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## Nanocomposites for Additive Manufacturing

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### ABSTRACT

Additive Manufacturing (AM) is one of several technological breakthroughs that is expected to lead the factories of the future, where conventional equipment will be transformed into smart and flexible systems, run by computers that will allow the fabrication of customized parts. Some authors have called AM the third industrial revolution, as it enables the accurate manufacture of pieces of virtually any shape in different scales, ranging from visual prototypes to specific functional end-use products at relatively short periods of time. Medical applications of AM is one of the key industries driving the innovations in the field, especially because of the possibility to fabricate products individually tailored to the patient's specific needs. The integration of nanomaterials in the area of AM has a lot of potential and there is a growing interest in academia and industry to explore for new developments. In this section, we examine some successful uses of nanocomposites in additive manufacturing processes.

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## Background

With the endless utility of chemistry and the integration of the outstanding potential of nanoscience, the incorporation of nanomaterials into other support materials employed in additive manufacturing (directed towards the improvement and/or modification of material properties so as to broaden their applications into unexplored areas) has become a very attractive field for research and innovation.

But, what is special about nanomaterials? citing Dr. Nelson on his editorial for *Material Matters* [1] the unique properties of nanomaterials come from the large surface area to volume ratio, which boosts conductivity, impart exclusive optical and confinement effects, improve catalytic and biological properties such as ease of transport, detection and localization of specific targets just to mention some. These characteristics have been extensively studied for energy and electronic applications, in particular for their use in solar cells, lithium ion batteries, supercapacitors, lighting, printed and flexible electronics, catalysis, drug delivery and imaging. Although nanomaterials hold enormous potential to improve the performance of materials and lower manufacturing costs in various devices, the full achievement of such benefits, in many cases, has yet to be addressed. In order to reach the full potential of nanomaterials, a better understanding of the fundamental processes associated with size and electronic characteristics, as well as solutions to more practical challenges (such as cost effective large scale production), is still needed.

In particular, magnetic, biomedic, lightness and mechanical properties can be directly induced in the already available AM materials by the addition of the appropriate nanomaterial. However, there are some difficulties related to the AM processing of materials since some of the layer formation processes and post-processing of AM manufactured pieces require high temperatures and/or high pressures, both variables could modify some properties of the nanomaterials by causing an increase in the size and/or modification of their structures. Consequently, the transformation of nanomaterials into AM-composites entail new challenges yet to solve.

## Composite Materials

Latest advances in the engineering sciences in combination with diverse technologies have opened the door to new era of advanced materials, which, in turn, has responded to the necessities of global social changes. In this sense, great outcomes have been achieved on the design and development of composite materials, which are defined as the combination of two or more materials, generally with significantly distinct physical and/or chemical characteristics, which results in a material with unique properties different to those of the individual components. To note, the individual components remain separate and distinct within the composite material. One of these components is the matrix, which surrounds and keeps together the filler made of a different material, called the reinforcement. The nature of the matrices comprises polymers, metals and ceramics, while the reinforcements, in general, will be harder, stronger and stiffer than the matrix and are usually fibers (i.e., boron, carbon and organic fibers) and particulates. The potential applications of composites materials are present in practically every field such as in the aerospace and automotive industries, electronics, energy storage and biomedicine, just to name a few [2,3]. In consequence, the understanding of the properties of the composites in conjunction with the development of novel ones is a truly multidisciplinary field including materials science and engineering, physics, chemistry and even biology.

## Nanocomposites

In the last decades, nanotechnology, which is the science, engineering, and technology conducted at the nanoscale (1 to 100 nanometers), has become one of the most popular areas of research. What is fascinating about nanotechnology is not that it involves investigating at a very small scale, but that it is about working with unique physical, chemical, mechanical, and optical properties that materials exhibit at that scale [4]. Hence, introducing nanotechnology to the field of composite materials represents an opportunity to generate “smart” multifunctional nanocomposite materials.

Subsequently, nanocomposites are multiphase solid materials in which at least one of their constituent phases has one dimension less than 100 nm. This definition also refers to structures hav-

ing nanoscale distances between the different phases that build up the material, which would include porous media, colloids, gels and copolymers [3,5]. Nanocomposites exhibit an exceptionally high surface to volume ratio of the reinforcing phase and properties (i. e., mechanical, electrical, thermal, optical, catalytic and electrochemical) very different to those of the composite obtained at the macro or microscale [6]. Additive manufacturing, alongside the production of nanocomposites that could be used in this technology, will accelerate the large production of daily-life products that include the benefits of improved properties by means of nanomaterials.

### Bionanocomposites

The term bionanocomposites refers to nano-sized biocompatible and/or biodegradable structures made of natural or synthetic polymers (the matrix) and an organic/inorganic filler [7,8].

Matrices include polysaccharides (chitosan, starch), aliphatic polyesters (poly(lactic acid) and poly( $\epsilon$ -caprolactone)) as well as biomacromolecules like proteins (collagen, gelatin, enzymes), polypeptides (poly(L-lysine)) and even polynucleic acids, whereas fillers include clays, silica, silicates, carbonates, phosphates, metal nanoparticles, metal oxides, hydroxides and carbon-based nanomaterials (CNT, SWCNT and MWCNT) [8,9].

The combination of biopolymers and inorganic components results in biocomposites with particular features. Furthermore, the inclusion of nanometer-size components will generate nanobiocomposites that will have electrical, optical and thermal properties (to name a few) different to those of the microbiocomposites. In this sense, fillers act as molecular bridges with the matrix, which result in superior mechanical properties of the composite [10]. Moreover, because of the nature of the matrix, the nanomaterial will be biocompatible and/or biodegradable, thus expanding their applications from biomedicine to ecology [10–12].

Years of intense research on chemistry and materials sciences has revealed that nature is an extremely accurate lab, producing a number of natural complex materials with fascinating properties and amazing architecture that range from the micro to the nano scales. Bone, teeth and

nacre are some examples of nanobiocomposites produced by living organisms. Excellent reviews about the complex hierarchical structures of these and other composites, and how nature has inspired scientists to design novel synthetic advanced materials, have been published recently [13,14]. The resulting bioinspired nanocomposites have been designed to exhibit either advanced functionalities (adhesive films, superhydrophobic materials and photonic coatings) or to mimic a specific biological function. In the latter case, the development of nanocomposites with applications in prosthetic devices, implants, drug delivery and tissue engineering has had a great impact on biomedical sciences, in particular, these last applications are the ones that have higher impact on AM processes.

