineering industries for everything beginning with designing parts for machines.

2.3 Parts of 3D printer

In order to sufficiently understand how three-dimensional printers work, it is necessary to examine its important parts.

2.3.1 Extruder

One of the most complex parts of a 3D printer is extruder. Figure 2 shows a complete extruder with filament driver and hot end. An extruder consists of two key elements: the filament drive and the thermal hot end.

An extruder is capable of laying down thin strands of thermoplastic—a type of plastic that will soften to a semiliquid state when heated. Extruder usually utilizes a geared arrangement to permit the stepper motor to apply more torque to the filament and to overcome forces like the tension of the spool or the weight and thickness of the filament. (Evans 3).

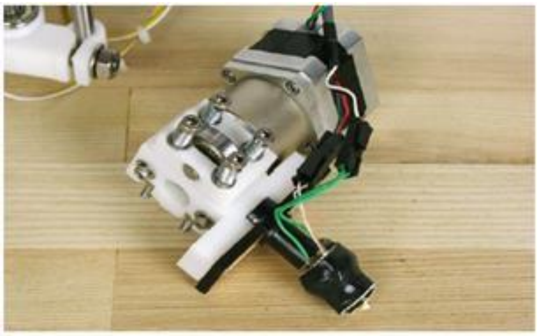

Figure 2 An example of the layout of the extruder and a spool of filament. Adopted from Evans (2012) "Practical 3D Printers"

Figure 3 illustrates a layout of the extruder and a spool of filament. The fiber is brought into the extruder (cold end) and after that pushed into the nozzle (hot end). When the plastic reaches the hot end, it is heated for about 200°C. When the filament is heated enough, it is extruded onto a flat surface, that used as the foundation for the object. Generally, the external sides of an object are printed before the interior edges. At that point, the interior of the layer is printed as a solid layer. The heated extrusion is colder than the filament from the spool because nozzle has a microscopic slot ranging average of 0,4 millimeters. (Bell 6). To facilitate understanding the representation of how the layer are built from various lines of heated fiber is demonstrated in Figure 3.

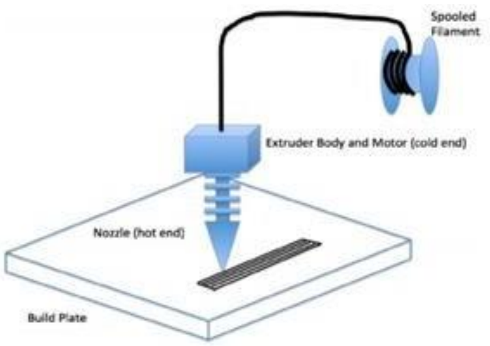

Figure 3. Fused Filament Fabrication extrusion with nomenclature. Adopted from Bell (2014) "Maintaining and troubleshooting your 3D printer"

2.3.2 Printbed

A printbed is one of the most important parts of a 3D printer, it is the surface of a 3D printer where 3D objects are built. A printbed must be flat and smooth in order to form proportional layers. The size of a printbed may significantly vary and depends on the type of the printer. Figure 4 shows a heated printbed that some three-dimensional printers have either as standard or as an option. The printbed is utilized to avert breaking of prints as they cool and to make better attachment between the primary layers of the print and the printbed surface.

The material of the printbed may differ.

Typically, it is made from aluminium or glass in order to spread the warmth across space and to create a level surface. These materials have their own benefits, for instance:

“Glass provides the smoothest surface to print on while aluminum conducts heat better for a heated platform. To prevent the object from lifting off the surface in midprint, these surfaces are often covered in one kind of tape or another to provide a surface that is inexpensive to replace periodically. These materials include Kapton or polyimide tape, PET (polyethylene terephthalate) or polyester silicon tape, or even hardware store–variety blue painter’s tape, depending on the type of filament used.” (Evans 4).

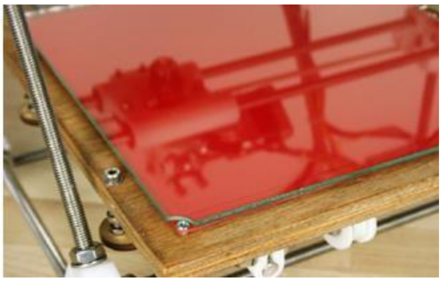

Figure 4. Heated printbed. Adopted from Evans (2012) “Practical 3D Printers”

2.3.3 Mechanical endsops

Figure 5 represents the mechanical endstops where the length of movement for every linear axis is limited. Endstops have switches that are able to control the movement. For instance, when the endstops reach a limit in direction, switches prevent motion by sending a command to the printer's controller electronics.

"*While endstops are not strictly needed for operation, having at the very least one endstop in the minimum position on each axis will allow the printer to home itself at the beginning of each print for repeatable and accurate prints every time."* (Evans 6).

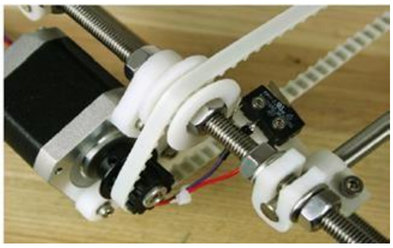

Figure 5. Mechanical endstops. Adopted from Evans (2012) "Practical 3D Printers"

2.3.4 Frame

The frame is responsible for holding everything together in the 3D printer. It forms the structural component of 3D printer and the ultimate precision of your printer depends on its material and construction. Various types of 3D printers have different designs of frames. One of them is "RepRap" style design that uses 3D-printed components along with threaded rod to manufacture the frame. On the other hand, another type of 3D printer model Box Bots, like the MakerBot or the MakerGear Mosaic, that is represented on the Figure 6 utilizes laser-cut plywood, the technology that bolts together the parts to make the frame.

