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TECHNOLOGIES OF ADDITIVE MANUFACTURING APPLIED IN THE MEDICAL FIELD

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This chapter gives an overview of the Additive Manufacturing concept, the general categories of technologies according to the standard classification, and the most typical technologies in the medical field, both for the production of prostheses, scaffolds, and pre-clinical evaluation and training.

Contents

1.1. Introduction to Additive Manufacturing technologies. General classification

According to 'ISO ISO/ASTM 52900:2015 Additive manufacturing — General principles — Terminology' [1], Additive Manufacturing (AM) is the process of joining materials, usually layer upon layer, to make parts from digital data (3D model). This manufacturing concept, colloquially known as 3D printing, differs from the traditional subtractive manufacturing, which is based on the removal of material (e.g. machining processes), or formative manufacturing methodologies, which consist in causing the plastic deformation of the material (plastics or metals) into the desired shape by applying stresses and, in some cases, temperature (e.g. injection molding, rotomoulding, forming processes, bending, etc.). These conventional processes require specific tools (molds, cutting tools, etc.) which hinder or constraint the manufacturing process in terms of design freedom. Additionally, in the case of short productions, the initial investment needed for these tools leads to expensive unit costs and, in some cases, long manufacturing times due to the production of these. However, the layer-upon-layer concept that characterizes AM has the advantage of not needing these tools or molds, making it more competitive especially for short production runs or complex geometries. Therefore, AM technologies stand out compared to traditional manufacturing process due to the possibilities in terms of design freedom/customization and reduced production time and manufacturing costs for short runs due to the avoidance of additional tools.

Despite these clear advantages and possibilities, AM commercially emerged in 1987, thus being a relatively new manufacturing concept, especially when compared with other conventional processes. In 1951, Munz proposed the first AM technology, which was based on layers of photopolymer that were selectively hardened according to the cross-section by a piston mechanism. Since then, different proposals were published such as the use of a laser to carry out the photopolymerization (1968), the earliest powder laser sintering process (1981), and, about the same time, the earliest AM system that used a computer to control the laser for the polymerization of the photopolymer [2]. However, the first AM equipment was formally

invented in 1986: StereoLithography Apparatus (SLA) and commercialized in 1987, which is considered the year of the birth of AM. This equipment consists in the photopolymerization of a thin layer of light-sensitive liquid polymer (photopolymer) by the application of a laser ultraviolet light. In 1991, several new AM concepts were launched to the market, being fused deposition modeling (FDM, from Stratasys) and laminated object manufacturing (LOM, from Helisys) the most innovative. In the case of FDM, a thermoplastic material in filament format is melted/extruded and deposited/solidified layer by layer to make the part. Although FDM was the name of the specific machine of Stratasys, nowadays this concept is still used when referring to material extrusion AM. Regarding LOM technology, the material, in the form of sheets, is bonded (adhesive coating) and cut by a laser. Later on, Selective Laser Sintering (SLS), which uses the heat of a laser to fuse a powder bed, was commercially available in 1992. Many different technologies have been patented and launched since then, contributing to the development and spreading of AM technologies. Additionally, the expiration of important patents such as the most critical ones related to FDM caused an exponential expansion of material extrusion-based machines with low prices [3], affordable even for private users. As a consequence, nowadays there is an important community of private users that has broadened the knowledge and advantages of AM.

Nowadays, there are several AM technologies, both for polymers, metals, ceramics or even composite feedstock. In order to have a standard classification, ISO/ASTM launched in 2015 the standard 'ISO/ASTM 52900:2015 Additive manufacturing — General principles — Terminology' [1], which classifies the existing technologies into 7 categories. The following subsections describe each one of these categories.

1.1.1. VAT photopolymerization

VAT photopolymerization (VPP) is an Additive Manufacturing process in which a photopolymer liquid is selectively cured in a vat by light-activated polymerization (ultraviolet photopolymerization). Figure 1 shows the principle of functioning of these technologies. The build platform, initially on the top of the vat, is submerged in the

photopolymer liquid until a thin layer of liquid (according to the selected layer height) is on the platform. Then, the laser (in the case of SLA) sweeps the desired section and cures the material according to the 3D data. Once the layer has been photopolymerized, the platforms goes down, placing an additional thin layer of liquid on the platform to repeat the process.
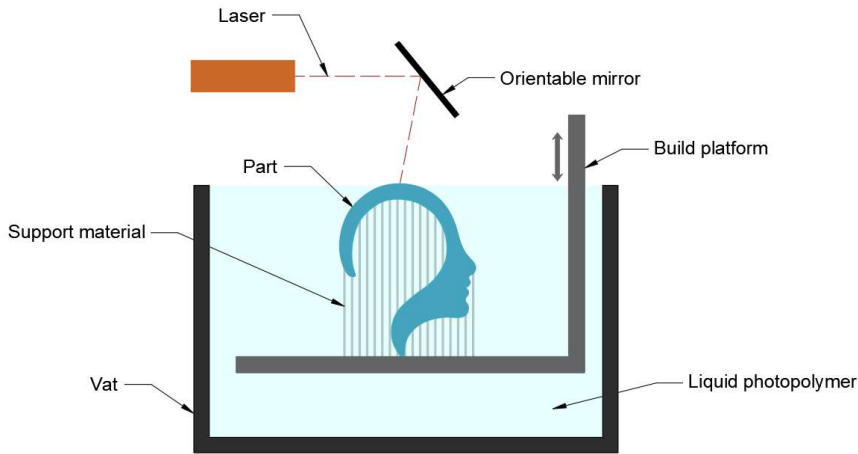
Figure 1. Vat photopolymerization scheme (stereolithography, SLA).