### Nanocomposites in tissue engineering

Tissue engineering is a multidisciplinary field that applies the principles of engineering, chemistry, biology and health sciences towards the development of biological substitutes that restore, maintain or improve tissue function[15]. Tissue engineering has emerged as a revolutionary approach with an enormous impact on clinical applied sciences and is considered to have a huge potential in the market [16].

In order to engineer a living tissue, cells must be grown on biocompatible and biodegradable substrates, known as scaffolds. These in turn, must be capable of promoting cell differentiation, assembly into 3D structures and, at the same time, must display physical and mechanical properties suitable to perform inside a living system. Therefore, materials and technologies employed to fabricate scaffolds are critical to succeed in the tissue engineering field.

Two fundamental properties of materials required to be used for scaffold construction are biocompatibility and biodegradability. However, it is also necessary that biomaterials show optimal mechanical properties. Several polymeric biomaterials are continuously investigated and it seems that no single biodegradable polymer fulfill the requirements to be used as tissue engineering scaffold [17]. Multicomponent systems, namely composite materials multicomponent systems, namely composite materials, emerge as a promising option for the successful development of tissue engineering applications. As

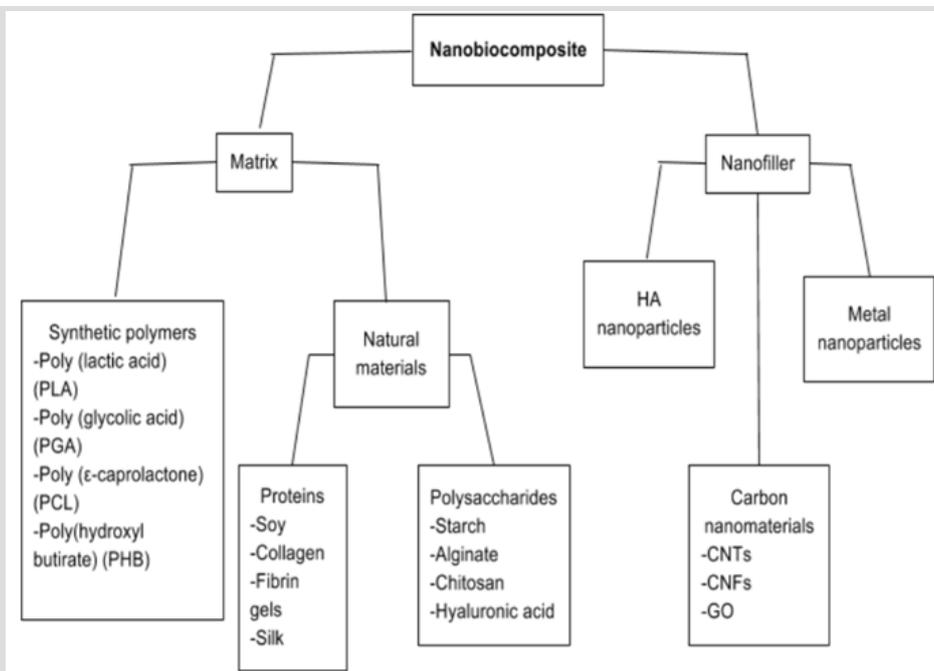


Figure 1. Matrices and nanofillers in nanobiocomposites.

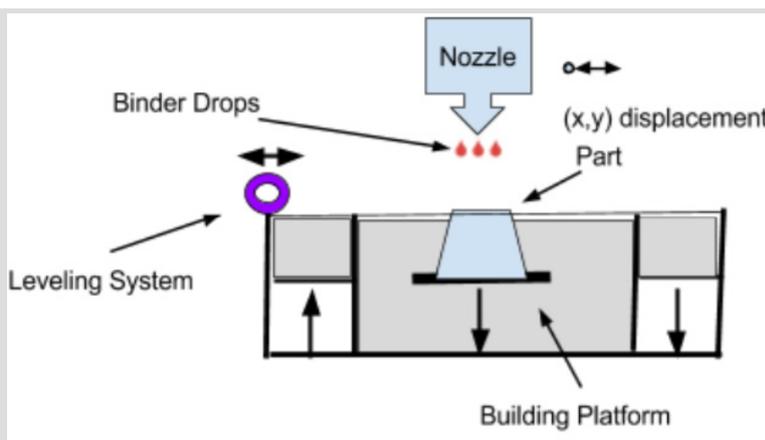


Figure 2. Binder Jetting Schematic

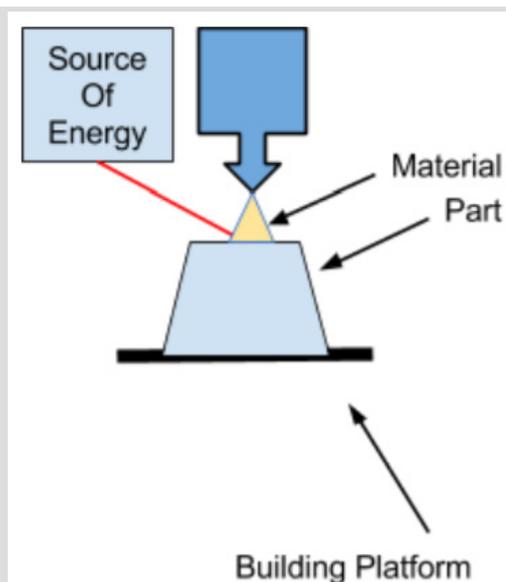


Figure 3. Directed Energy Deposition

it was mentioned above, micro and especially nanocomposite materials may present an optimal balance between strength and toughness compared to their individual components. On the one hand, depending on the nature of nanofillers, additional features (i.e., electrical conductivity) could be incorporated into the scaffold. On the other hand, the surface modification of the nanostructures will determine the dispersion of the the interfacial adhesion to the matrix. Hence, the mechanical, electrical and degradation characteristics will be influenced by the properties of the matrix, the nature and distribution of the nanofillers and also by the synthetic and processing methods employed for that matter.