A laser-cut plywood frame uses slot-and-tab construction, where two pieces of plywood are held together with tabs from one piece fitting into slots in the other, and connected with nuts and bolts. This is the most convenient and the easiest type of frame, allows assembling and offers better up-front accuracy so that printer calibration is accessible. The main disadvantages of these frames are loud noise during the operation, and lack of sustainability of screws, nuts and bolts.

"Some of the more recent printer designs are using commercial aluminum extrusions to build a frame that is rigid and easy to assemble, although it can cost as much as $100 to $200 more." (Evans 7).

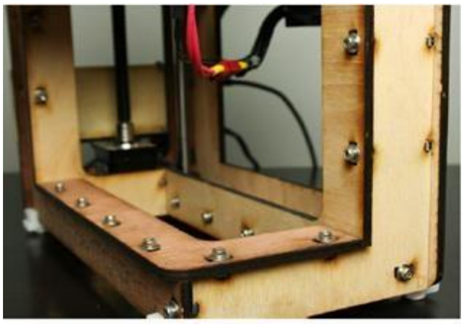

Figure 6. "MakerGear Mosaic" plywood frame. Adopted from Evans (2012) "Practical 3D Printers"

2.3.5 Cartesian robot

Fundamental role in a 3D printer is the Cartesian robot. It is a machine that moves in three dimensions, along the x-, y-, and z-axes. It is also known as the Cartesian coordinates. 3D printers can operate only with the assistance of small stepper motors that can move with great precision.

"All of the 3D printers use timing belts and pulleys along their x- and y-axes to provide fast yet accurate positioning, and most use threaded rod, or lead screws, to position the z-axis with even greater precision." (Evans 3).

Figure 7 represents the example of cartesian coordinate robot that numerically controlled by the computer software and arranges thermoplastic extruder along each of these linear axes layer upon layer.

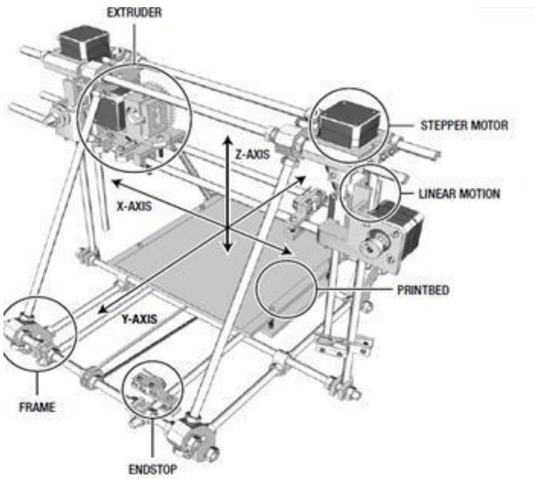

Figure 7. Basic structure of cartesian coordinate robot. Adopted from Evans (2012) "Practical 3D Printers"

2.4 Linear motion

The properties of 3D printers such as its accuracy, speed and sustainability often determine a type of linear motion system. Linear motion system or mechanical assembly which oblige individual axis to act for a 3D printer is fundamental to supply a smooth, flat and leveled motion of the payload for reproducing a real object from digital data.

"Most personal 3D printers use smooth, precision ground rods for each axis, and either plastic, bronze, or linear ball bearings to glide across each rod." (Evans 4).

Endurance and smooth operation of linear ball bearing systems earned a great reputation among the consumers. However, the main drawback of these systems is loud noise during operation. The Figure 8 illustrates self-aligning bronze bearings, that are definitely quieter than the ones described above. Self-aligning bronze bearings take a bit more work to align during the process of constructing objects.

Each type of linear motion system is unique and depends on the person's requirements. Normally, 3D printed bushings are inexpensive, but their longevity is low. Machined plastic bushings are likely to deform under heavier utilization, but its smoothness allows to operate properly for the slow-moving z-axis.

"On the other hand, the reliability of linear bearings discussed earlier depends on the quality of the smooth rails they ride on and they cost more. Other, more exotic materials, like felt, have also been tried with mixed results. Some printers even use industrial linear glides that have the potential for greater accuracy and longevity at increased cost and mechanical complexity." (Evans 5).

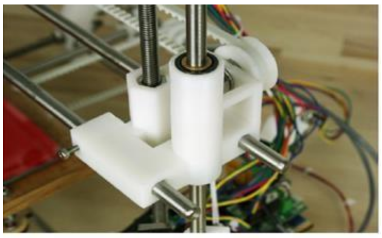

Figure 8. Self-aligning bronze bearings. Adopted from Evans (2012) "Practical 3D Printers"

In part it took a lot of hard work over the years to analyze what worked well and what didn't to end up with such outstanding printers today. Thanks to an open and sharing community, these designs and improvements have been shared freely, further improving the technology.

3 DIFFERENCE BETWEEN INDIVIDUAL TECHNOLOGIES AND THEIR ADVANTAGES AND DISADVANTAGES

There are numerous approaches to adding the material in an additive fashion. Each layer could be added to the first layer and then to the next layer till the object will be completely printed by dispensing the material with an extruder (fused filament), by using a chemical agent (binder) or a laser (sintering/melting), changing the state of the material. Each technique varies in the methods in which layers are formed and printing materials used. A comprehensive overview of different technologies is given below.

3.1 Resin-based systems

3.1.1 Stereolithography

Stereolithography (SLA) is the oldest method of 3D printing, that is used nowadays. The origins of conventional 3D printing traced back to the 20th century. In 1980 the first 3D printing stereolithography (SLA) technology was invented by Charles Hull. It was the first commercial 3D printing project that uses a laser to construct a various 3D objects within a tank of liquid photopolymer. In this method, UV laser beam scans the surface with the help of optical device which solidifies particular sectors on the space of the liquid over a chain reaction.

