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# Industrial Revolution 4.0 and the 3D printing in Biotechnology of tissue regeneration

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**Abstract:** When portrayed to the current society, the industry is considered as part of the society economically responsible for the development and production of consumer goods. The processes of industrial revolution were highlighted by phases of improvement and technological advances (1st Industrial Revolution), the use of electric energy (2nd Industrial Revolution), and the dissemination of the digitalization of technology (3rd Industrial Revolution). In addition, nowadays such developments can be associated with the use of the internet and the automation of processes by artificial intelligence, thus reaching the 4th Industrial Revolution. The concept of Industry 4.0 is directly linked to the concept of intelligent fabrics, starting from factors such as innovation, which allows companies to have complex production models including mainly sustainable character and applied biotechnologies. In addition, both the 4th Industrial Revolution and biotechnology can be correlated in terms of 3D bioprinting. Thus, the work shows a brief history of 3D printers and their potential in applications in the area of tissue engineering. It reveals the need for multidisciplinarity and increasingly qualified professionals in the face of the new phase of socioindustrial evolution.

**Keywords:** 3D printing. Additive manufacturing. Biotechnology. Tissue engineering.

## Introduction

In the context of social technological developments, areas such as the industrial sector undergo direct modifications as technological advances develop. Thus, more significant changes in the market in the worldwide result in major changes. In the last decades, one of these transformations that marked all scenarios was the insertion of the internet. Together with the internet, the industry entered a new stage in its evolutionary process, with the emergence of the Industrial Revolution 4.0. This process has brought great scientific technical advances where processes have become more reproducible and agile, with this, the growth of the market for 3D printers, especially in relation to rising areas such as biotechnology.

Thus, the objective of this review is to highlight the main points of Industrial Revolution 4.0, relating the area of biotechnology by its presenting concepts, and relating points to the professional future for such technological junction in tissue engineering.

## Industrial revolution 4.0

Following the terms of the industrial revolution, the industry is considered as part of the society, which is economically responsible for the development, and production of consumer goods, using highly mechanized procedures to achieve this goal.[1] When portrayed the vision of future in industrial production, the tendency of modular application and high efficiency manufactured industrial systems rose, which has its self-control of production quality and standardization.[2]

In addition, the evolution of industrial processes has been highlighted by phases of improvement and technological advances, such as mechanization of manufactures (1st Industrial Revolution), intense electricity use (2nd Industrial Revolution), and the spread of technology digitization (3rd Industrial Revolution).[2] However, combining such technologies with the use of the internet, artificial intelligence and processes automation, it is possible to achieve the 4th Industrial Revolution.

Thus, the internet becomes a key factor in the advances of this revolution, especially because it is a public technology and not a technology owned by a single owner.[3] Based on this factor, the application of the internet in economic scenarios causes their total transformation, as mentioned by Rifkin.[4] This trend is confirmed by the concept of zero marginal cost, emphasizing connectivity in anticipation of a collaborative economy. For this reason, it replaces the capital system in its current form, especially when it comes to internet products, that helps directly the faster progress and a more collaborative world, resulting in increasingly intelligent cities.[5]

In view of these claims, the 4th Industrial Revolution affects political, social and mainly economic organizations around the globe. Moreover, its main scope modifies the production structure, enabling its increase, and supplying previously unseen pressures such as the sustainability and protection of the environment.[1]

In addition to this new production structure, new structuring models are also required with regard to resource preservation and management. The development directly affects the industrial model, so the final disposal of products and waste is also affected. Thus, the model of Industrial Sustainability 4.0 emerges on the global stage.[6]

When referring to this term, Industrial Sustainability 4.0 is primarily the basis of the concept of sustainability in its entirety, emphasizing that it find out the requirements of the current generation without compromising the future generations.[7,8] Thus, the base pillars that form sustainability as a simple structure are constituted by economic, social and environmental factors. The pillars adhere to the transition circle between technological innovation and social innovation, of which they are responsible for providing sustainable solutions that meet the three sustainability criteria, and can also act as a mechanism for assessing any related Industry 4.0.[8]

Moreover, when associated with the evolution of these technologies, the cyber-physical union makes this revolution increasingly applied to the areas related to computational technology. Thus, as an example of industries that grew exponentially with the development of this new stage

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of technological advancement, it is possible to mention the industries of smartphones, internet services and related goods, and improvements of services previously considered basic.[2,9]

Therefore, the concept of Industry 4.0 is directly linked to the concept of intelligent manufacturing, or smart factory. Presenting as essential feature, factors such as innovation, which allows companies to have complex production models as well as ensure the possibility of unexpected interruptions as well more efficient products. In short, in a smart factory, staff, machinery, and production resources have communication that flows naturally and constantly as if they were directly interconnected.[10]

In addition, areas that grew together with the 4th Industrial Revolution are the areas of biological sciences and health. Unlike previous revolutions, these areas have had a great scientific technical support, which generated great expectation in the development of technology.[11] Together with the rise of Revolution 4.0 to the joining of biological and math areas, the rise of a previously existing but still developing area, the Biotechnology has gained momentum across the globe.