### Matrices

Polymeric materials constitute the matrices of nanobiocomposites employed in tissue engineering applications [18]. The natural and synthetic polymers most commonly used in this field are shown in Figure 1.

Naturally derived polymers are suitable for cell adhesion because they can be easily recognized by biological components, however, they have poor mechanical properties. In contrast, synthetic polymers can be modified to modulate their mechanical strength and degradation profile, but generally with hydrophobic surfaces, which hampers the biological recognition.

### Nanofillers

Current nanostructures employed to build bionanocomposites comprise three main groups [16] (Figure 1).

#### Hydroxyapatite

Hydroxyapatite (HA) is the most used ceramic material in the biomedical field, HA nanocomposites can combine the toughness of the polymer phase with the compressive strength of fillers mimicking the natural bone with improved properties [18].

#### Metal nanoparticles

Electromagnetic, optical and catalytic properties of metals are strongly influenced by shape and size. Thus, the recent progress of nanosciences has expanded the possible applications of metal nanoparticles to several fields including biologi-

cal and biomedical areas. Gold, silver, iron [11] and platinum [19] nanoparticles have drawn special attention towards the construction of multifunctional bionanocomposites. For example, scaffolds with silver nanoparticles embedded in the polymeric matrix could control bacterial infections [20, 21]. Gold nanoparticles, on the other hand, have been widely studied in medicine and biology [22, 23].

#### Carbon nanostructures

Carbon nanostructures, the most studied materials to date, include carbon nanotubes (CNT), carbon nanofibers (CNFs) and graphene oxide (GO). Carbon-derived nanomaterials incorporated into a polymeric matrix have been widely investigated and it has been demonstrated that CNTs provide a good structural reinforcement for biomedical scaffolds. They can also add electrical features and improve mechanical properties of biopolymers, which would be useful to direct cell growth and tissue healing, processes in part governed by electric stimuli [24–26]. With respect to CNFs, it has been evidenced that they improve the function of conventional biomaterials and have shown a great potential to be used in scaffolds for bone tissue regeneration [27,28]. GO, is a nanomaterial that has gained enormous attention in the recent years and has become particularly attractive in both the drug delivery and biomaterial fields. The high degree of reinforcement provided by GO in composite materials offers excellent mechanical properties, thus evidencing its potential to be used in tissue engineering [29–31].

### Processes

The successful engineering of a tissue relies on the scaffolds, because they facilitate cell adhesion in order to promote cell distribution and guide tissue regeneration. We have briefly described the influence of composite materials towards the development of scaffolds with the aforementioned features. However, there is another critical requirement that will define the tissue regeneration: porosity. Scaffolds must have an adequate pore size to facilitate cell seeding and diffusion of both cell and nutrients. Additionally, pore interconnectivity will be necessary to increase the specific surface area for cell adhesion and growth, as well as the distribution and transport of nutrients and cellular waste prod-

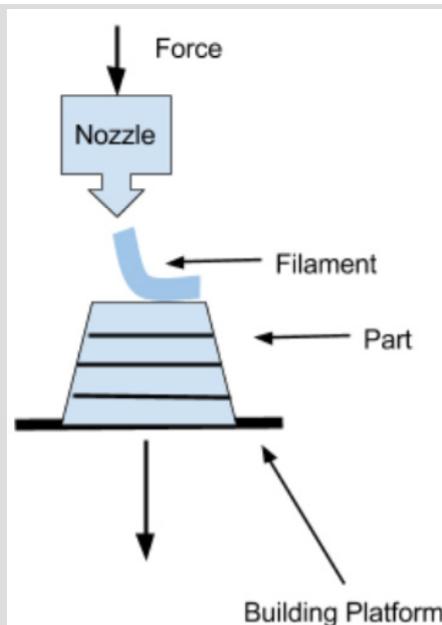


Figure 4. Material Extrusion general process.

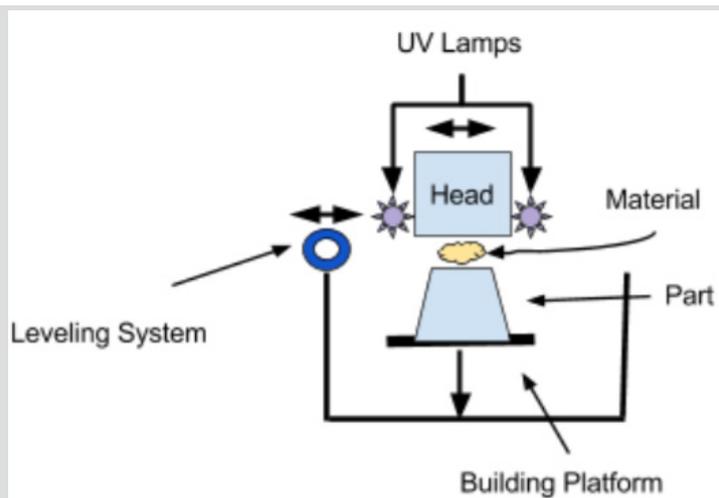


Figure 5. Material Jetting general process.

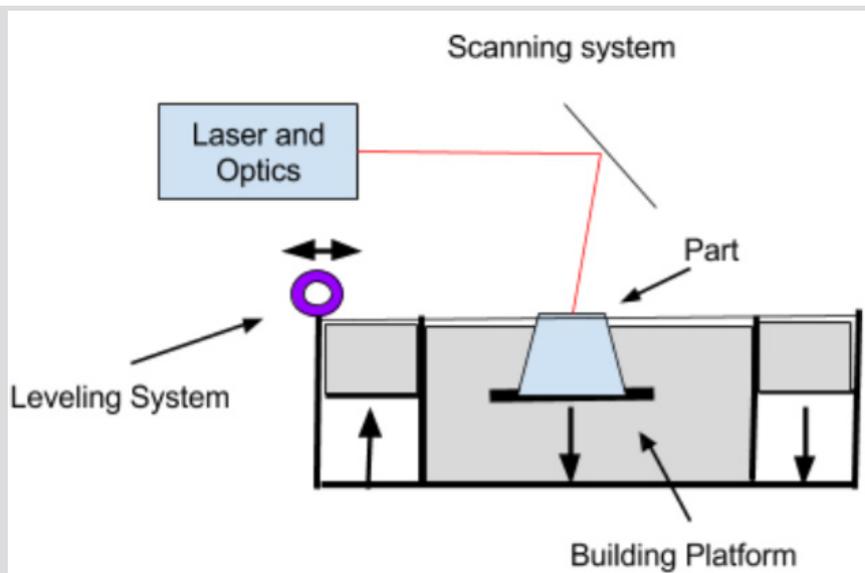


Figure 6. Powder Bed general Process.

ucts.