“Stereolithograpghy is an additive manufacturing process in which photons from an ultraviolet (UV) laser light source is targeted onto the surface of a photo-curable

liquid monomer bath and scanned in different patterns. The scanned monomers are sensitive to light, hence can be crosslinked by using a suitable light source. When exposed to photons these monomers harden to form the required 2D cross-sections, while the unexposed monomers remain unchanged in the bath." (Kalaskar 2).

After the first layer of the liquid resin is paved, the platform stage is lowered slightly, permitting the next layer of liquid to cover the now-solid planar portions. When the planar portions are done, the prototype is then post-cured in a regulated heating mechanism, or an ultraviolet curing apparatus, for a specified period of time, to allow final polymerization. A visual representation of the basic parts of the stereolithography machine is shown on the Figure 9.

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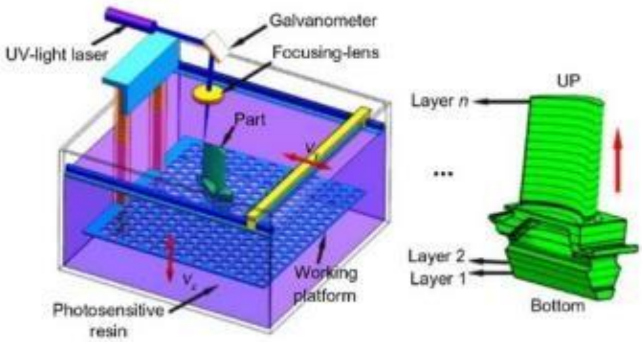

Figure 9. Basic parts of the stereolithography machine. Adopted from Kalaskar (2017) "3D printing in medicine"

"In SLA, control of the thickness of the cured layer is crucial for obtaining the optimal resolution. For a given resin, the cure depth is determined by the energy of the light to which the resin is exposed. This energy can be controlled by adjusting the power of the light source, and the scanning speed (for laser systems) or the exposure time (for projection systems)." (Kalaskar 25).

The Stereolithography constitutes as a “gold standard” for medical rapid prototyping applications and generally is a more efficient method for greater parts. By the way, it is significantly expensive and more labor intensive in relation to other 3D printing methods.

Another lack of SLA is the time, required to print objects. Obviously, it depends on size, for instance, a small object can be printed for about 5 hours, while large items amounting to several meters can be printed within two or three days. Usage of SLA technology brings a set of benefits such as high precision of product and quality of the parts, due to the high thinness of every layer applied in SLA, the objects are obtained with very complex shapes and great surface quality.

3.1.2 Microstereolithography

A better version of SLA method has been developed for completing layer thickness of less than 10μm and a faster fabrication speed is known as microstereolithography (MSL). *“With projection MSL, a dynamic pattern mask is created using a LCD (liquid crystal display) screen or DMD (digital micromirror device) chip and a light source shone through or across the mask onto the photopolymerizable resin, curing a patterned layer in a parallel fashion.” (Kalaskar 26).*

MSL has been used to construct microscale composite scaffolds containing hydroxyapatite nanopowder.

3.1.3 Digital light projection

Digital light projection (DLP) is a rapidly developing technology for the microfabrication of high resolution, dimensional patterned tissue engineering scaffolds. Larry Hornbeck invented simple and quick, layer-by-layer microstereolithography system that consists of an UV light source. A digital micromirror device (DMD), that allows the creation of comprehensive internal features along with an accurate spatial allocation of biological factors inside a single scaffold.

"*In this system, a digital micromirror device, an array of up to several millions of micromirrors that can be rotated independently to modulate the UV light and project an optical pattern, is used." (Kalaskar 26).*

The layer of resin can be cured only one time by designing a two-dimensional pixel model upon the transparent plate. In that case, the time spends to create objects are remarkably reduced, because it only depends on the thickness of the layer and exposure time, in contrast to their size in the XY-plane or on the number of structures being constructed at the same time. That technology widely used in bioprinting industry. Figure 10 illustrates a scheme of the DLP based bioprinter.

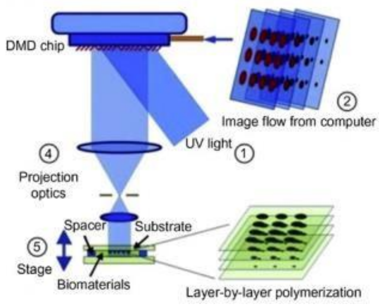

Figure 10. Schematic of the digital light projection based bioprinter.
Adopted from Kalaskar (2017) "3D printing in medicine"

3.2 Powder-based systems

3.2.1 Selective laser sintering

Selective laser sintering technology is based on powder process, that characterized by various complex features that include powders and binders, sintering, depowdering, and post- processing treatments. SLS was the first powder-based system announced several years after the SLA technology, contains a smooth powder bed of thermoplastic, metal or ceramic materials. The 3D object is being built using a high-power carbon dioxide laser beam, that scans the area of the powder bed in a particular 2D pattern, selectively sintering the powder particles in a layer by layer technique. Mechanical and structural properties of manufactured parts may have affected by other factors such as the properties of the material and operation features (laser energy density, temperature of bed, layer thickness). According to Kalaskar:

"The major advantages of the SLS technology is the ability to process about any material in a powdered form: polymers, metals, ceramics and including a variety of composite materials such as glass reinforced polymers, metal/polymer composite, metal/metal composites" (29).

Additionally, SLS does not involve the use of organic solvents and could be used to build intricate biphasic scaffold geometries at macro and micro scale. Due to such possibilities, numerous medical applications become possible starting with the fabrication of high- performance biomaterials to biodegradable polymers.

SLS technology is not perfect because of poor surface, dimensional precision and bad material characteristics, that do not meet the necessary requirements for industrial applications in terms of microstructure and mechanical strength.