### Biotechnology definition

With the beginning of the twentieth century, great scientific technical advances allowed the development of new technologies. Mainly when related to areas of genetics, which the application of Mendel's laws, along with Morgan's discoveries provided new models of knowledge. Based on this assumption, the rediscovery of biological inheritance followed by gene localization became even more applicable, as gene manipulation allowed great progress in the scientific community.[12]

Moreover, in 1990, with the sequencing of the human genome, the use of genetic engineering became even more popular, opening fields not previously explored in the political–social–scientific scenario.[13] Since then, biotechnology has become increasingly noticeable in scientific circles, gaining greater prominence in the areas of food production and health.

However, when related to the term "Biotechnology", there is still a great divergence about its concept, in short, as quoted by Faleiro, Andrade and Reis Junior,[14] "Biotechnology is a set of techniques that uses living beings, or part of them, in the development of processes and/or products that have an economic and (or) social function".

In addition, other definitions are presented as: "It is the use of knowledge about biological processes and the properties of living things in order to solve problems and create utility products."[15] When related to classical biotechnology, we can also find even broader definitions: "It is the industrial use of fermentation processes ... technology that allows the use of biological material for industrial purposes."[16] "It is a set of techniques that use living things, or part of them, to produce or modify products, increase plant and animal productivity efficiently, or produce microorganisms for specific uses."[17]

In portraying modern biotechnology, we can find definitions as: "It's the use of cells and biomolecules for problem solving or product transformation. It is a set of techniques that enhances the best characteristics of cells, such as productive capacities, and makes available biological molecules, such as DNA and proteins, to be used".[18] "It is the development of products by biological processes using recombinant DNA technology".[19] "Spectrum or set of molecular technologies applied to the study of microorganisms, plants and animals."[20,21]

### Biotechnology application areas

When looking at to the term biotechnology, it is noted that it has a wide spectrum of actions, including the need for a multidisciplinary professional, precisely due to the union of areas such as biology, engineering and chemistry for applications in the production of goods (Figure 1).

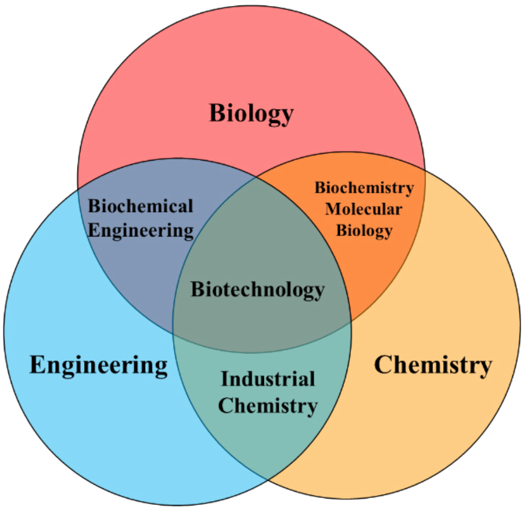


**Figure 1 –** Outline of the major constituent areas of biotechnology. Source: Biotechnology Information Council.[21]

Thus, the use of biotechnology associated with its various factors applicable to industry 4.0 has been highlighted in the current scenario, in which numerous biotechnological methodologies bring about and new production systems, increasing the economic, social and environmental benefits, besides the industrial application.[14]

Finally, the parallel growth of biotechnology coupled with the Industrial Revolution 4.0, especially in healthcare, leads to increasingly sophisticated new techniques and their broader applicability using the most advanced and efficient technological methodologies. For this reason, the use of nano–technology, nanobiotechnology, gene therapy, molecular biology, genetic engineering and mainly the area of tissue engineering can be mentioned.[22]

### Tissue engineering concept

The term tissue engineering was first described in 1988 as: "the application of engineering and life science principles and methods, toward the fundamental understanding of structure–function relationships in normal and pathological mammalian tissues, and the development of biological substitutes to restore, maintain or improve tissue function".[23]