Within this category, there are two main technologies: stereolithography (SLA), which uses a laser that sweeps the desired section oriented by a mirror, and Digital Light Processing (DLP), which uses a light projector to cure the complete section at once. This second option is represented in Figure 2. Usually, the light projector is placed on the bottom and the part is built from the bottom to the top of the vat, thus being hanging from the build platform, which moves from the bottom to the top.
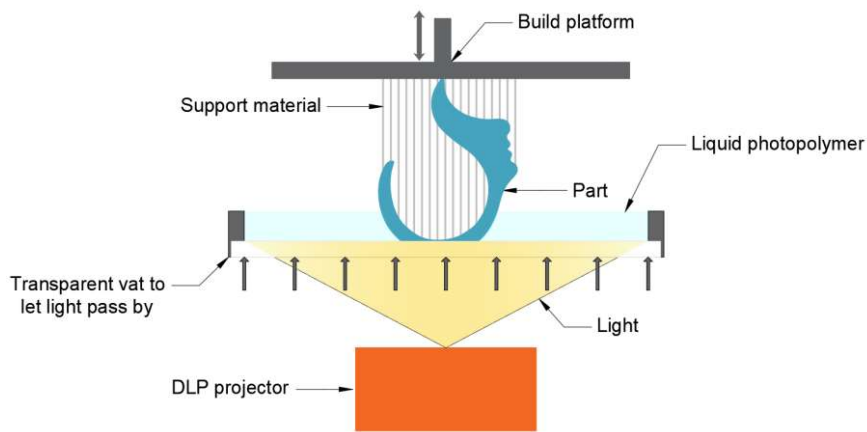
Figure 2. Vat photopolymerization scheme (Digital Light Processing, DLP).

Depending on the manufacturing configuration, this category is also divided into three different types.

The first one is the 'bottom-up printing' (according to the movement of the build platform), in which the liquid is cured through a window placed in the bottom of the vat by a light source (as depicted in Figure 2). The build platform is raised out of the resin vat and a 'peel' step is required to detach the last cured layer from the bottom of the vat. This 'peel' step is by far the slowest stage, thus being the bottle neck of the process. However, this configuration uses less resin, which means smaller vats (less material) and consequently smaller printers with fewer mechanical parts. Several printers such as Projet 1200 (Figure 3), Formlabs Form2, Envisiontec Vida or Structo Orthoform use this configuration, being the most typical due to these advantages.

Figure 3. ProJet 1200, vat photopolymerization machine with DLP technology and 'bottom-up printing'.

The second type is the 'top-down printing'. In this case, the resin is cured by using a light source placed above the vat. Therefore, the build platform is lowered down into the liquid photopolymer during the process, as depicted in Figure 1. The 'top-down printing' has the advantage of using a continuous light exposure to polymerize the photopolymer. As a consequence, the alternating light exposures and 'peel' steps are avoided and the printing speed is considerably improved, especially due to the avoidance of the 'peel' step. For this reason, this configuration is preferred for industrial printers where the speed is more important (e.g. Juell Flash OC).

The third configuration is the 'Continuous Liquid Interface Production (CLIP)'. In this configuration, the liquid photopolymer is cured through an oxygen permeable window (placed on the bottom of the vat) by a light source from below. This oxygen layer avoids the sticking of the resin to the vat and, consequently, the 'peel' step is not needed. As a result, a continuous light exposure can be used, thus improving the printing speed. Therefore, this configuration is similar to

the 'bottom-up printing' but with the advantage of not needing the 'peel' step, which leads to similar speeds to the 'top-down printing'. However, this configuration is more expensive. One example of this configuration is the Carbon M1.

1.1.2. Material jetting

Material Jetting (MJT) is an AM process in which droplets of build material (photopolymer) are selectively deposited and cured immediately by ultraviolet light. This concept is similar to a two dimensional ink jet printer, but in 3D. The material is jetted onto a build platform from a nozzle. This nozzle moves horizontally on the build platform. The material layers are then polymerized using ultraviolet light. Figure 4 shows the functioning scheme of material jetting technologies.
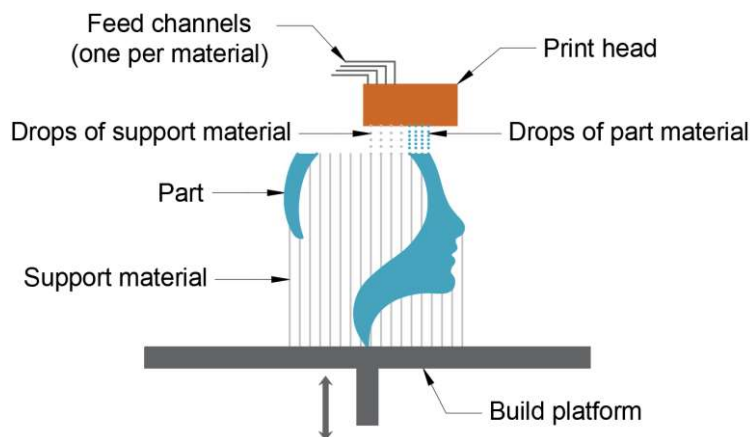

Figure 4. Material jetting scheme.

Within this category, there are two main nozzle configurations: the inkjet printing, which applies a continuous stream of material (jet of material), and the 'Drop on Demand' (DOD), in which droplets are dispensed only when needed, thus being more accurate and using less material, but also with lower printing speeds.

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On the other hand, these technologies are characterized by needing support material in all the cantilever areas. However, the support material can be removed using a sodium hydroxide solution or water jet.

Additionally, material jetting technologies can print with two different configurations: matte or glossy. The matte setting will add a thin layer of support to the entire part. This provides more accuracy and uniform finish to the part (matte), but uses more material, requires more cleaning post-processing and the surface is softer. The glossy setting, otherwise, will only use support material when necessary (cantilever areas). This setting leads to higher strength on thin walls, material reduction and gives a smoother finish. However, the finish is not uniform throughout the part (the zones requiring support material will have a matte finish, while the other ones will be glossy) and small rounding are obtained at sharp corners on the top surfaces.

Polymers and waxes are the commonly used materials due to their viscous nature and ability to form drops.