Nanocomposite-based scaffolds have been produced by different techniques which include particulate leaching, gas foaming, electrospinning, solvent casting, among others. However, recently AM technologies have expanded their applications to tissue engineering [32,33]. The next section describes in detail the fundamentals of additive manufacturing and presents some examples of its application on the development of nanocomposite-based scaffolds for tissue engineering.

### Additive Manufacturing

“According to the ISO/ASTM [34], there are seven broad categories of AM: binder jetting, directed energy deposition, material extrusion, material jetting, powder bed fusion, sheet lamination, and vat photopolymerization. All of which, are currently commercialized. Current applications for AM are for products that have complex geometries and for which the production run is small. For service parts with demanding properties, like , the part cost is driven generally by the AM fabricator machine cost, plus the feedstock. Reduction in these costs, improvements in production rates, increased part geometrical complexity, and reduced feedstock scrap rate, contribute to increasing the break-even production number to the point that AM competes equally on a cost basis with a traditional manufacturing process” [35].

Binder jetting uses a nozzle to jet drops of binder selectively over a powder bed. The powder is spread usually by a roller or by a blade [17]. Figure 2 shows an schema of the Binder Jetting Process. For this process, there is a variety of materials such as starch based and plaster based materials, plastics, sand, metals, soda-lime glass, among others [17].

Directed Energy Deposition. This process allows the growing of parts by melting and deposition of material from powder or wire feedstock, by focusing energy into a narrow region, which is used to heat a material that is being deposited [36]. Figure 3 depicts the Directed Energy Deposition process, which is focused to use metals as materials.

Material Extrusion. This process consists on the

deposition of material forced out through a nozzle when an external force is applied at specific temperature conditions. If the pushing force remains constant, the resulting extruded material (filaments or rasters) will flow at a constant rate and will maintain a constant cross-sectional diameter [36]. Figure 4 shows Material Extrusion general process. This process encompasses a wide variety of materials such as thermoplastics, ceramics, metals, composites, biomaterials, among others.

Material Jetting Process locates layers of photopolymers from heads containing individual nozzles and cure, by ultraviolet light, immediately as they are located. It is possible to locate more than one material at the same time by means of different heads [36]. A general scheme of material jetting process is shown in Figure 5. Photopolymers employed in this process can be doped with others materials such as ceramics, fibers or metals to generate composites.

Powder Bed Fusion, consists on one or more thermal sources (typically lasers or an electron beam) for fusing powder particles layer by layer; the source and the layer size [36]. Figure 6 shows Powder Bed Fusion general process. This process supports metals, thermoplastics, composites and ceramics.

Sheet Lamination, or layer by layer lamination, consists of the bounding process of a cross sectional laminated and cutted area of the building geometry, Figure 7 illustrates a generic representation of the process. Different processes have been developed based on sheet lamination, depending on building materials and cutting strategies [36]. The most common material used in this process is paper, but there are other materials such as plastics, metals and ceramics [17].

Vat Photopolymerization uses photocurable resins as building materials, typically sensible to UV wave range, but various types of radiations can be used such as: X rays, Gamma, electron beam and visible light. Three basic configurations, shown in Figure 8, were developed for Vat Photopolymerization: single scanning, layer projection and multi-photon configuration [36]. Materials suitable for this process are similar to the materials employed in material jetting processes.

Freeform manufacturing capabilities and no tool-

ing requirements are two of the main advantages of AM. One of the more growing research fields for additive manufacturing are related with their materials. AM builds pieces by the deposition of materials which includes polymers, composites, ceramics, metal alloys, bio-materials, among others. Several applications were developed since AM was commercially available [35,37–40], but it is still a growing research field since materials, and their properties, are the base for AM process capabilities, processing speed, layer thickness, geometric and accuracy features, cost, etc. [36].

The top three fields driving research activities in the area of materials for additive manufacturing are: automotive, aerospace, and biomedical, since the “AM is most advantageous in market environments characterized by demand for customization, flexibility, design complexity, and high transportation costs for the delivery of end products” [41].

Automotive field takes advantage of AM because of the ability to develop new products in a shorter period of time. Aerospace companies are interested in AM technologies as a result of the capability to produce high-performance products based on high complex geometries. Biomedical field is particularly interested in AM by virtue of the capacity to convert 3D medical imaging data (typically DICOM format) into 3D devices [42], and the incorporation of key properties from the used materials into the final 3D device.

Layer thickness can be an issue during the manufacturing process by additive technologies. Small size layers increase the resolution and typically the surface finishing of the built devices, but it also increases the building time. On the other hand, rough layers decrease the building time, but affect the geometry accuracy. In 2014 J. Gardan compiled information about layer size according to different technologies, which moves from 1 $\mu$ m to 1mm depending on technology [42].

AM standards for materials and process became a necessity in terms of performance measurement of the process, the materials and the final device results, thus ISO and ASTM have developed the family of documents 17296: Additive manufacturing – General principles and ISO/ASTM DIS 20195: Standard Practice – Guide for Design for AM: It is being developed since 2015 and will bring together good practices in design

for getting a reliable product. [42]

### **Materials available for AM**

One of the most attractive characteristics of additive manufacturing (and possibly one of its main constraints) is the diversity of suitable materials. The chemical and physical properties of parts fabricated by any AM process are determined by the synergism between the raw material and the manufacturing process. On one hand, raw material properties arise from the structural arrangement of its molecular components whereas the properties of a final part depends also on the AM building process. It is then not surprising that a part fabricated layer by layer will display clear differences in the final properties, when compared to a piece fabricated by subtractive methods made of the same starting material.

Early AM machines were built around materials already available, materials that were designed to fit other processes and were not optimal for additive fabrication, resulting in the production of parts with poor properties and undesired performance. As AM processes evolved, materials were developed to specifically suit the operating parameters of the different additive systems and thus producing parts with higher performance and improved properties.