In short, the tissue engineering is related to the use of principles from the cell transplants, associated with the material science with the objective to develop biological substitutes leading to regeneration to a normal tissue function. Moreover, it is possible to divide it in two classifications: the first is the use of acellular matrices, the regeneration depends directly of the body's natural ability to orientate the tissue regeneration; normally this technique use scaffolds application followed by chemical stimuli for starting the tissue reconstruction. The second is related to the use of cellular matrices that are correlated to applications of material contend incorporated cells, these cells can be heterologous (such as bovine), allogeneic (same species, different individual), or autologous. In this case, the use of autologous cells is preferred because of the lower rejection possibility, and avoids the deleterious side effects caused by the immunosuppressive medication after application.[24,25]

In addition, it has a multidisciplinary character, encompassing chemical, physical, biological and medical knowledge for the development of via–ble biological substitutes for their restoration, maintenance and suitability. Thus, it aims to develop therapeutic options to be applied under specific clinical conditions, by tissue replacement and/or regeneration using biomaterials.[26–28]

### Tissue engineering applications

Tissue engineering directly utilizes porous 3D supports to condition the most conducive environments for tissue and organ regeneration. These supports, called scaffolds, essentially function as a model for tissue formation, where they are typically cultured with cells and growth factors, or occasionally subjected to biophysical stimuli in the form of a bioreactor.[29] These cell scaffolds are cultured ***in vitro*** to synthesize tissues that can be implanted at the wound site or directly at the site of injury using the patient's own body as a system, in which tissue or organ regeneration is induced ***in vivo***. This combination of cells, growth factors and scaffolds is often referred to as the tissue engineering triad.[23]

The success of this methodology depends directly and mainly on the nature of these biomaterials, which can be modified to mimic the extracellular matrix (ECM) architecture of the target tissues, which are characterized by a complex organization of structural proteins and fibers such as collagen and a diversity of proteoglycans and polysaccharides.[26,27] Thus, biomaterials are used to act in the biological interface of systems enabling, treating, increasing, improving or replacing any tissue, organ or function of the body, partially or totally.[30]

Following this reasoning, when considering an ideal biomaterial, characteristics such as the variety of sizes and shapes, as well as the resistance to places where they may suffer impact loads should be taken into account. Another point to be emphasized is biocompatibility, material resorption and possible substitution by the formation of a new tissue.[31] Due to the fact that after implantation of the "substitute" tissue would occur an increase in cellular functions, and the induction of cell growth on the porous surface and internal pores, resulting in the tissue formation process.[32]

When related to the types of biomaterials, two types can be found: natural and synthetic. Natural biomaterials simulate the structure and com–position of the native extracellular matrix, allowing the insertion of growth factors and other proteins capable of boosting cellular functions. However, they easily deteriorate and allow the transfer of pathogens to the host, their variability depends on the structure of the original natural polymer.[33,35] Synthetic biomaterials, on the other hand, do not have the characteristic of simulation of the native extracellular matrix, and generally consist of self–assembling peptides that can be modified in order to acquire biologically active characteristics. In addition, they are easy to handle since they have a controlled degradation rate and do not allow the transfer of pathogens to the host. However, they often require signaling molecules to aid in the interaction between cells and material, and further degradation can produce undesirable byproducts.[33,35]

Tissue engineering involves culturing cells by sowing them in biocompatible scaffolds, allowing them to grow and mature (***in vitro*** or via biore–actor) to form the desired tissues. Today, 3D bioprinting technology enables systems to obtain greater precision in the spatial relationship between individual elements of the desired tissue, and holds great promise for applications in biotechnology and regenerative medicine.[35] However, to portray 3D bioprinting, a prior background on the technique of additive manufacturing or 3d printing is required.

### Additive manufacture or 3D printing

### Definition of additive manufacturing or 3D printing

Three–dimensional printing is a method whereby materials such as plastics, metals or polymers are deposited in layers to produce an object in three dimensions.[36] Its use has been applied for the most diverse purposes.[37] In addition, the advancement of technologies driven by the evolution of production processes, such a technology has been explored further as even in biomedical areas.[38]

### 3D printing company history

When related to 3D printing companies, the story begins with Helisys, founded by Feygin in 1985. Its main product is the sheet lamination pro–cess. Its first delivery was in 1991, however the company closed in 2000.[39] Also in 1985, Deken (Japan) introduced its first stereolithography machine (SLP–3000) in 1993.[39,40] In 1986, Hull and Freed formed 3D Systems, which was considered the first modern additive manufacturing machine, the SLA–1, and was launched in 1987, with its first sale taken place in 1988, and its patent approved in 1992.[41] In 1988, Stratasys was founded as the first company to develop fused deposition modeling in 1991 and its patent was accepted in 1992.[42,39]