1.1.3. Binder jetting

Binder Jetting (BJT) is an AM process in which a liquid bonding agent is selectively deposited to join powder materials. The binder (usually in liquid form) acts as an adhesive between the layers of the build material (in powder form). The print head moves horizontally (x-y axes) to deposit the binding material (sometimes together with colored ink to obtain different colors) on the build material. After each layer, the build platform is lowered down and a new layer is added to continue the process (Figure 5). It is a fast process even though it requires a certain cooling time for the binder to solidify. However, a porous surface finish and slow post-processing are typical due to the powder format of the build material.
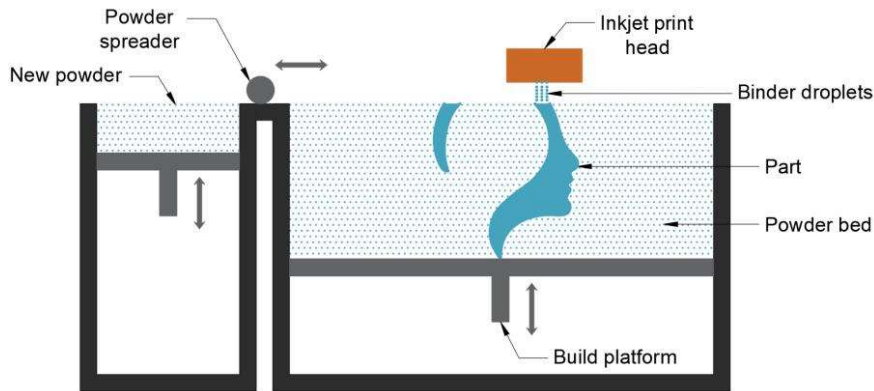
Figure 5. Binder jetting scheme.

Due to the binding method, the resulting 3D printed objects are not always suitable for structural parts. On the other hand, despite the relative speed of printing, the additional post processing required (powder removal and powder conditioning for the subsequent run) can add significant time to the overall process. The main advantage of this category is that the powder bed acts as a self-supporting structure, which allows adding complex parts in the build volume, as well as using different materials.

Additionally, apart from full-color parts, this technology allows the use of metal powder to obtain metal parts. The resulting 3D printed parts (usually known as 'green parts') are very brittle (metal powder joined by the binder) and subsequent steps such as infiltration or sintering are required to improve the mechanical properties. Both in the infiltration and sintering postprocesses, high temperatures are used to burn the binder. However, in the infiltration process, bronze infiltration is carried out by the capillary action of the melted metal, while in the sintering process, the high temperature sinters the metal particles, causing an important shrinkage (around 20 %). As the resulting parts are not 100 % dense (approximately 90% in the case of infiltration and 97 % for sintering), their mechanical properties are also limited, especially for dynamic conditions in which the voids can lead

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to crack initiation and failure by fatigue. However, this process can be less expensive than other technologies for metal parts production.

1.1.4. Material Extrusion

Material Extrusion (MEX) is the AM process in which material is selectively dispensed through a nozzle or orifice. Usually, this process starts with the stock material (thermoplastic or composite material with thermoplastic matrix) in filament format (spools). The most common diameter is 1.75 mm, although 2.85 and 3 mm are also possible. The use of pellets as stock material is also possible in some technologies with screw extruders, but the deposition speed is reduced and the flow is less stable, thus leading to more defects on the deposited filament. In the most typical case, an extrusion mechanism feeds the filament into the hot end, where the filament is heated by electrical resistances and melted. The filament that is being introduced to the hot end pushes the melted material out the nozzle tip, thus depositing new material on the last deposited layer (Figure 6). The extruded filament, in a melting state, sticks to the to the previous layer (or build platform) and solidifies after a certain time. Once the entire layer has been deposited, the build platform is lowered down and the process is repeated again.
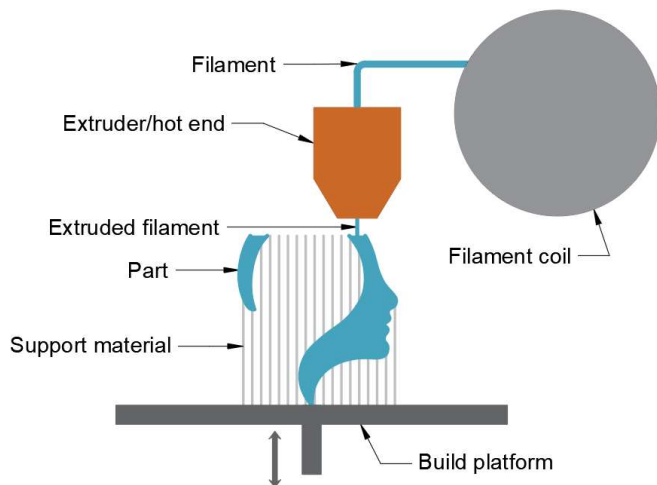
Figure 6. Material extrusion scheme.

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The most common diameter of nozzle tip is 0.4 mm, but other diameters from 0.1 to 0.8 mm can be found. This value has a great influence on the speed of the process, as the layer height must be lower than the diameter to guarantee a good bonding between layers (Figure 7). As a consequence, in general, the higher the diameter of the nozzle tip, the lower the printing time. However, the accuracy of the deposited part is also dependent on the nozzle tip diameter (smaller nozzle tips lead to higher accuracy). Additionally, thicker layers can have a negative effect on the finishing of the part, as the layers can be easily noticeable, especially in near horizontal surfaces.

Poor bonding ————▶   ◀——— Good bonding

Figure 7. Bonding of layers. On the left, poor bonding due to too high layer height. On the right, good bonding.

This technology is also characterized by having a high anisotropy behavior due to the reduced properties in the printing direction (Z axis). The mechanical properties of the bonding between layers are usually lower than the corresponding to the deposited filaments (XY plane). This effect is typical in any other AM technologies, but in the case of MEX category the level of anisotropy is considerable.