It is natural to think that there is a need to study (and probably to develop) the material and the processes simultaneously. Several authors have conducted important reviews about the different type of materials available for additive manufacturing technologies [43], which mainly include polymers, ceramics, metals and biological tissues.

Diversified applications will demand different product performance and characteristics, and will define the different ways and levels that AM will be involved: elementary products may use AM only for visualisation purposes, as it is the case of medical models that represent anatomical structures; while more complex products such as a multifunctional bioactive materials, that require a careful engineering content, will probably involve AM during more than one stage and in several times throughout the manufacturing process.

A characteristic highly desired in products man-

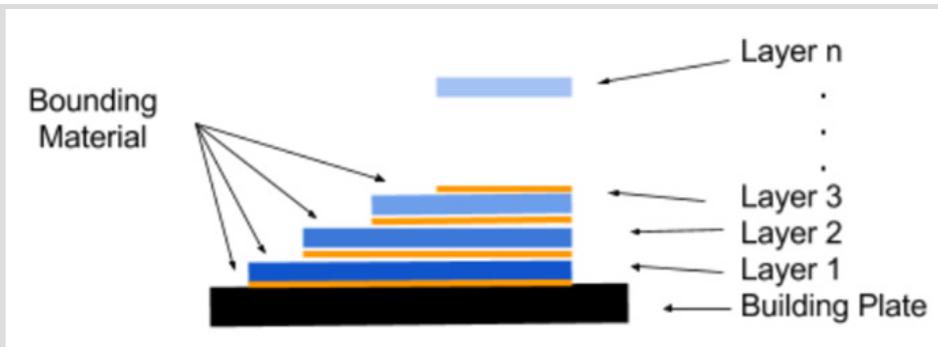


Figure 7. Sheet Lamination generic process

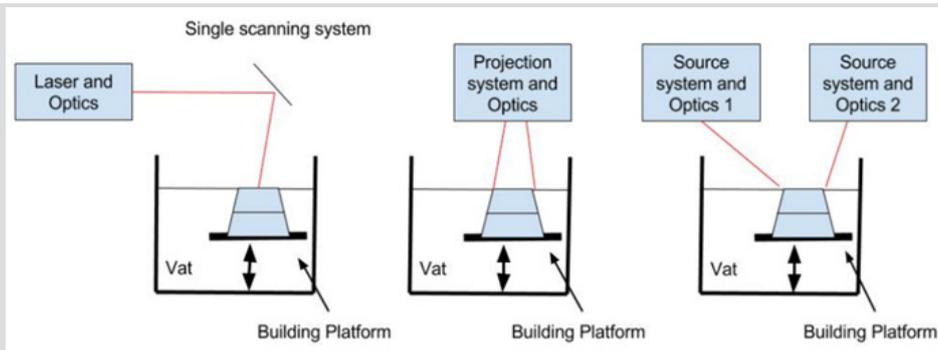


Figure 8. Configurations for Vat Photopolymerization process.



Figure 9. AM-fabricated medical models.

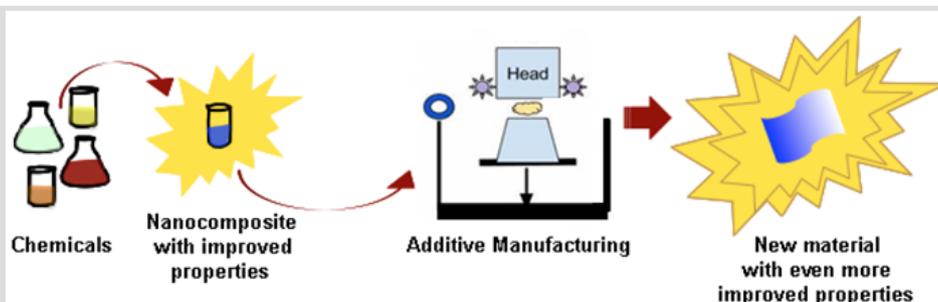


Figure 10. Cartoon of nanomaterials included in new AM materials.

ufactured by AM technologies, includes the introduction of biological material, such as honeycombs, scaffolds, trusses, and lattices, since they exhibit numerous advantages over dense materials due to their high surface areas, energy absorption, specific stiffness, damping and strength. For instance, devices developed by sintering process to obtain different cells could possibly develop properties as varied as energy storage, emissions control, catalyst supports, structural applications, among others by the incorporation of different materials such as nickel and iron, as it has beautifully show by Dunand and collaborators [44].

### Materials available for AM for medical applications

In recent years, additive manufacturing has been used in medical reconstruction procedures along with traditional CT scanning techniques and Computer Aided Design (CAD). These technologies allow better 3D visualisation of patient's injuries, the simulation and preoperative planning of surgical procedures and even serve as models for the manufacture of implants [58]. Even though 3D imaging data was originally used for visualisation and diagnosis purposes, it has been employed jointly with AM technology to build medical models, especially because of the unique organic shapes involved.

In 2015, Gibson wrote about the materials used on AM, in particular for medical applications, quoting "only a few AM polymer materials are classified as safe for transport into the operating theater and fewer still are capable of being placed inside the body. Metal systems, on the other hand, are being used regularly to produce implants using a range of technologies. Of these, it appears that titanium is the preferred material, but Cobalt Chromium and Stainless Steel are both available candidates that have the necessary biocompatibility for certain applications" [45]. As it can be seen, the importance of the materials employed in biomedical applications is still one of the most important challenges to solve in the area of AM.

Evolution of AM process along with advances in materials science are opening new possibilities to develop more complex applications in the medical industry not only as models, but also as advanced products in some of the following divi-

sions:

- a. Customized prosthetics
- b. Tailor-made implants
- c. Functional implantable devices
- d. Drug delivery
- e. Tissue engineering

Material selection for the manufacture of patient-specific biomedical product is not an easy task, especially for those advanced materials with unique properties that may require control during its production. Materials such as high-performance polymers, metals, ceramics or even biomaterials can provide good level of strength, rigidity, and heat resistance but some others have to be modified in order to improve their properties.