Figure 11 demonstrates the scheme of the SLS process

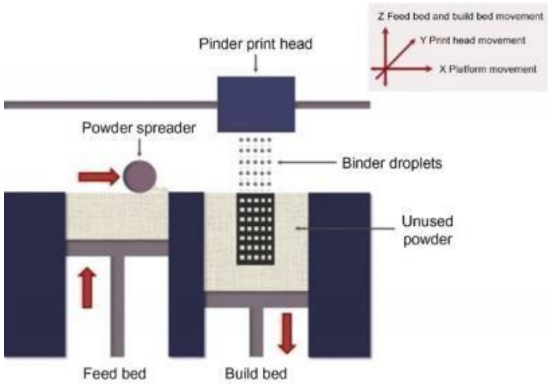

Figure 11. Scheme of the selective laser sintering process. Adopted from Kalaskar (2017) "3D printing in medicine"

3.2.2 Other powder-based technologies

There are some other powder-based technologies such as direct metal laser sintering (DMLS), selective laser melting (SLM), and direct laser forming (DLF), that use the same concept as SLS except that material is not sintered but melted.

The last powder-based system technology is electron beam melting (EBM) which differs from SLM only with the use of an electron beam instead of a high-power laser beam.

3.3 Extrusion-based system

One of the most popular system in recent years is the extrusion-based system since they are mechanically simple and profitable processes compared to other solid freeform fabrication methods.

3.3.1 Fused Deposition Modeling

Fused deposition modeling (FDM) is the most frequently used extrusion-based technology nowadays. A spool of thermoplastic filament that heated enough, feeds into a FDM extrusion head. The computer controlled head controls an exact outline of every cross-section layer of the part. As the head runs horizontally in x and y-axes, the thermoplastic material is extruded from the nozzle by a pump with high resolution. When the first layer is done, the extrusion head moves up a programmed range in z-axes direction, creating the next layer, which will connect to the previous layer through thermal heating.

Traditionally, the materials used in this technology are polycarbonate, acrylonitrile butadiene styrene, polyphenylsulfone, and others. Moreover, the range of the materials is increasing due to the possibility to form new materials in filament form. Various thermoplastic biomaterials can be used in filament as well, providing the opportunity of growth in the development of three-dimensional bioprinting. Another great benefit of this technology is that it is not necessary to use a toxic solvent and allows continuous inexpensive production without replacing feedstocks with high flexibility in material handling.

However, Kalaskar states that: *"Despite these benefits, the FDM technique includes restrictions in the input filament material properties and diametric size to feed it through the rollers and nozzle. Any changes in the properties of the material require a considerable effort to recalibrate the setting of the feeding parameters."* (31).

Also, the part fabricated by the FDM process has the dimensional inaccuracy compared to other additive techniques because of the variety of conflicting operation parameters. Figure 12 shows the scheme of the FDM extrusion and deposition process.

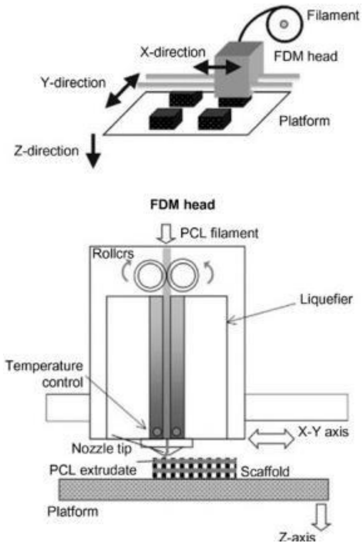

Figure 12. Scheme of the fused deposition modeling extrusion and deposition process. Adopted from Kalaskar (2017) "3D printing in medicine"

3.3.2 Multi Jet Modeling

Further extrusion-based system technology is MJS that was initially developed for manufacturing high density metallic and ceramic components using low melting point alloys or a powder-binder mixture. Dr. Kalaskar describes this process as following: *"The material is loaded in a form or powder, pellet or bar and heated in a process chamber above the melting point of the binder, thus liquefying only the binder during* *the process. At this stage, the heated paste is pushed out through a heated jet nozzle and deposited onto a computer-controlled build table.*" (31).

The main benefit of this technology is the capability of manufacture smooth and accurate components with highly comprehensive geometries at a relatively low-cost printer.

4 UTILIZATION OF 3D PRINTERS IN VARIOUS FIELDS

4.1 3D printing of food

Printing food is not a simple thing. It is complicated and resource-intensive technology because the whole food-extrusion chain has to be food-safe. Chocolate has similar properties as thermoplastics, other products can be extruded as a gel, and the other ones can be sprayed as a liquid using a “sprinkling” type of system. One of these three-dimensional devices was invented by the Dovetailed design studio in England. Figure 13 demonstrates a printer that is able to create a raspberry by the food piece droplet by droplet.

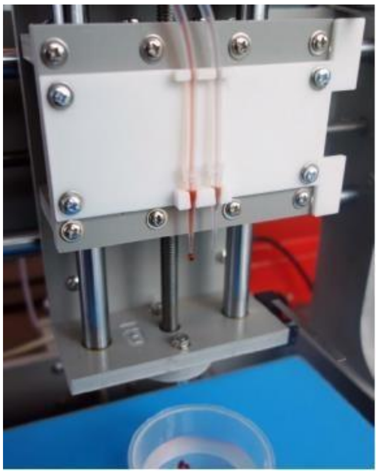

Figure 13. The “fruit” 3D printer. Adopted from Horvath (2014) “Mastering 3D printing”

"It takes tiny drops of a fruit juice mixed with a gelling solution like sodium alginate. This mix is dripped into a liquid solution to make thin-skinned droplets using a molecular gastronomy technique called spherification." (Horvath 179).