On the other hand, some MEX printers have a heated bed or even chamber to control the environment temperature. This characteristic is crucial to avoid the warping effect (Figure 8), especially in materials with high coefficient of thermal expansion and high processing temperatures. When the upper layers solidify and cool down, the associated shrinking pulls the lower layers, producing delamination or, most commonly, detaching the corners of the first layer from the build platform. This can ruin the printing in some cases, as the corners of the part are distorted and the nozzle tip may collide with them and completely detach the part. The warping defect can be reduced by

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homogenizing the temperature between layers through a controlled bed temperature and, in some industrial machines, a controlled environment temperature. In the case of 3D printers without heated bed, the common practice to reduce the warping is the use of brims [4], which are an extension of the cross section of the fist layer to increase the contact surface between the first layer and the build platform, thus enhancing the adherence. However, additional postprocessing is required (removal of the brim to obtain the desired geometry).
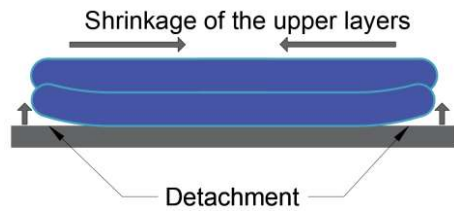
Figure 8. Warping defect.

This category of AM has become the most used technology for private users due to the emergence of low cost manufacturers of this type of 3D printers (Figure 9). As the initial patent was Fused Deposition Modeling (FDM), these 3D printers are also named as FDM technologies, referring to MEX AM equipment.
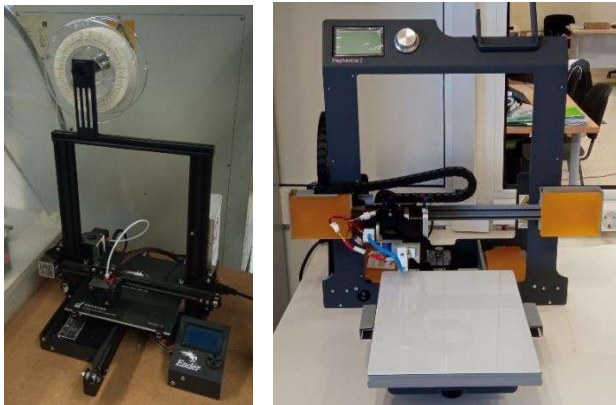
Figure 9. Low-cost MEX 3D printers (left: Creality Ender 3; right: BQ Hephestos 2).

Apart from the typical thermoplastic extrusion AM equipment, there are other AM technologies also based on extrusion but working with other materials and applications. This is the case of bioplotters or bioprinters (Figure 10), 3D printers that allow working with biomaterials and cells, in sterile environments, for AM applied in tissue engineering and tissue biofabrication. These technologies usually have several type of printheads, which allow the manufacturing of multi-material parts. Among the type of printheads, there are 2 main groups: the specific ones for hydrogels (viscous fluids that are extruded by pneumatic and mechanical mechanisms), and the specific ones for depositing thermoplastic materials (also based in the feeding, melting and extrusion of the material).

Figure 10. Bioplotter (Bio X, Cellink).

Finally, there is another group of innovative AM technologies that use an extrusion process to produce the parts: Atomic Diffusion Additive Manufacturing (ADAM) [5]. ADAM is based on a MEX AM process but using a filament with metal powder embedded in a thermoplastic matrix. The initial step of ADAM is the same as in a conventional MEX 3D printer, but obtaining a composite part with metal powder inside (also called 'green part', as in binder jetting with

metal powder). After this, the green part is submerged in a liquid (debinder) to remove almost all the plastic matrix, thus obtaining a porous part. Finally, the part is subjected to a sintering process in a high temperature oven where the remaining binder is burnt out and the metal powder is sintered to achieve an almost fully-dense part (approximately 1% of porosity). Therefore, ADAM technology allows the manufacturing of 3D printed metal parts with very competitive cost compared to metal Powder Bed Fusion AM technologies.

1.1.5. Powder bed fusion

Powder bed fusion (PBF) is an AM process in which thermal energy selectively fuses regions of a powder bed. For this to happen, a thin layer of powder material is spread by a powder spreader system on the build platform (this step is considered the most time consuming of the entire process). After that, an energy source (usually a laser beam, although it depends on the technology) sweeps the section of the part, sintering the powder particles and joining them together. Once the layer has been sintered, the build platform is lowered down and the process is repeated again until the part is completely manufactured (Figure 11).
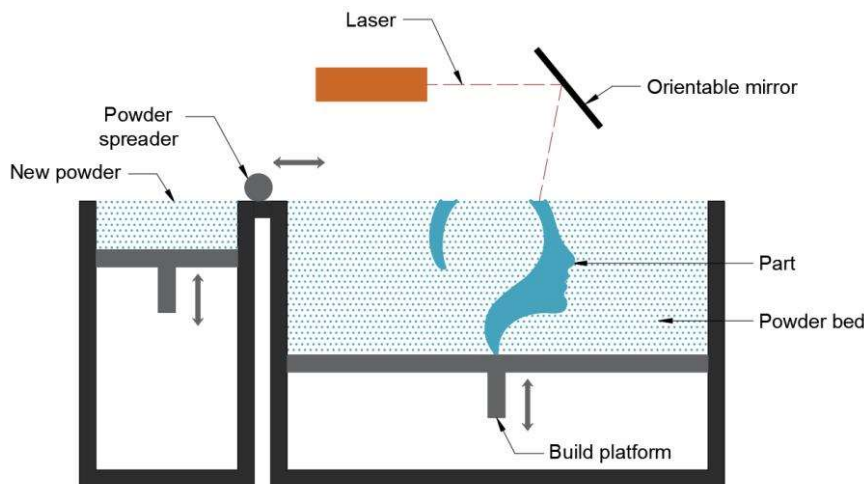
Figure 11. Powder bed fusion scheme.

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As in the category of binder jetting, powder bed fusion stands out due to the use of a powder bed that acts as a self-supporting structure for the part. For this reason, support material is not usually required, except in metal technologies where the energy to join the particles is so high that the powder itself is not enough to support it. Moreover, the high temperature gradients of these metal processes are also critical for the warping effect. For this reason, support structures are not only useful to withstand the energy of the process, but also to cool down the printing area and attach the new layer to a solid base. As a consequence, in metal technologies the general rule is to add support structures in walls with less than 45° with respect to the horizontal plane. However, in the case of plastic technologies of this category, support structures are not needed and it is possible to allocate parts all over the build volume without the use of support material. This possibility is also very powerful for the production of assembled parts. The non-sintered powder acts as a support and separation element between the different components of the assembly. Once the manufacturing is finished, the powder is removed in the postprocessing step, obtaining the final assembly. As a result, no assembly steps are required.

