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# Biomedical production of implants by additive electro-chemical and physical processes

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ABSTRACT

Biomanufacturing integrates life science and engineering fundamentals to produce biocompatible products enhancing the quality of life. The state-of-the-art of this rapidly evolving manufacturing sector is presented and discussed, in particular the additive electrical, chemical and physical processes currently being applied to produce synthetic and biological parts. This fabrication strategy is strongly material-dependent, so the main classes of biomaterials are detailed. It is explained the potential to process composite materials combining synthetic and biological materials, such as cells, proteins and growth factors, as well the interdependences between materials and processes. The techniques commonly used to increase the bioactivity of clinical implants and improve the interface characteristics between biological tissues and implants are also presented.



## 1. Introduction

The ageing population, high expectations for a better quality of life and the changing lifestyle of modern society require improved, more efficient and affordable health care. This poses new challenging problems regarding the increasing number of implants required, new diseases to be treated (*e.g.*, Parkinson's and Alzheimer's) and organ shortage problems. On the other hand, some medical devices ideally should survive without experiencing any failures for the patent's lifetime.

The loss or failure of an organ or tissue is a frequent and costly problem in health care. Today, treatments include either transplanting organs from one individual to another or performing surgical reconstructions by transferring tissue from one location in the patient's body into the diseased site. The disparity between the need and availability of donor tissues has motivated the development of tissue engineering approaches aimed at creating cell-based substitutes of native tissues [16,17,151].

To address some of these demanding issues, a new scientific domain called biomanufacturing emerged in 2005, during the Biomanufacturing Workshop hosted by Tsinghua University in China and defined as "the use of additive technologies, biodegradable and biocompatible materials, cells and growth factors to produce biological structures for tissue engineering applications" [22]. More recently, in a meeting sponsored by the American National Science Foundation in the spring of 2008, biomanufacturing was defined as "the design, fabrication, assembly and measurement of bio-elements into structures, devices, and systems, and their interfacing and integration into/with larger scale structures *in vivo* or *in vitro* environment such that heterogeneity, scalability and sustainability are possible." In 2009, during the 59th CIRP General Assembly, a Collaborative Working Group (CWG) on biomanufacturing was established based on three main pillars: Biofabrication, Biomechatronics and Biodesign, and Assembly. The goal of this CWG is to contribute to a coherent strategy for the development, dissemination and exploitation of biomanufacturing. To pursue this goal, the CWG aims to optimise current technologies and develop new ones in the areas of computer-integrated surgical systems, tissue engineering, bio-informatics and nano diagnosis/medicine, based on the theories and the technologies established in each CIRP Scientific Technical Committee (STC).

This review follows the establishment of the CIRP CWG's focus on current healing and repairing strategies. Despite the complexity associated with the design, fabrication and implantation of appropriate medical implants, this paper addresses only three critical topics: biomaterials, manufacturing processes and surface treatments for the fabrication of clinical implants, the only biomedical implants considered here (Fig. 1). Biomanufacturing

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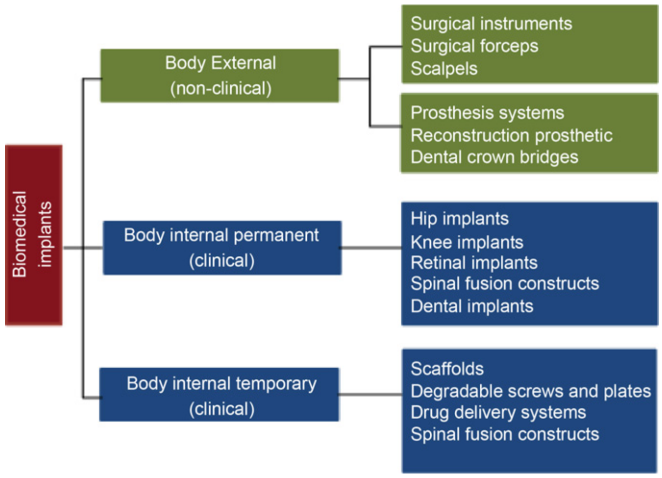


**Fig. 1.** Classification of biomedical implants.

is a strongly material- and process-dependent fabrication procedure in which materials not commonly used in conventional production engineering are considered. The main characteristics of those materials strongly determine the electro-chemical and physical additive manufacturing processes to be used, as well as the application range of these production technologies. The application context of this work is detailed in Section 2, where the main characteristics of the considered clinical implants (permanent and temporary) are described. Section 3 is fully dedicated to the four main classes of biomaterials (metals, polymers, ceramics and composites) used to produce the considered implants. Understanding of the main properties of these biomaterials and the interdependences between materials and biological tissues is fundamental not only for selecting the right material for a specific application but also for selecting the appropriate manufacturing process. Materials such as hydrogel and biomaterials/cells composites are also introduced due to their relevance. Section 4 introduces the most relevant electro-chemical and physical additive processes used for the production of clinical implants. The main characteristics, applications and materials used by each of these technologies are explained. The integration between materials (Section 3), processes (Section 4) and applications (Section 2) are summarised at the end of Section 4 (Table 7). Finally, in Section 5, some techniques are introduced to enhance the bioactivity and the establishment of strong connections between biological tissues and implants.