Despite the complexity of technology, there is a huge demand in printing pancakes, pizza, chocolate and lots of other types of foods.

4.2 3D printing in automotive industry

3D printing technology plays a very important role in the automotive industry and additive manufacturing is increasing with every new year in that sector.

According to 3D printing industry.com: *"The recent advances in additive manufacturing, allowing for newer designs, reduced lead times, and decreased costs, are already paving the way for novel ways of conceiving and producing motor vehicles.*"

Traditional manufacturing of complex rare parts in the automotive industry is very costly, compared to 3D printing technology, that is advantageous, inexpensive and efficient.

An extra benefit of the additive manufacturing process is that it provides greater design freedom if a component needs to handle multiple functions, for example, current or cooling.

3D printing industry.com states that *"Creating complex metal lattice structures with Selective Laser Melting (SLM), engineers on the FLAC project aim to reduce the weight of components of by decreasing their density. SLM technology could also improve their performance in contrast to traditional subtractive manufacturing processes. By structuring the* *components in layers, the process allows for more complex lattice structures, such as hollow ducts for airflow."* [16]

4.3 3D printing in aerospace

The aerospace industry is growing rapidly. Three-dimensional printing has a great impact on it. The aerospace industry includes a number of various departments that manufacture, research and maintain the aircraft. 3D printing is widely used in the airline industry for both manufacturing end-use parts and prototyping. Airlines depend on 3D printing to facilitate supply chain constraints and reduce the number of wasted materials from traditional manufacturing processes. Saving enormous amounts of space and minimizing the weight of different parts of aviation is a major aim of aerospace manufacturing companies because it economizes money, time, and affects an aircraft's payload as well as emissions and safety. Unfortunately, traditional methods cannot provide such benefits as 3D printing technology, that can create a part using fused deposition modeling from the base up layer-by-layer.

Blog trimech.com states that *"Adding the material rather than removing it, reduces waste during manufacturing. Air ducts, wall panels, seat frameworks and even engine components have all benefited from reduced weight enabled by 3D printing.*" [11] The technology has found a niche in aircraft manufacturing, for instance, the air company "Finnair" has used 3D printing for small-batch manufacturing.

4.4 3D printing in architecture industry

Architecture is one of the important and high demanded areas where 3D printing is making a big breakthrough. This cost-effective, developing technology will allow people to build cheap houses and various other unique buildings. Architecture often involves a lot of resources such as manpower, various complex equipment and complex designs of impressive structures. Three-dimensional printers help to build structures in the most effective way. 2D drawings do not illustrate much about how an end structure will be shown. That is why architects use artist's impressions and 3D models to illustrate their creations. Nowadays, thanks to the advancement of 3D printing technologies, this process has become and continues to get much simpler, cheaper and faster.

According to 3D insider.com: *"Australian researchers think this is going to bring a lot of unique advantages to housing markets around the world. There's still a lot of experimentation going on with building structures right now, but it's only a matter of time.*" [5]

5 3D PRINTING BIOMATERIALS

Recent and future development in 3D printing is useless without the preparation of new multifunctional, innovative materials that have to be compatible with the processing methods devised. The chapter mostly deals with the various 3D printed materials directly in clinical use and those under research for use in medicine for tissue repair, regeneration, and specific implants. Lots of different factors need to be considered in selecting materials such as material properties, host tissue response after implantation and compatibility.

The main requirement for the biomaterial is that they must be "bioinert" that means their wear and corrosion resistant as well as their favorable response from the host system.

5.1 Metals

Metals are broadly used in the manufacture of medical devices. Due to their durability and strength, they generally used to produce implants and fixtures to change injured or diseased tissue in load-bearing applications.

Figure 14 shows the example of titanium bone as an implant material, that is extensively used because of its extreme strength, biocompatibility and relative easiness of processing.

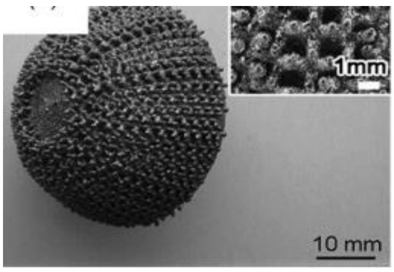

Figure 14. Photograph of additive manufactured bone scaffold from titanium. Adopted from Poologasundarampillai and Nommeots-Nomm (2017) "3D printing in medicine"

Due to these perfect characteristics, titanium has been 3D printed for utilization as porous implants for the repair of bone defects (Poologasundarampillai and Nommeots-Nomm 46).

Several different types of metals and their alloys that extensively used in 3D printing technology will be reviewed.

5.1.1 Titanium and its alloys

Titanium and its alloys are the prevalent options for additive manufacturing for durable implantation. According to Gowsihan Poologasundarampillai and Amy Nommeots-Nomm from University of Manchester and from University of Technology:

"Titanium readily passivates itself to form a thin oxide layer that makes it biocompatible as well as displaying osseointegration properties (the formation of a direct bond between bone and implant leading to permanent fixation of the implant within the implantation site)" (47).

Titanium is usually exploited in dental implants, femoral stems, knee replacement, pacemaker cans, heart valves, fracture plates, and spinal cages.

Implants which are fabricated from titanium are quite expensive because the process of obtainment such metal from its ore is laborious. However, AM technology is more economical compared to traditional methods.

5.1.2 Stainless steel and other metals

Another type of metal that extensively utilized in the medical industry is stainless steel. It is inexpensive, strong, durable, corrosion resistant biomaterial that is suitable for implants for load bearing applications. Nonetheless, the progress of stainless steel in additive manufacturing is very poor due to various difficulties associated with processing stainless steel powder.