Depending on the energy source and material type, different PBF technologies can be found. In the case of thermoplastic materials (and thermoplastic composites), the most common technology is the Selective Laser Sintering (SLS) (Figure 12). In this case, a thermoplastic is spread on the build platform and a laser sinters together the particles. In order to speed up the process, the environment is preheated, so that the laser only provides the additional energy required to sinter the particles.

Figure 12. First Selective Laser Sintering machine with desktop format (Sinterit Lisa Pro). Left: sandblaster unit for post-processing. Middle: 3D printer with optional nitrogen atmosphere. Right: sieving unit for material preprocessing (mixing of virgin and reused material and sieving).

In the case of metal powder, there are three main technologies: Direct Metal Laser Sintering (DMLS), Selective Laser Melting (SLM) and Electron Beam Melting (EBM). DMLS is similar to SLS since the particles are sintered, but not completely melted. However, in the case of SLM, the particles are completely fused as the energy source is more powerful (leading to lower porosity parts). Moreover, an inert atmosphere is required to avoid the oxidation and reaction of the melted powder with the environment gases. Finally, EBM has a similar concept to SLM as it melts the particles, but the energy source is an electron beam instead of a laser. The main characteristic of this technology is that the surface is usually rougher compared to the previous ones. This could an advantage for some specific applications (e.g. cell attachment in the case of internal prostheses for tissue regeneration), but also a limitation for other applications and for the strength under fatigue loads.

Apart from the aforementioned technologies, there is another technique called Multi Jet Fusion (MJF) in which the fusion of the

powder is triggered by the jetting of fusing agents and the application of an energy source. This energy produces the reaction between the fusing agent and the powder bed, causing the selective melting of the material. Additionally, detailing agents are also jetted around the contours to produce accurate details and obtain smooth surface finishing.

On the other hand, it is important to note that the characteristics required in PBF powders (e.g. particle size distribution) make them expensive, especially in the case of metal materials. For this reason, one of the main design rules for these technologies is to optimize the use of powder by allocating as many parts as possible in the printing volume. The non-sintered powder can be reutilized but, as it has received a thermal cycle during the PBF process, it must be refreshed with around 30-50% of new powder (otherwise, the printed part will have lower mechanical properties). This means that the powder removal must be done very carefully to reutilize as much material as possible. Moreover, the recycled material must be blended and sieved with the new powder to be in good conditions for the following printing. All these steps are very time consuming and require manual work, which is one of the main limitations of these technologies. Apart from this, the working conditions must be appropriate and with the correct personal protective equipment as handling so small powder particles implies certain health risks.

1.1.6. Sheet Lamination

Sheet Lamination (SHL) is an AM process in which sheets of material are bonded to form a part. This process in summarized in Figure 13. A spool of material is fed into the build platform and glued to the build platform or previous layer by using compression or welding. Then, each layer is cut by a laser or cutting tool according to the desired cross section of the 3D model. Once the layer is finished, the build platform is lowered and the material spool is fed again, repeating the process and making the part layer by layer. This process is fast and low cost, but it is limited to sheet format materials and requires postprocessing to obtain the final part.

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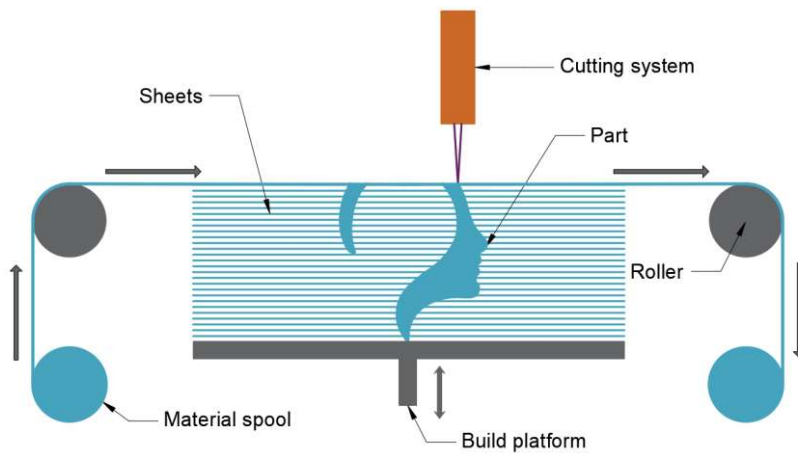
Figure 13. Sheet lamination scheme.

Within this category, there are two main technologies: Laminated Object Manufacturing (LOM) and Ultrasonic Additive Manufacturing (UAM). LOM uses adhesive paper (in sheet format) that is glued by compression and cut by a laser. In the case of UAM, metal alloy sheets (mainly of aluminum, copper, stainless steel or titanium) are used and joined by ultrasonic welding.

1.1.7. Directed Energy Deposition

Directed Energy Deposition (DED) is an AM process in which a thermal energy source such as a laser, electron beam, or plasma arc, is used to melt materials at the same time they are being deposited on the substrate (part or build platform) (Figure 14). The technologies of this category usually work with metal materials in powder or wire format.

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Figure 14. Directed energy deposition scheme.

