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Biomedical Applications from a Direct Digital Manufacturing Perspective

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Abstract

Tissue and organ printing has strengthened in the scientific and medical community as a response to the severe and worldwide problem of organ transplantation shortage. Direct Digital Manufacturing (DDM) is an important technical innovation that reduces capital required to achieve scope economies and break the current constraints creating opportunities for companies to improve innovation, growth and performance. This quite recent area of expertise has gain strength on the development of biomedical implants, mainly due to its capability of generate almost any geometry being able to mimic the native tissue despite their high complexity. It has also been largely applied in the pharmaceutical field on the development of drug delivery systems, and another really important application of this type of technologies relies on the diagnostic and new therapeutic studies for cancers based on human models.

Keywords: Biomedical implants, Direct digital manufacturing, Drug delivery systems, Printing, Tissues.

In the past several years, Direct Digital Manufacturing (DDM) has exploded into public consciousness. Also known as Rapid Prototyping (RP) or Rapid Manufacturing, DDM is a technology that converts three-dimensional (3D) computer models into physical parts typically by building layers upon layers of material. Actually, it has been employed throughout a wide spectrum of areas/industries, due to its capability of rapid and custom production of highly complex parts at low cost. Flexibility and ability to directly produce objects makes it an attractive alternative to conventional techniques such as, moulding and casting of customised parts [1]. DDM has been rapidly expanding and taking ground on the medical field with special regards to the emerging topics of regenerative medicine [2], prosthetics [3], drug delivery systems [4], cancer therapies [5], biomanufacturing and bioprinting [6]. Nowadays, it has become particularly appealing once it enables surpassing difficulties of product design, development and fabrication for patient specific applications.

DDM is an important technical innovation that reduces capital required to achieve scope economies and break the current constraints creating opportunities for companies to improve innovation, growth and performance. The scope economies supplied by DDM technologies allow a diversity of new custom-product opportunities that might be used to create and expand markets that differently could not economically be served. These alternatives establish an advantage foothold in a variety of medical device sectors due to the ability to adapt the design of individual implants to the requirements of the users [7]. In 2012, medical applications accounted for 16.4 percent of the total system-related revenue for the DDM market [8,9]. As DDM technologies advance, with the inclusion of new and innovate materials and processes, more opportunities will arise for the establishment of new products, in particular for medicine, due to the specific and complex requirements to create customised medical devices. These devices combine high value with relatively small physical volume. In addition, the high level customisation available with DDM makes this technology suitable for custom-fitting products to individual patients [8]. Presently, medical products created by DDM technologies intend to closely replicate the human form. In recent years, biomedical engineers have developed processes to use patient's cells to directly manufacture skin tissue and other tissues of the human body [7]. According to one industry expert, "the ability to manufacture living human tissue for medical research and clinical practice has the potential to reshape the future of medicine" [10].

The increasing importance given to Biomedical Sciences, which uses different strategies and technologies to increase the quality of the population life, in the worldwide economy is well known. In part, due to the ageing population which is increasing its number daily, leading to an increase of lifetime expectation. However, the creation of a model of sustainable development of society is one of the major challenges faced by decision-makers, science, industry and the society itself. This concern is reflected in the European strategy for sustainable development where one of the main areas for prioritization effort to concentrate resources is on the innovation platform: quality of life technology. As mentioned above, one of the areas where DDM and manufacturing technologies is having a major impact is on the development of biomedical applications, namely implants for medical usage by taking advantage of one of the major strengths of RP: the ability to generate almost any geometry. To do so, both anatomical and functional characteristics must be addressed. In fact, a combination of scaffolds, cells and/or growth factors can aim the production of implants (temporary or permanent), so that damaged or degenerated tissues can be fully restored. Bearing that in mind, our research group has designed and developed an equipment with the ability of joining different composites layer-by-layer enriching hybrid 3D structures aiming to mimic native tissues and adding a new degree in freedom of design, improving the knowledge of host tissues responses to new and more tissue/person specific implants.