5.1.3 Bio-ceramics and bioactive glasses

Bio-ceramics and bioactive glasses have a huge field of application in medicine, specifically for use in orthopedics. Unfortunately, the breakthrough has been quite slowed down because of strict protocols for reliability, reproducibility, and safety. However, the opportunities for creating degradable patient-specific implants with customizable porosity has resulted in 3D printing of bioactive elements.

5.1.4 Nondegradable bio-ceramics

The ceramic substance is frequently utilized within the body joint and bone applications.

Conventional ceramics are bioinert with such properties as toughness and great compressive strengths coupled with low coefficients of fiction that perfectly fit for hard tissue and joint repairs.

One of the excellent materials for joint replacement is the alumina. It can be used for ball and socket section in hip replacement.

There are several drawbacks such as poor fracture toughness, leading to implants suffering from premature failure. Nonetheless, thorough research has led to improvements and optimization of microstructure by reducing grain size and surface finish.

5.1.5 Polymers

Polymer materials have been utilized in the medical industry for decades. They are used either for degradable or nondegradable materials, stimulating a range of different responses.

There are several different 3D printing methods to formulate porous scaffolds – *"three-dimensional polymeric porous scaffolds with higher porosities and a homogeneous interconnected pore network are highly useful for tissue engineering."* (Grumezescu 246), based on melting or extrusion technique.

Gowsihan Poologasundarampillai and Amy Nommeots-Nomm state that:

"3D printing techniques have been utilized to formulate porous scaffolds by a variety of different methods, predominantly based on melt and solution extrusion techniques. The 3D printing process allows the inclusion of reinforcement materials, such as fibers and particulates, to enhance the mechanical properties. Hydroxyapatite, calcium phosphates, bioactive glasses have all been used to formulate composite scaffolds for biomedical applications." (56).

6 TYPES OF TECHNOLOGIES USED IN 3D PRINTING IN MEDICINE

6.1 Bioprinting techniques

The expansion of using such technology in every branch of industry has resulted in vast majority bioprinters in the medical field. At the present time, three-dimensional bioprinting is in demand in that field. Medical devices-network.com states that

"Rather than printing using plastic or metal, bioprinters use a computer-guided pipette to layer living cells, referred to as bio-ink, on top of one another to create artificial living tissue in a laboratory. These tissue constructs or organoids can be used for medical research as they mimic organs on a miniature scale. They are also being trialed as cheaper alternatives to human organ transplants." [9]

Medical laboratory Organovo based in the United States currently is experimenting with printing liver and intestinal tissue to help with the learning of organs in vitro, and with drug development for certain diseases. [9]

6.1.1 Laser-assisted bioprinting

One of the most innovative technology is laser-assisted bioprinting (LaB) technology. Shibu Chameettachal and Falguni Pati from Indian Institute of Technology, Hyderabad describe the idea of that technique as:

"A pulsed laser source, an absorption layer, and a substrate are present to position biological components and multiple cells directly onto an arbitrary surface, using laser beams. Prior to laser exposure, the absorption layer, which is transparent to the laser radiation wavelength, is coated with biological materials (bio-ink)

encapsulating the living cells or proteins. A focused laser beam is then exposed on the absorption layer to generate a high-pressure bubble that propels cell-containing materials toward the collector substrate" (123).

The absorption layer is the crucial element, that prevents direct interaction between the biological materials and laser. The main advantage of that technology is the ability to print small droplets with very high resolution. Moreover, it is possible to print high cell densities and highly viscous hydrogels. Currently, LaB is extensively used to print tissue constructs.

6.1.2 Inkjet-based bioprinting

Inkjet printers or drop-on-demand printers are the frequently utilized type of printer for biological applications. This is one of the great promising bio fabrication approaches. According to Chameettachal and Pati:

"It is a non-contact technique that prints the 3D constructs layer-by-layer by depositing controlled volumes of liquid or ink and delivering them to predefined locations on successive layers. It is a useful method for depositing proteins or multiple cells in very small droplets onto a previously targeted spatial position." (124).

The main benefits are very high throughput capability, high resolution, and simplicity of use. Notably, commercially accessible inkjet printers can be modified for printing cells and bioparticles.

Researchers from the Wake Forest Institute for Regenerative Medicine have modified inkjet technique to construct a difference of tissue and organ prototypes by classifying numerous cell types and other various tissue elements in predetermined locations with great accuracy.

“It has been shown that the substrate onto which the cell droplet is deposited should be soft enough to absorb the kinetic energy of droplets so that the impact force on cells is reduced substantially.” (Chameettachal and Pati 124).

There are several disadvantages of inkjet bioprinting technique. The material has to be in a liquid form to provide droplet formation. Therefore, the liquid must make a solid 3D structure with fundamental organization and functionality.

“This limitation could be addressed by using materials that can be crosslinked after printing using ultraviolet exposure, chemical. However, the requirement for crosslinking often slows the bioprinting process and involves chemical modification of naturally occurring ECM materials.” (Chameettachal and Pati 125).

Finally, users faced with the problem of complication in achieving relevant cell densities.

6.1.3 Extrusion-based bioprinting

Another concept for generating 3D tissues or organs is micro extrusion-based or simply extrusion bioprinting technologies, comprising a syringe, nozzle, and pressure system. This types of printer function by the use of robotically controlled extrusion of a component which is deposited onto a substrate by a head.

Chameettachal and Pati describe that technique as:

“Prior to printing with this technique, cells or proteins encapsulated in hydrogels, copolymers, or cell spheroids are loaded into sterilized syringes holding a micronozzle. As directed by the CAD software, beads of material are deposited in two dimensions; the stage or microextrusion head is moved along the z-axis, and the deposited layer serves as a foundation for the next layer.” (125).