According to Dipaola[43], the evolution of bioprinting companies is divided into ages, in which the first era (1970–1980) is marked by the first de–monstration of a prototype additive manufacturing. Followed by the second era (1980–1990), marked by the emergence of models of stereolithography and selective leisure sintering, along with the birth of 3D Systems. The third era (1990–2005) was marked by the increase in computing resources and the maturation of industrial 3D printing spurred the emergence of other new printing companies in the world. The fourth era (2005–2012) has the rapid expansion and greater awareness of 3D printing as its main factor, which results in an expansion of the printing area, especially with the increasing applicability of the technique. The fifth and sixth eras (2012–2017) were the period where second–generation 3D printers and the begin–ning of medical application of this technology appear. Finally, with the end of the patent period, 3D printing became very popular across the globe, reaching even domestic sectors, and, under the influence of the Industrial Revolution 4.0, became a much–targeted tool in all areas of knowledge.

### 3D printing evolution perspective

According to a study by the US National Center for Manufacturing Sciences (1998), 3D printing techniques were unified in mid–1998, process trifurcation was expected to occur by the year 2010, and considerable increased production volume when referring to prototype applications.[44]

In this way, the use of 3D printers, are increasing as technologies are discovered. Thus, by associating such technology with the evolution brought about by the computer age, new part design methodologies emerge. Which guarantees the reproducibility of the process, relating the customization, mass and volume of the part without the loss of quality of the final product.[40] In this context, the various applications of 3D printers because the differences between their models can be highlighted, which may vary directly or indirectly depending on their purpose and/or used material.

### Types of 3D printers

Among 3D printer development models, there is a great diversity of shapes and models. However, despite its wide range of applications the basis of printing is the same, from a virtual image (usually in computer aided design or CAD format) to obtains a real object in three dimensions. Thus, the foundation of this "3D printing" is differentiated by its application methodology as described below.

#### *Selective laser fusion*

Selective laser fusion (SLF) arose from the need to manufacture full–density parts in which the mechanical properties similar to those of bulk materials are guaranteed, as well as avoiding long post–processing cycles.[45,46]

During SLF processing, the beam is scanned over a thin layer of a powder (usually metallic or ceramic). Thus, the process of object formation continues along the direction of the laser beam. Later, each layer is sequentially filled with elongated fillets of melted powders. As a result, the object is constructed from overlays of fillets and layers.[47]

#### *Deposition of molten material*

Fused deposition modeling is based on the principle of depositing a thermoplastic material on a platform. Subsequently, the layers are deposited on the previously printed layers, while the other wires support the new layer, thus forming the new object.[48]

#### *Electron beam fusion*

Electron beam melting (EBM) is given by melting the pulverized material layer by layer using an electron beam in a high vacuum condition. Thus, this technique can delineate high density parts, without extremely strong voids, which differs from some metal sintering techniques. Moreover, this technique is generally used for metals that have high reactivity with oxygen, which makes it an advantage, since the vacuum is used, preventing interaction with it.[49,50]

#### *Digital light processing*

Digital light processing is characterized by the use of UV light to solidify a liquid photo polymer.[51] Such technique is widely used due to its high print speed and its simple mechanisms when related to its software. In which, photocurable liquid polymerization is performed layer by layer, thus obtaining the object in three dimensions.[52]

### 3D bioprinting

Three–dimensional bioprinting technology is directly related to the deposition of biomaterials, cells, biological structures and layer–by–layer growth factors in order to produce biosimilar and biocompatible tissues and organs. In addition, such technology enables the use of cell suspension printing in a scaffolded or nonscaffolded structure.[35,53]

One of the main points to be emphasized in the process of bioprinting is its soft and friendly characteristic to the cells, since such technique should allow the impression of them without damage, which would allow the maintenance of cell survival after the procedure. Thus, this requirement limits many 3D printing techniques that are suitable for such purpose. These techniques include direct ink writing, which allows the extrusion of high viscosity solutions, hydrogels, colloidal suspensions, cell suspensions and/or aggregates with or without chargers.[53]

Unlike other conventional printing techniques, the main advantages of using 3D bioprinting are accurate deposition, repeatability, simplicity and controlled cell distribution, and the constant development of this technique in recent years. Thus, bioprinting has become a major field of application, being represented mainly as the great technical–scientific advance in the face of the Industrial Revolution 4.0.

### Conclusion

The Industrial Revolution 4.0 has become a major factor in perfecting previously unexplored techniques. In addition, the use of new technologies associated with biotechnology has contributed to a better quality of life. Nowadays, in the age of computerization and technological improvement, the increase in development, especially in areas such as engineering, reflects enhancement and advances not previously aimed at all areas of application and knowledge. In other words, this evolution tends to need more and more qualified professionals, mainly due to the multidisciplinarity required to new production processes.


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