The functioning of this category could be similar to a metal arc welding technology, but with controlled motion by Computer Numerical Control (CNC) in a multi axis arm (4 or 5 axis machines). This arm feeds the material (wire or powder) and deposits and melts the material, at the same time, on the surface of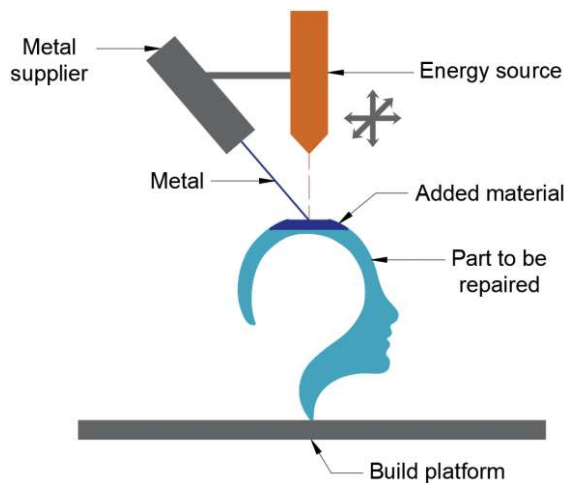 the part, where it solidifies. The process could be also similar to material extrusion, with the different that the beam can move in multiple directions and the material is usually a metal such as cobalt, chrome and titanium. Powder DED machines often use inert gas, which is added together with the powder or wire from the nozzles to reduce the reaction of the melted metal with the atmosphere. Moreover, these machines may have multiple nozzles to work with different metal powders at the same time, which allows mixing them to produce functionally graded components, also known as Functionally Graded Additive Manufacturing when the part is obtained by AM [6].

Depending on the format of the material and energy source, there are different technologies within this category. Regarding the energy source to melt the material, there are three main groups:

- Laser-based systems such as Laser Engineering Net Shape (LENS), Laser Metal Deposition (LDM) or Laser Cladding (LC).

-       Electron beam based systems such as Electron Beam Additive Manufacturing (EBAM).
-       Plasma or Electric arc based systems such as Wire Arc Additive Manufacturing (WAAM).

With regards the format of the material feedstock, there are two main groups:
-       Powder-based systems (LENS, LDM or LC), which use powder material.
-       Wire-based systems (e.g. WAAM), which work with wires.

These technologies are commonly used to repair parts, taking advantage of the existing part to be used as substrate for the addition of new layers. Despite the finishing is rough, these technologies are usually combined with subtractive manufacturing (multi axis machining) to improve the final surface quality. These combination of additive and subtractive manufacturing in the same equipment is known as 'hybrid manufacturing'.

1.1.8. Main advantages and disadvantages of AM by categories

Table 1 shows the main advantages and drawbacks of AM technologies, sorted by category and from the medical perspective.

Table 1. Main pros and cons of AM technologies by category [7].

AM category	Pros	Cons
VAT photopolymerization (VPP)	High resolution and accuracy, complex parts, decent surface finish and flexible printing setup	Lacking in strength and durability, sensitivity to UV light after print, and not for structural use
Material jetting (MJT)	High accuracy, low material waste and multimaterial and multicolor parts	Required support material and limited materials (only polymers and waxes)

AM category	Pros	Cons
Binder jetting (BJT)	Multicolor, multimaterial, fast AM and different binder-powder combinations to adjust mechanical properties	Not always suitable for structural parts and long postprocessing (cleaning)
Material extrusion (MEX)	Inexpensive, widespread and availability of different materials with interesting properties	Quality depends on the nozzle radius, low accuracy and speed, and contact pressure needed to increase quality
Powder bed fusion (PBF)	Large material options	Low speed, lack of structural properties in materials, limited sizes and dependence on powder size
Sheet lamination (SHL)	Speed, inexpensive, ease of handling	Dependence on paper or plastic material, need of postprocessing and limited material range
Direct energy deposition (DED)	High control of grain structure, fully dense parts and good process for part repair	Limited materials, poor surface quality and low accuracy of wire process

1.2. Additive Manufacturing technologies in the medical field

The medical industry is one of the largest users of AM since the high customization and complexity degree required in this field matches perfectly with the main advantages and capabilities of AM technologies.

For example, the manufacturing of a specific and optimized implant or scaffold (structure that serves as support for the growth of extracellular matrix of the damaged tissue) requires a unique and complex design that cannot be easily manufactured with conventional technologies. In the specific case of scaffolds (or implant areas where the tissue regeneration is important), a cellular structure with a large volume fraction of interconnected pores is needed (the greater the surface of the scaffold, the better the cell adhesion) and the shape and size of the cellular structure have a great influence on the regeneration efficiency. Therefore, the design must be tailored according to these considerations, but also ensuring the appropriate mechanical properties (trying to mimic the replaced tissue) and a minimal mechanical integrity for a proper handling during surgery [8]. As a consequence, the resulting optimal design (unique design) is usually quite complex and almost impossible to produce with conventional processing techniques. However, AM technologies and the continuous evolution of materials in this field (which must be biocompatible and, in some cases, bioresorbable) make these designs feasible to be manufactured and in a short period of time, without additional tools needed. For these reasons, the most cutting edge uses of AM are usually related to the medical field.

Apart from the direct application of AM for specific medical parts such as prostheses or scaffolds, AM technologies are also useful for the production of personalized anatomy models from patients' scans. These anatomy models can be very valuable for training and, specially, for preclinical practice since surgeons can practice tricky surgery techniques before the real operation, thus reducing risks during the surgical procedure. Finally, AM capabilities can be also applied for the production of specific and personalized tools for medical applications.

The following subsections summarize the most typical AM technologies used in the medical field and classified by category. In this case, three different medical applications have been considered for the classification of AM technologies: prostheses, scaffolds, and training/pre-clinical models production. According to the literature [9], directed energy deposition is only used in isolated cases of implants and sheet lamination rarely used for medical models or phantoms. In the

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case of material jetting, this technology is not used for internal prostheses. However, the remaining AM categories (VAT photopolymerization, powder bed fusion, material extrusion and binder jetting) have been utilized in all the medical applications considered in this chapter, although some of them are more common depending on the specific application. Table 2 summarizes these medical applications of the seven AM categories.

Table 2. Application of AM technologies in the medical field sorted by AM category.

	Prostheses	Scaffolds	Pre-clinical and training
VAT photopolymerization (VPP)	☒	☒	☒
Material Jetting (MJT)	Not for implants	☒	☒
Binder Jetting (BJT)	☒	☒	☒
Material extrusion (MEX)	☒	☒	☒
Powder bed fusion (PBF)	☒	☒	☒
Sheet Lamination (SHL)	☒	☒	Rarely used
Directed Energy Deposition (DED)	Rarely used for implants	☒	☒

Table 3 also summarizes the most typical materials and medical uses of the seven AM categories.