Polymers and composites are the most employed materials in AM-fabricated biomedical devices. Examples include poly-propylene fumarate (PPF) as a model material for extrusion-based printing applications, where 3D printed scaffolds can incorporate bioactive molecules, composites, and cells, in which FDM (Fused Deposition Modeling) holds the advantage over STL (Stereolithography) techniques [46]. Polycaprolactone (PCL) hybrid, formulated from PCL polymer and cell-impregnated hydrogel, was studied with good results on biofabrication enabling good biological performance (viability, proliferation, and cartilage ECM secretion) of three different cell types (two primary embryonic cell populations and an established chondrocyte line) [47]. Another material commonly found in the literature is polymethylmetacrylate, and as a composite, the medical example is found on the fabrication of a placenta model, to study the preeclampsia phenomena in a in-vitro process using, gelatin methacrylate [48].

A second category of materials commonly found in the literature is apatite type materials, mainly for bone repair applications. Such is the case of 3D printed mesoporous  $\text{CaSiO}_3$  containing  $\text{CeO}_2$ , where the incorporation of Ce into Ca-Si system stimulated the in-vitro proliferation and osteogenic differentiation of hBMSCs. The

authors reported that their results indicate that CeO<sub>2</sub>-MCS scaffolds induced similar apatite deposition and cell attachment of human bone marrow stromal cells. In addition, CeO<sub>2</sub>-MCS scaffolds enhanced expression of alkaline phosphatase, osteogenesis genes (bone morphogenetic protein-2, collagen type I), and angiogenesis gene markers (fibroblast growth factor and vascular endothelial growth factor), compared to that for MCS scaffolds [49]. On the same direction, research informed by Adam Jakus, showed that the hybrid material obtained from hydroxyapatite microspheres (Hyperelastic Bone, HB) and other materials that contain graphene nanoflakes (3D-Graphene, 3DG), exhibits mixed characteristics of the two distinct systems, while maintaining 3D-printability, electrical conductivity, and flexibility. In-vitro assessment of HB-3DG using mesenchymal stem cells demonstrates the hybrid material supports cell viability and proliferation, as well as significantly upregulates both osteogenic and neurogenic gene expression over 14 days. Advancing on the construction of materials to the composite tissue engineering [50]. Another example with the use of apatite, includes the use of bioactive glass particles in a crosslinking reaction of alginate with calcium ion from 3D printed bioactive glass scaffolds, with excellent results on the good maintaining; there were a calcium controlling release, and the as obtained biocompatible alginate protected cells from the alkaline environment stage, which promoted early cell adhesion, suggesting that it could have the potential for bone regeneration [52].

A different approach for bone substitution, integrate the use of poly-lactic-co-glycolic acid (PLGA) scaffolds that enables the development of materials capable to promote early vascularization, in this case, after transplantation [51]. Regarding materials structure, a paper published by Ting Pan is dedicated to the study of a material that can provide sufficient amount of pores in order to get adequate mechanical properties, using to this end Gelatin/Alginate scaffolds, so they can be used for cells and/or drugs materials encapsulation [53]. An approximation where the activity of the hybrid material is tested with similar scaffolds, is found on Chen's paper [54], where the potential application of this gel scaffold in bone tissue engineering was confirmed by encapsulation behavior of osteoblasts.

Injectable and biodegradable alginate-based composite gel scaffolds doubly integrated with hydroxyapatite and gelatin microspheres (GMs), were cross-linked via in-situ release of calcium cations. As triggers of calcium cations, CaCO<sub>3</sub> and glucono-D-lactone (GDL) were fixed. Synchronously, tetracycline hydrochloride (TH) was encapsulated into GMs to enhance bioactivity of composite gel scaffolds. Similar to the results obtained for the strontium-substituted, hydroxyapatite microspheres (SrHA) incorporated alginate composite microspheres as pH responsive for drug delivery [55].

The use of magnetic nanomaterials has become one of the more prolific research areas in medicine applications, thus their inclusion in the production of materials for AM technologies is automatic; some examples of this studies are included in Concalve's paper, where the authors use magnetic scaffolds aim for its use in tendon tissue engineering (TTE), developing magnetic polymer scaffolds with aligned structural features, aimed at applications in TTE. Tissue engineering magnetic scaffolds were synthesized by incorporating iron oxide magnetic nanoparticles (MNPs) into a 3D structure of aligned starch and polycaprolactone (SPCL) fibers fabricated by rapid prototyping (RP) technology. The authors concluded that the effect of the magnetic aligned scaffolds structure combined with magnetic stimulation, has a significant potential to impact the field of TTE towards the development of more efficient regeneration therapies [56].

Electrical properties are also of interest in the medical application of AM processes as shown attractively on the research of fibres composed of polypyrrole (PPy) nanoparticles and reduced graphene oxide. These composite fibres showed promising mechanical and electrical properties, while cell growth was not significantly impeded, opening up a wide range of potential applications, including nerve and muscle regeneration studies [57]. Each process has its own limitations, as also a narrow variety of materials is suitable for each specific AM process.

#### Concluding remarks

Technological evolution of nanomaterials alongside with the progress in additive manufacturing is still a young field for research and innovation, where efforts should be directed towards the de-

velopment of customised biomedical products with enhanced properties and improved geometrical, biological and mechanical performance, at relatively low cost and short period of times.

This paper aims to bring the reader a glance of some of the fundamentals in the areas of nanocomposites and additive manufacturing, and some of the most representative research results in the field, underlining the need to study the nanomaterials development simultaneously with AM processes, so as to address some of the most critical technical challenges yet to overcome.

Nanocomposites for additive manufacturing is a promising area that has the prospective to develop high-value products, particularly for biomedical applications, that may soon reach the general population and improve the quality of life in our society, as it has the potential to bring less invasive and personalised therapies.

New nanomaterials and AM processes are still to be explored and the synergy between these two fascinating areas will soon define the way AM and nanocomposites will affect our lives in the near future.