## 2. Medical implants

Medical implants are devices placed either inside or on the surface of the body to accomplish some particular function, such as to replace, assist or enhance the functionality of some biological structure(s). Many implants are prosthetics, intended to replace missing body parts, while other implants deliver medication, monitor body functions, or provide support to organs and tissues.

Implants are classified as permanent or temporary. According to the United States Food and Drug Administration (FDA), a "permanently implantable device is a device that is intended to be placed into a surgically or naturally formed cavity of the human body for more than one year to continuously assist, restore, or replace the function of an organ system or structure of the human body throughout the useful life of the device." Examples of permanent implants include stents and hip implants. Temporary implants are commonly used in sports and medical surgeries, especially in shoulder and knee ligamentous reconstruction and spinal reconstructive surgery [203]. They are usually made of biodegradable polymers like screws, suture threads and plates. Scaffolds are permanent or temporary porous structures implanted to favour tissue or bone regeneration.

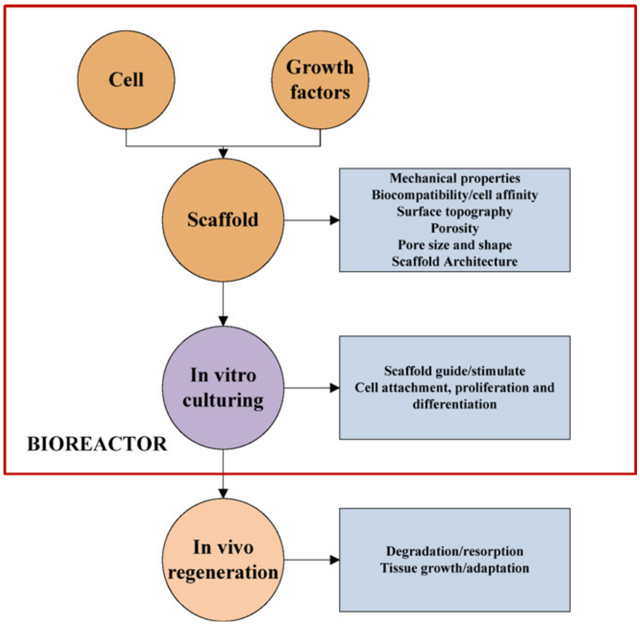


**Fig. 2.** Tissue engineering process, involving seed cells on scaffold, culturing *in vitro* and implant into the patient.
Adapted from [142].

### 2.1. Biodegradable implants

Degradable implants or scaffolds serves as temporary skeletons to accommodate and stimulate new tissue growth (Fig. 2). They play a major role in tissue engineering representing the initial biomechanical support for cell attachment, differentiation and proliferation [16,17,142,148].

An ideal scaffold must satisfy the following requirements [16,17,92,142,144,182]:

- *Biocompatibility.* Both raw and processed materials should interact positively with the host environment without eliciting adverse host tissue responses.
- *Biodegradability.* Scaffolds must degrade into non-toxic products with a controlled degradation rate that matches the regeneration rate of the native tissue. The *in vivo* degradation process of polymeric scaffolds is influenced by different and often conflicting variables, such as those related to the material's structure (*i.e.*, chemical composition, molecular weight and molecular weight distribution, crystallinity, morphology, *etc.*), its macroscopic features (*i.e.*, implant shape or size, porous shape, size and interconnectivity, *etc.*) and environmental conditions (*i.e.*, temperature, pH of the medium, presence of enzymes or cells and tissues).

The chemical degradation of polymers may principally proceed *via* either degradation by biological agents (enzymes), hydrolytic degradation (hydrolysis), which is mediated by water, or a combination of both coming into contact with living tissue. Several authors have investigated the degradation process of a wide range of biomaterials [55,68,80,197]. Lee et al. [129], Sung et al. [197], Agrawal et al. [2,3] and Lu et al. [146] studied the degradation of poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) and found that the degradation rate depends on the molecular weight and hydrophobicity. Lam et al. [124] showed that the hydrolytic degradation of PCL scaffolds is governed by their high molecular weights, crystallinity, hydrophobicity, surface-to-volume and porosity. On the other hand, incorporating certain other materials, such as calcium phosphate, significantly increases the degradation rate [124]. Domingos et al. [55,56] observed the *in vitro* degradation of PCL scaffolds in simulated body fluid (SBF) and the phosphate buffer solution (PBS) for 6 months. Results show a more significant degradation process of the