Table 3. Common materials and medical uses of the seven AM categories [7].

AM process	Materials	Medical use
VPP	Photopolymer resin	Bone, dental models, dental implant guides and hearing aids
MTJ	Polymers (PP, HDPE, PS, PMMA, PC, ABS, HIPS, EDP)	Medical models, dental casts and dental implant guides
BJT	Stainless steel, polymers (ABS, PA, PC) and ceramic (glass)	Color parts (especially for coding anatomy models)
MEX	Polymers (ABS, PA, PC, etc.)	Medical instruments and devices and rapid prototyping exoskeleton
PBF	Powder-based materials (depending on the technology: PA, stainless steel, titanium, aluminum, cobalt chrome, steel and copper)	Models with cellular structures, medical devices such as implants and fixations
SHL	Paper, plastic and sheet metals	Limited (orthopedic modelling of bone surfaces)
DED	Metals (cobalt chrome and titanium)	Limited (used to repair existing parts and build very large parts)

1.2.1. Additive Manufacturing technologies for prostheses

Prostheses are artificial devices used to meet the biomechanical needs of people with physical disabilities. Traditionally, these devices were fabricated by time-consuming and labor-intensive processes. However, the evolution of AM technologies is changing this trend, since AM prostheses can achieve the biomechanical performance of

traditional prostheses, with the inherent advantages of AM. In the traditional fabrication of external prostheses, a negative cast mold is produced by wrapping plaster bandages around the affected part. This mold is then used to pour plaster and obtain the positive mold. Subsequently, sheets of thermoplastic are heated and adapted to the positive mold by vacuum forming. Once solidified, they are cut with the correct shape. Moreover, the final prosthesis usually requires some additional adjustments to achieve the desired comfort and functionality. All these problems can be significantly reduced by using body scanning techniques, CAD modelling and AM technologies [10].

There are several technologies used for the development of prostheses, especially depending on the location of the prosthesis. In the case of internal prostheses (implants) the materials used must be biocompatible. Moreover, in some cases the implants are designed not only to substitute the damaged tissue in the initial recovery stage, but also to biodegrade so that the regenerated tissue can replace the implant progressively. In these cases, the implant must degrade into non-toxic components easily resorbable by the body (bioresorbable materials).

In the case of internal prostheses, usually metal parts are required to achieve the desired mechanical properties, although high performance and biocompatible plastics are also used, such as PEEK (mainly with material extrusion technologies [11], [12] or SLS powder bed fusion). Among the AM technologies that can work with biocompatible metals, powder bed fusion is the preferred category for this application (SLM, DMLS or EBM technologies). The most common materials for powder bed fusion in implants applications are titanium alloys (or pure titanium), stainless steels, tantalum, NiTi, and CoCr alloys. The use of biodegradable metals in AM such as magnesium (Mg), iron (Fe), and zinc (Zn) is currently under research, although still in its initial steps. According to the literature, element loss and porosity are the most common processing problems for AM of biodegradable metals like Zn and Mg [13].

Regarding external prostheses, plastic materials are more common as the required mechanical properties can be achieved by adjusting the design. As a consequence, almost all the AM categories working with plastic material (material extrusion, SLS powder bed fusion, material

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jetting, vat photopolymerization and binder jetting) can be used, especially for prosthetic arms and hands. However, other prostheses such as the ones used for lower limbs must withstand higher and dynamic loads and, at the same time, provide sufficient durability. Therefore, the application of plastic-based AM technologies is limited in these cases. For this reason, some researches focus on the development of composite materials for AM with the objective of improving the mechanical performance of the 3D printed plastic prostheses [14].

1.2.2. Additive Manufacturing technologies for scaffolds

As mentioned before, scaffolds are porous 3D structures used to replace or regenerate native tissues in human body (Figure 15 and Figure 16). These porous structures allow cell activity such as migration, proliferation, attachment, and differentiation, thus promoting the regeneration. For this to happen, the materials used for the production of scaffolds have to be biocompatible, easily sterilizable and non-toxic, as in the case of implants. The most commonly used materials are natural or synthetic polymers (e.g., hydrogels, proteins, thermoplastics, thermoplastic elastomers), metals (titanium and magnesium alloys), bioactive ceramics and glasses, and also composites of polymers and ceramics [15].
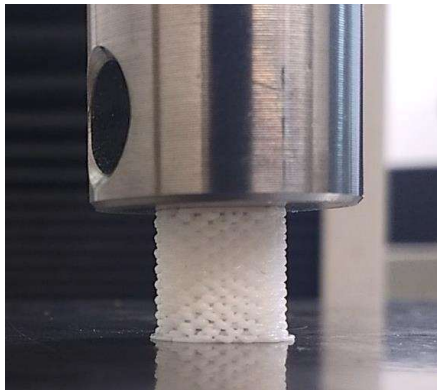
Figure 15. PLA scaffold made by MEX AM technology during compression test.

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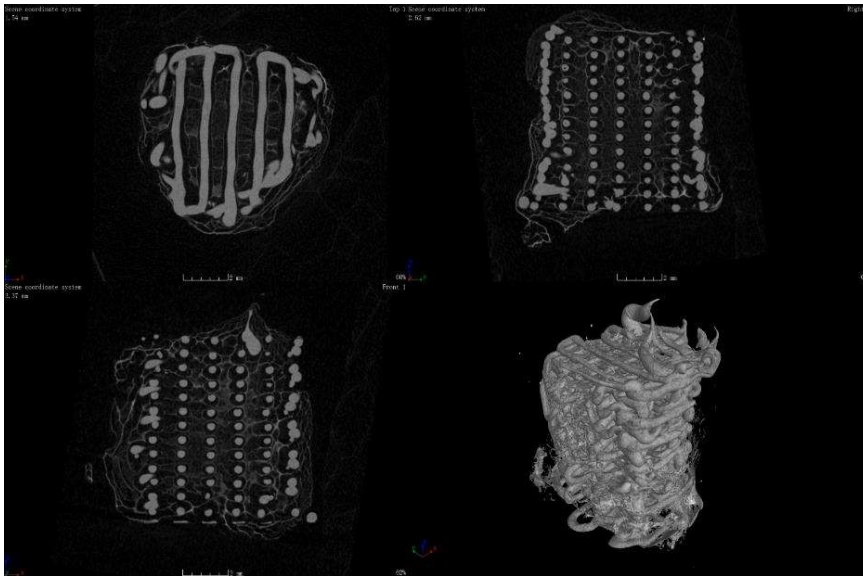
Figure 16. Micro CT scan of PCL scaffold made with extruded PCL in bioplotter and subsequent casting of alginate with nanocellulose.