The most accepted technique to extrude biological materials for 3D printing applications is the mechanical or pneumatic dispensing arrangement. The hydrogel allocated by air pressure or mechanized plunger onto the substrate in accordance with a customized design. One of the progress criteria of a tissue structure design is maintaining cell density with the physiological tissue. The main benefit of such technology is the opportunity to deposit very high cell densities. There are some drawbacks such as low print resolution and speed.

6.2 3D bioprinting in practice

6.2.1 3D bioprinting in vitro

One of the available methods to create a 3D form is to organize cells in a scaffold.

A scaffold is made from plastic and biodegradable materials and cells are added to it. Scaffolds are extensively exploited by scientists because of the simplicity of its structure and its good bioprintability. Nonetheless, there is a great challenge of designing blood vessels utilizing the scaffold-based technique. Dr. Gabor Forgacs developed new scaffold-free technology. The principle of operation is that cells encapsulated in the hydrogel and were used to create tissue blocks with unique geometric design to simulate the target tissue or organ. Dana Akilbekova and Damel Mektepbayeva from Nazarbayev University, Astana interpret this process as:

"They clustered cells into spheroids and glued them together using biopaper made from hydrogel to print 3D blood vessels. Experimental blood vessels have been bioprinted using bio ink spheroids comprised of an aggregate mix of endothelial, smooth muscle, and fibroblast cells. Once placed in position by the printing head, the

endothelial cells migrate to the inside of the printed blood vessel, the smooth muscle cells move to the middle, and the fibroblasts migrate to the outside.” (95).

Figure 15 demonstrates an example of a printed segment of the vascular tree, using the scaffold-free technology.

Figure 15. The printed segment of a vascular tree. Adopted from Akilbekova and Mektepbayeva (2017) “3D printing in medicine”

And last but not least possibility of 3D bioprinting to build complex geometry by printing a human artificial ear. The operation starts with sketching and printing the mold, adding the collagen gel and bovine auricular chondrocytes. The process is ending with trimming and incubating the ear. (Akilbekova and Mektepbayeva 97).

6.2.2 In situ 3D bioprinting directly to defect site

Despite huge 3D printing technology progress, recreating a completely functional organ with an elementary structure is still a challenge.

A new way of printing massive vascularized organs via direct in situ printing to the defect site was invented by Weiss in 2007. The idea was to use a new inkjet printing technology. The authors exploit 3D printing of stem cells to treat full-thickness skin wounds in mice. Akilbekova and Mektepbayeva describe this process as: *“Several layers of fibrinogen/collagen and thrombin were deposited and then equal amount of* *bio inks were printed per wound. Additionally, control wounds were treated with only gel. Wound closure, re-epithelization, and blood vessels density notably increased for cell treated wounds compared to the only gel treated wound"* (98).

Moreover, scientists used laser-assisted 3D printing technology to recover mouse calvarial defect of critical size in situ. In 3D bioprinting system for an in situ printing procedure thirty 12 week-old male mice with 4mm wide calvaria bone defects were placed. Layer by layer nanohydroxyapatite material was deposed to the wound site. This operation was successful and most of the mice recovered without inflammation and other defects. Later, defect sites were tested with x-ray microtomography and results indicated mature bone tissue in sites.

However, that technique can be also applied to larger calvarial and craniofacial damages but requires appropriate vascularization and structural support.

Despite the fact that in situ 3D bioprinting is only tested in mice, hopefully, in near future it can work on humans leading to great possibilities. Akilbekova and Mektepbayeva defines several advantages of such technology:

"Scaffolds will be printed directly into the defect site and therefore avoiding the time-consuming stage of scaffold preparation and the risks related to contamination. Stem cells will be printed in situ, and will be exposed to the natural environment and therefore can differentiate into required cell lineage without any in vitro manipulations. Additionally, in situ printing provides better control over standard or unexpected defects during the surgery." (102).

6.3 Patient specific medical devices

Due to the fast development of 3D printing technology, the enormous variety of customized implants has become the reality and the only way out for patients.

Traditionally, medical devices and services are not available to every patient or and are very expensive. Any medical product requires several clinical tests and approvals and there is no guarantee that it will be suitable for patients. Furthermore, it can take a very long time to produce implants, while 3D printing technology requires a few hours for the even better quality implants.

Prosthetics is the major product application of 3D printing. Using a Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) prosthetic limbs of any complexity can be printed within a day. Patients with diseases of the musculoskeletal system have a great promise because of prosthetics technology which allows printing huge, patient individual bone constructs and implants that integrate into the surrounding bone and include collagenous matrix elements. Inkjet-based printing and laser-induced forward transfer technologies make possible to print osteogenic cells and hydrogels.

Customized scaffolds, that mimic the growth of new bone tissue were developed by a group of scientists from Washington State University. Theoretically, that technology might be exploited in dental work and give a promise for patients who need medicine for treating osteoporosis. (Akilbekova and Mektepbayeva 102-103).

Patient's skull can be substituted by printed cranial implants and can be customized according to the patient CT or MRI scan. Moreover, there is a possibility of producing plastic implants that will have several advantages compared to traditionally-used implants. This is an essential aspect because it saves time and money for patients and decrease the risk of infection and brain damage.

Making personalized dental implants is definitely one of the earliest medical application of the 3D printing technology that generally used for the preparation of rapid prototypes, trial restorations, and dental crowns. Traditional method “subtractive process” has its own shortcomings such as low precision, the opportunity of introducing tiny cracks and waste of the raw material. Additive manufacturing technology can significantly enhance the speed and quality of dental prostheses preparation process.

Figure 16 illustrates the process of titanium implant placement.

Figure 16. Implant placement. Adopted from Akilbekova and Mektepbayeva (2017) “3D printing in medicine”

7 FUTURE OF 3D PRINTING

This chapter aimed to describe the probable future of 3D printing technology, its influence on people's lives and the search for new applications. In fact, a 3D printer is a real multifunctional factory, small and compact. At the expense of it, the future of 3D printing quite definitely can be prosperous.