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## References

1. Well S as. Aldrich Materials Science. Available from: <http://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Aldrich/Brochure/1/material-matters-v11-n1.pdf>
2. Campbell FC. Structural Composite Materials. ASM International; 2010.
3. Chawla KK. Composite Materials: Science and Engineering. Third. Springer New York; 2012. (SpringerLink : Bücher).
4. United States National Nanotechnology Initiative. National Nanotechnology Initiative [Internet]. Nano.gov. [cited 2016 Aug 13]. Available from: <http://www.nano.gov/>
5. Thostenson ET, Li C, Chou T-W. Nanocomposites in context. *Compos Sci Technol.* 2005/3;65(3-4):491-516.
6. Ajayan PM, Schadler LS, Braun PV. Nanocomposite Science and Technology. Wiley; 2006. 239 p.
7. Braun PV. Natural Nanobiocomposites, Biometric Nanocomposites, and Biologically Inspired Nanocomposites. In: *Nanocomposite Science and Technology.* Wiley-VCH Verlag GmbH & Co. KGaA; 2003. p. 155-214.
8. Hule RA, Pochan DJ. Polymer Nanocomposites for Biomedical Applications. *MRS Bull.* 2007;32(04):354-8.
9. Ruiz-Hitzky E, Aranda P, Darder M. Bionanocomposites. In: *Kirk-Othmer Encyclopedia of Chemical Technology.* John Wiley & Sons, Inc.; 2000.
10. Darder M, Aranda P, Ruiz-Hitzky E. Bionanocomposites: A New Concept of Ecological, Bioinspired, and Functional Hybrid Materials. *Adv Mater.* 2007 May 21;19(10):1309-19.
11. Yu H-Y, Qin Z-Y, Yan C-F, Yao J-M. Green Nanocomposites Based on Functionalized Cellulose Nanocrystals: A Study on the Relationship between Interfacial Interaction and Property Enhancement. *ACS Sustainable Chemistry & Engineering.* 2014;2(4):875-86.
12. Guigo N, Vincent L, Mija A, Naegel H, Sbirrazzuoli N. Innovative green nanocomposites based on silicate clays/lignin/natural fibres. *Compos Sci Technol.* 2009/9;69(11-12):1979-84.
13. Wegst UGK, Bai H, Saiz E, Tomsia AP, Ritchie RO. Bioinspired structural materials. *Nat Mater.* 2014 Oct 26;14(1):23-36.
14. Zhang C, Mcadams DA 2nd, Grunlan JC. Nano/Micro-Manufacturing of Bioinspired Materials: a Review of Methods to Mimic Natural Structures. *Adv Mater.* 2016 Aug;28(30):6292-321.
15. Langer R, Vacanti JP. Tissue engineering. *Science.* 1993 May 14;260(5110):920 LP - 926.
16. Okamoto M, John B. Synthetic biopolymer nanocomposites for tissue engineering scaffolds. *Prog Polym Sci.* 2013;38(10-11):1487-503.
17. Armentano I, Dottori M, Fortunati E, Mattioli S, Kenny JM. Biodegradable polymer matrix nanocomposites for tissue engineering: A review. *Polym Degrad Stab.* 2010;95(11):2126-46.
18. Pina S, Oliveira JM, Reis RL. Natural-based nanocomposites for bone tissue engineering and regenerative medicine: A review. *Adv Mater.* 2015;27(7):1143-69.
19. Yang J, Liu W, Sui M, Tang J, Shen Y. Platinum (IV)-coordinate polymers as intracellular reduction-responsive backbone-type conjugates for cancer drug delivery. *Biomaterials.* 2011 Dec;32(34):9136-43.

20. Rhim JW, Wang LF, Hong SI. Preparation and characterization of agar/silver nanoparticles composite films with antimicrobial activity. *Food Hydrocoll.* 2013;33(2):327–35.
21. Yang C-H, Wang L-S, Chen S-Y, Huang M-C, Li Y-H, Lin Y-C, et al. Microfluidic assisted synthesis of silver nanoparticle–chitosan composite micro-particles for antibacterial applications. *Int J Pharm.* 2016;510(2):493–500.
22. Daniel M-C, Astruc D. Gold Nanoparticles: Assembly, Supramolecular Chemistry, Quantum-Size-Related Properties, and Applications toward Biology, Catalysis, and Nanotechnology. *Chem Rev.* 2004 Jan 1;104(1):293–346.
23. Matteini P, Ratto F, Rossi F, Centi S, Dei L, Pini R. Chitosan films doped with gold nanorods as laser-activatable hybrid bioadhesives. *Adv Mater* [Internet]. 2010;22. Available from: <http://dx.doi.org/10.1002/adma.201002228>
24. Veetil JV, Ye K. Tailored Carbon Nanotubes for Tissue Engineering Applications [Internet]. Vol. 25, *Biotechnology progress.* 2009. p. 709–21. Available from: <http://dx.doi.org/10.1002/bp.165>
25. Vila M, Cicuéndez M, Sánchez-Marcos J, Fal-Miyar V, Manzano M, Prieto C, et al. Electrical stimuli to increase cell proliferation on carbon nanotubes/mesoporous silica composites for drug delivery. *J Biomed Mater Res A.* 2013 Jan 1;101A(1):213–21.
26. Balint R, Cassidy NJ, Cartmell SH. Conductive polymers: Towards a smart biomaterial for tissue engineering. *Acta Biomater.* 2014;10(6):2341–53.
27. Vasita R, Katti DS. Nanofibers and their applications in tissue engineering [Internet]. Vol. 1, *International Journal of Nanomedicine.* 2006. p. 15–30. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17722259>
28. Saito N, Aoki K, Usui Y, Shimizu M, Hara K, Narita N, et al. Application of carbon fibers to biomaterials: A new era of nano-level control of carbon fibers after 30-years of development. *Chem Soc Rev.* 2011;40(7):3824–34.
29. Zuo P-P, Feng H-F, Xu Z-Z, Zhang L-F, Zhang Y-L, Xia W, et al. Fabrication of biocompatible and mechanically reinforced graphene oxide-chitosan nanocomposite films. *Chem Cent J.* 2013;7(1):1–11.
30. Dong HS, Qi SJ. Realising the potential of graphene-based materials for biosurfaces – A future perspective. *Biosurface and Biotribology.* 2015;1(4):229–48.
31. Yang Y, Asiri AM, Tang Z, Du D, Lin Y. Graphene based materials for biomedical applications. *Mater Today.* 2013;16(10):365–73.
32. Melchels FPW, Domingos MAN, Klein TJ, Malda J, Bartolo PJ, Hutmacher DW. Additive manufacturing of tissues and organs. *Prog Polym Sci.* 2012/8;37(8):1079–104.
33. Akkineni AR, Luo Y, Schumacher M, Nies B, Lode A, Gelinsky M. 3D plotting of growth factor loaded calcium phosphate cement scaffolds. *Acta Biomater.* 2015;27:264–74.
34. F42 Committee. Standard Terminology for Additive Manufacturing - General Principles - Terminology [Internet]. Available from: <http://dx.doi.org/10.1520/f3177-15>
35. Bourell DL. Perspectives on Additive Manufacturing. *Annu Rev Mater Res.* 2016;46(1):1–18.
36. Ian Gibson, David W. Rosen, Brent Stucker *Additive Manufacturing Technologies- Rapid Prototyping to Direct Digital Manufacturing 2009.pdf.*
37. Stansbury JW, Idacavage MJ. 3D printing with polymers: Challenges among expanding options and opportunities. *Dent Mater.* 2016 Jan;32(1):54–64.
38. Godoi FC, Prakash S, Bhandari BR. 3d printing technologies applied for food design: Status and prospects. *J Food Eng.* 2016/6;179:44–54.
39. Gao W, Zhang Y, Ramanujan D, Ramani K, Chen Y, Williams CB, et al. The status, challenges, and future of additive manufacturing in engineering. *Comput Aided Des Appl.* 2015 Dec;69:65–89.
40. Sarobol P, Cook A, Clem PG, Keicher D, Hirschfeld D, Hall AC, et al. Additive Manufacturing of Hybrid Circuits. *Annu Rev Mater Res.* 2016;46(1):41–62.
41. Weller C, Kleer R, Piller FT. Economic implications of 3D printing: Market structure models in light of additive manufacturing revisited. *Int J Prod Econ.* 2015/6;164:43–56.
42. Gardan J. Additive manufacturing technologies: state of the art and trends. *Int J Prod Res.* 2016;54(10):3118–32.
43. Andreas Gebhardt. *Layer Manufacturing Processes.* In: *Understanding Additive Manufacturing.* Carl Hanser Verlag GmbH & Co. KG; 2011. p. 31–63.
44. Taylor SL, Jakus AE, Shah RN, Dunand DC. Iron and Nickel Cellular Structures by Sintering of 3D-Printed Oxide or Metallic Particle Inks. *Adv Eng Mater* [Internet]. 2016 Sep 1; Available from: <http://dx.doi.org/10.1002/adem.201600365>
45. Gibson I, Rosen D, Stucker B. *Applications for Additive Manufacture.* In: *Additive Manufacturing Technologies.* Springer New York; 2015. p. 451–74.