As depicted in Table 2 and Table 3, not all the AM categories are commonly used for biomedical applications, mainly due to restrictive material requirements. Moreover, some AM categories apply, during the layer-upon-layer manufacturing process, high temperatures that may damage the used material for this application. In any case, different AM technologies are used for scaffolds production.

For the fabrication of metal scaffolds, the most typical technologies are those of the powder bed fusion category such as SLM, EBM [16] and DMLS [17] (as it also happens with AM metal prostheses). Among them, SLM and EBM are more used than DMLS.

Regarding AM used for the production of polymeric scaffolds, the most common technologies are binder jetting, stereolithography (SLA, vat photopolymerization category), material extrusion and SLS (powder bed fusion) [15].

Binder jetting technologies has the advantage of not needing support structures to produce complex geometries since the powder

bed does this function (as it happens in SLS). For this reason, binder jetting can be used to produce complex scaffolds with a relatively low cost. The main problem of binder jetting technologies is the lack of adhesion between layer, which limits the mechanical performance of the 3D printed parts. The print resolution is also a limitation of this technique for scaffolds production. However, binder jetting can process a wide variety of powder materials such as polymers, sand, metals and ceramics, but also cells and hydrogels, which is very interesting for scaffolds fabrication.

In the case of stereolithography (SLA), the main disadvantage for its use in scaffolds production is the limited number of potential materials that can be used. The free radicals that are formed during the photopolymerization process can damage cell membrane, protein, and nucleic acids, which limits its application in this specific field.

Regarding material extrusion, this category has many advantages, such as good efficiency, easy material replacement and low cost. However, the narrow list of available biomedical materials is a limitation for scaffolds production. The most typical materials used are acrylonitrile butadiene styrene (ABS), polylactic acid (PLA), polycaprolactone (PCL), polyethylene terephthalate glycol (PET-G), tricalcium phosphate (TCP) and polyamide (PA). The incorporation of cells or bioactive molecules is not possible in the conventional material extrusion AM equipment. Additionally, the inherent poor surface finish also limits its application for scaffolds. This can be solved by reducing the layer height, as lower values of this parameter will reduce the surface roughness and increase the mechanical properties (improved contact between layers). However, a lower layer height would also increase the production time and costs.

Despite these limitations, bioplotters, which are also based on extrusion processes, are one of the best options for the development of scaffolds, mainly due to the capability to work with biomaterials and cells in sterile environments (biomanufacturing). This capability, together with the option of producing multi-material parts with adjusted properties in different zones according to the desired functionality (e.g. combination of thermoplastic and hydrogels with embedded cells to improve the regeneration rate), places this

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technology as the most promising AM equipment for scaffolds production.

Finally, Selective Laser Sintering (SLS) has the advantage of having a higher accuracy (although it depends on the size of the powder and laser spot) and better mechanical properties of the 3D printed parts compared with other technologies such as FDM or SLA. Moreover, the powder bed allows more design freedom due to the avoidance of support structures, although the powder removal can be very tedious in the case of scaffolds (structures with small interconnected porous which hinders the powder removal). On the other hand, the main drawback of SLS for scaffolds fabrication is that the use of high temperatures (laser radiation) limits the number of materials that can be used. The most typical are polycaprolactone (PCL), poly(D,Llactide) (PDLLA), poly(ether-etherketone) (PEEK), poly(lactic-co-glycolic acid) (PLGA), poly(vinyl alcohol) (PVA), composite of polycaprolactone/hydroxyapatite (PCL/HA) or poly(ether-etherketone)/hydroxyapatite (PEEK/HA).

1.2.3. Additive Manufacturing technologies for pre-clinical evaluation and training

The design freedom of AM technologies together with the capabilities of medical imaging technologies such as computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound allow the production of medical models based on the patient anatomy. Therefore, the combination of scanning technologies, image treatment, 3D modelling and Additive Manufacturing can lead to very realistic synthetic models of personalized patient's anatomy. These synthetic models can be very useful for pre-operative planning/training, especially in the case of complex surgeries that require a deep analysis or practice before the operation. Additionally, these models can also be used to train medicine students, which in many cases have limited access to real cases. Therefore, AM allows increasing the practice of students as phantoms can be easily produced and managed. In fact, these synthetic models could replace, in a certain extent, the use of cadavers for training, which are more difficult to manage and expensive. Moreover, as cadavers are unique, it is not possible to train several

students exactly with same case, while AM does allow this option. Apart from this, medical models obtained by AM can also be useful to inform patients or patients' families about anomalies, surgical procedures, etc.

Although many different technologies have been used for pre-clinical evaluation and training, the most typical AM category used for this specific application is material jetting. In fact, nowadays there is a specific material jetting technology called J750 Digital Anatomy Printer (DAP, from Stratasys), which was specifically developed to produce anatomy models. The main difference between DAP and conventional material jetting printers is that the materials available try to mimic anatomy materials. In fact, the laminator used in this machine (GrabCAD Print) allows users to choose from different anatomy families and anatomy elements which are basically made of the following three type of materials [18]:

1.   TissueMatrix™: ultra-soft material to mimic muscle and soft organs.

2.   GelMatrix™: Gel-based material to emulate blood vessels and cavities.

3.   BoneMatrix™: Material with high toughness to replicate cortical bone and connective tissue.

Depending on the specific anatomy family and anatomy element, these materials are combined to mimic the real tissue. Moreover, the softness/stiffness can be manually adjusted, thus covering a wide range of applications.

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