Regenerative medicine (RM) poses a particular multidisciplinary challenge once it requires a broad knowledge from anatomy and physiology to biomaterials science and engineering [2]. Furthermore, it must fulfil requirements of detecting and quality control, and regulatory and legal compliance in order to attain an optimum design, zero-error and just-in-time production suitable for individual clinical cases. RM can be seen as an alternative to palliative care perspectives as it focus on the production of biological substitutes able to re-establish the biological function to a damaged tissue or organ. To do so, through an engineering process scaffolds are biofabricated and e.g. further seeded with patient's cells and/or growth factors [11]. These scaffolds play a major role in the regeneration process and have been extensively studied in the last years [12]. The optimum architecture, the idyllic biomaterials, the best degradation rate, are some of the approaches developedhighlighting the question if a perfect scaffold is feasible. These structures are designed (primarily using medical imaging) with complex internal architecture (channels, porosity and surface) suitable for cell attachment and proliferation, and release of growth factors and biomolecular signals to promote a favourable post-implantation response.

In clinical scenarios where tissue loss is extensive and irreparable by an autonomous biological process, DDM may provide a solution to produce patient-customised implants. On one hand, we have the conventional manufacturing of implants which are somewhat roughly designed and standardised to a group of patients. This may lead to an out of shape implant regarding the patient defect, leading to medical complications after surgery. On the other hand, current layer-by-layer technologies (e.g. Selective Laser Melting and 3D printing) are able to produce implants with complex geometries which are accurately designed in size, shape and mechanical properties; according to the MRI and/or CT scans of the anatomical defect and tissue properties [13].

DDM has been also widely applied in the pharmaceutical field in order to produce drug delivery systems based on a Drop-on-Demand (DoD) inkjet printing. The use of this technique enables pharmaceutical companies to obtain uniformly dispensed droplets in the picoliter range useful for drug delivery/dose personalisation systems with high placement accuracy [14]. By changing the droplet size and the 1ratio of active pharmaceutical ingredient and polymeric substrate, DoD printing allows drug dosage suitable to the patient's need and layering of multiple drugs [4]. Such procedure enables site-specific and disease responsive drug release and also a stringent control over in vivo biodistribution of the drug [14]. Newest application of DDM to medicine has gained attention from several cancer therapy research groups where recreation of tumour microenvironments for cancer related studies has been discussed. Additive technologies are now advantageous to produce in vitro three-dimensional human cancer models (replacing 2D cell culture and animal models) useful for diagnostic and new therapeutics studies [15,16]. Finally, a very ambitious idea of tissue and organ printing has strengthened in the scientific and medical community once it directly responds to a severe and worldwide problem of organs transplantation shortage. Although this idea is still maturing, 3D bioprinting uses a "bio-ink" composed by cells and extracellular matrix to fabricate three-dimensional vascularized and functional living organs ready for implantation [17].

DDM technologies have been gaining great strength among the scientific community and becoming a real solution for severe health problems unable to be solved up today. Despite its exponential growing and development over the last decades, there is still a lot of effort to be done in order to fully understand the biological features and complexity of the tissues. It is known and accepted that solutions for the shortening on organs transplantation is a requirement. The strategy to reach the final goal is still blurred. However, the search for 3D hybrid and/or hierarchical structures seems to be the new viable approach to solve the present problems, since the bioprinting of organs and tissues is still far to be accomplished in a near future, due to ethical and policy issues that are lifted and still have to be overcomed [18], as well as other complex requirements regarding the integration of technologies from different fields of engineering (biomaterials science, cell biology, physics, chemists and medicine) [19]. This is proved to be a far future, because the increasing knowledge regarding this subject is opening new and undiscovered realities. The continuous development of equipments, which incorporate different techniques and a much higher variety of materials, as our group has focused on, slowly closes the existing gap between engineers, scientists and physicians "demands" towards a common goal which is fully understood by all the parts involved, resulting in a successful approach to the present limitations.

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