7.1 Pharmacy

Recently, 3D printing technology allows creating personal pills and medicines by printing them on a three-dimensional printer. Such pills and medicines can gradually improve the effectiveness of traditional medicines because they have special dosage dispensers for certain doses of medicine or slowly soluble capsules that gradually inject the right amount of medicine into the body. This approach will save patients from having to calculate their own portion of the medicine. According to all3dp.com:

"This could include integrating multiple patient-specific drugs into a single form as well as adjusting the rates at which various medications dissolve." [14]

An interesting form of the capsule will be interesting for children who often do not want to take medicines. Your task will only be to make sure that the child does not get carried away with the process and does not eat too many treatment capsules at once. This problem can also be solved with the help of a special safe dispenser for medicines, which gives out a certain income at a time and does it clearly at a given time of day, issuing the appropriate reminder signal. [12]

Figure 17 illustrates the example of pills with an image produced with the help of 3D printing technology.

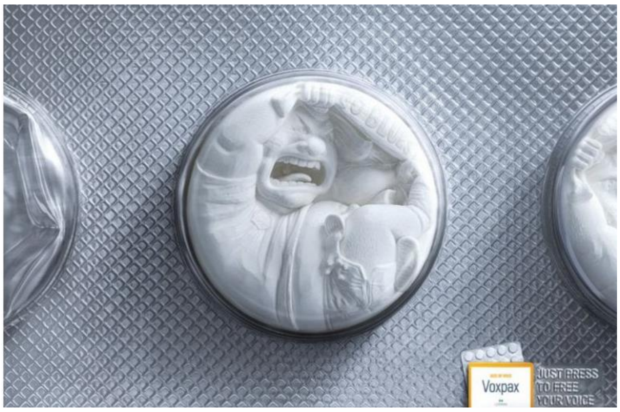

Figure 17. 3D printed pill. Adopted from lifeglobe.net

7.2 4D printing

4D printing basically is an evolution of 3D printing technology. 3D printing implies creating objects in one particular shape, while 4D printing technology uses unique materials that can change their shape depending on special conditions. According to tektonikamag.com: *"The key difference is that the 4D printing process uses a special material that can also be programmed to self-assemble and change its shape later on upon encountering heat, ice, water, movement, pressure, or a certain type of chemical."* [13]

Application for 4D printing is tremendously thrilling for example underground pipes that can "repair" themselves, after detecting a leakage or 4D print bricks that can modify itself to accommodate more or less stress on the wall.

Such technology is still in development by a group of researchers from MIT university, 3D printing manufacturer Stratasys, and 3D software company Autodesk. [15]

Figure 18 demonstrates the example of 4D printing material

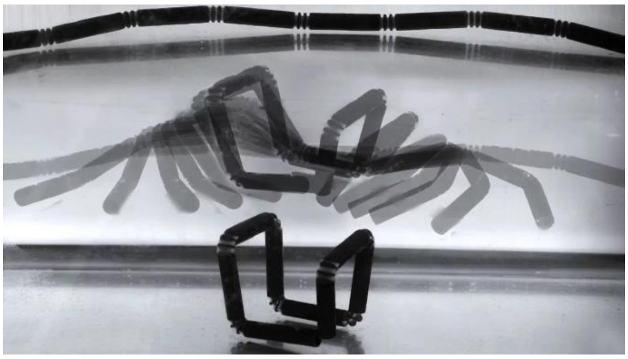

Figure 18. 4D printing experiment from MIT. Adopted from all3dp.com

Tektonikamag.com states that: *"4D printing still is a bleeding edge technology. 4D printers and the materials they use are expensive, so it'll be a while before the world begins welcoming 4D-printed objects into offices and homes en masse."* [13]

8 CONCLUSION

In conclusion, it should be mentioned that three-dimensional printing technology is getting more demanded by people from various fields and industries. 3D printing is getting cheaper and develops new ideas for printing different products. It's very exciting to imagine how the 3D printing will affect people's lives. It is possible to say with certainty that in a few years there will be great changes in people's lives. Perhaps the 3D printing of organs and tissues will help to prolong the life of many people. Many diseases such as cancer can be defeated by literally replacing the affected organ with a new one printed with the help of 3D printer. Thanks to this technology, human development will increase several times and the goals that could be achieved in hundreds of years will be achieved within a decade. In the nearest future, almost every single product will be printed using that technology. Every family will have a 3D printer and it will be a major and integral part of household appliances.

The aim of that bachelor’s thesis was to examine the parts of 3D printer, its principle of operation and how it utilized in medicine. The thesis is divided into 2 main parts - theoretical and practical one. The first part describes the parts of the printer and its operation as well as differences between individual technologies, its advantages and disadvantages. The first, most popular as well as the latest technology developments are described from industrial, operational advantageous and disadvantageous point of view. The practical part is considered from the point of view of the possibility of using printers in various fields, including medicine.

9 LIST OF FIGURES

10 LIST OF ABBREVIATIONS

3D – Three-dimensional

SLA – Stereolithography

SLS - Selective laser sintering

FDM - Fused deposition modeling

MSL - Microstereolithography

DLP - Digital light projection

MJM - Multi Jet Modeling

UV – Ultraviolet

CAD - Computer-Aided Design

FFF - Fused Filament Fabrication

PET - Polyethylene terephthalate

LCD - Liquid crystal display

DMD - Digital micromirror device

DMLS - Direct metal laser sintering

DLF - Direct laser forming

SLM - Selective laser melting

EBM - Electron beam melting

AM – Additive manufacturing

LaB - Laser-assisted bioprinting

MRI - Magnetic Resonance Imaging

CT - Computerized Tomography

MIT - Massachusetts Institute of Technology

4D – Four-dimensional

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