46. Trachtenberg JE, Placone JK, Smith BT, Piard CM, Santoro M, Scott DW, et al. Extrusion-Based 3D Printing of Poly(propylene fumarate) in a Full-Factorial Design. *ACS Biomaterials Science & Engineering*. 0(0):null.
47. Zohreh I, Tuanjie C, William K, Xiongbiao C, Frank EB. Analyzing Biological Performance of 3D-Printed, Cell-Impregnated Hybrid Constructs for Cartilage Tissue Engineering. *Tissue Eng Part C Methods*. 2016;22(3):173–88.
48. Kuo C-Y, Eranki A, Placone JK, Rhodes KR, Aranda-Espinoza H, Fernandes R, et al. Development of a 3D Printed, Bioengineered Placenta Model to Evaluate the Role of Trophoblast Migration in Pre-eclampsia. *ACS Biomaterials Science & Engineering*. 0(0):null.
49. Zhu M, Zhang J, Zhao S, Zhu Y. Three-dimensional printing of cerium-incorporated mesoporous calcium-silicate scaffolds for bone repair. *J Mater Sci*. 2015 Sep 10;51(2):836–44.
50. Jakus AE, Shah RN. Multi- and mixed 3D-printing of graphene-hydroxyapatite hybrid materials for complex tissue engineering. *J Biomed Mater Res A [Internet]*. 2016 Feb 10; Available from: <http://dx.doi.org/10.1002/jbm.a.35684>
51. Schumann P, Kampmann A, Sauer G, Lindhorst D, von See C, Stoetzer M, et al. Accelerated vascularization of tissue engineering constructs in vivo by preincubated co-culture of aortic fragments and osteoblasts. *Biochem Eng J*. 2016 Jan 15;105, Part A:230–41.
52. Zhao F, Zhang W, Fu X, Xie W, Chen X. Fabrication and characterization of bioactive glass/alginate composite scaffolds by a self-crosslinking processing for bone regeneration. *RSC Adv*. 2016 Sep 12;6(94):91201–8.
53. Pan T, Song W, Cao X, Wang Y. 3D Bioplotting of Gelatin/Alginate Scaffolds for Tissue Engineering: Influence of Crosslinking Degree and Pore Architecture on Physicochemical Properties. *J Mater Sci Technol*. 2016/9;32(9):889–900.
54. Yan J, Miao Y, Tan H, Zhou T, Ling Z, Chen Y, et al. Injectable alginate/hydroxyapatite gel scaffold combined with gelatin microspheres for drug delivery and bone tissue engineering. *Mater Sci Eng C Mater Biol Appl*. 2016 Jun;63:274–84.
55. Li H, Jiang F, Ye S, Wu Y, Zhu K, Wang D. Bioactive apatite incorporated alginate microspheres with sustained drug-delivery for bone regeneration application. *Mater Sci Eng C Mater Biol Appl*. 2016 May;62:779–86.
56. Gonçalves AI, Rodrigues MT, Carvalho PP, Bañobre-López M, Paz E, Freitas P, et al. Exploring the Potential of Starch/Polycaprolactone Aligned Magnetic Responsive Scaffolds for Tendon Regeneration. *Adv Healthc Mater*. 2016 Jan 21;5(2):213–22.
57. Schirmer KSU, Esrafilzadeh D, Thompson BC, Quigley AF, Kapsa RMI, Wallace GG. Conductive composite fibres from reduced graphene oxide and polypyrrole nanoparticles. *J Mater Chem B Mater Biol Med*. 2016 Jan 4;4(6):1142–9.
58. Leopoldo Ruiz-Huerta Yara Cecilia Almanza-Arjona Alberto Caballero-Ruiz Homero Alberto Castro-Espinosa Celia Minerva Díaz-Aguirre Enrique Echevarría y Pérez , (2016), "CAD and AM-fabricated moulds for fast cranio-maxillofacial implants manufacture", *Rapid Prototyping Journal*, Vol. 22 Iss 1 pp. 31 - 39

