3D Stem cell bioprinters in Tissue Engineering

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1.Introduction

Organ bioprinting with three-dimensional (3D) stem cell printing technology is one of the approaches being studied nowadays in order to satisfy the organ demand of patients with a death risk who have a loss of function of some organ (caused by aging or an injury).

Organ printing consist in three basic steps:
- **Pre-processing:** Generation of a 3D model .
- **Processing:** Construction of a Scaffold and cell deposition.
- **Post-processing:** Maturation of the tissue construct and transplanting.

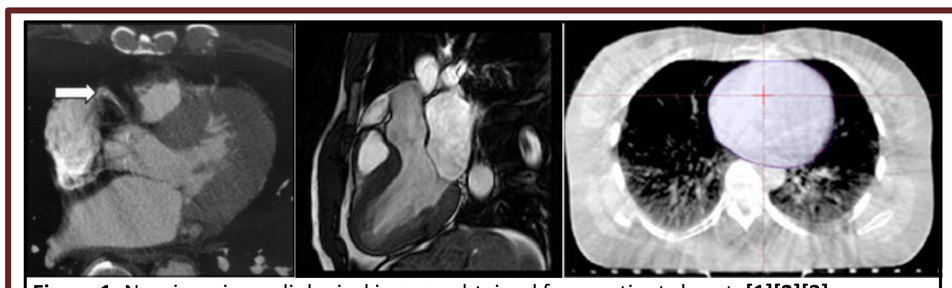

Figure 1. Non-invasive radiological images obtained from patients heart. **[1][2][3]**

High-resolution images are basically taken by **Multidetector computed tomography (MDCT)** and **Magnetic Resonance Imaging (MRI)**.

2. Image collection

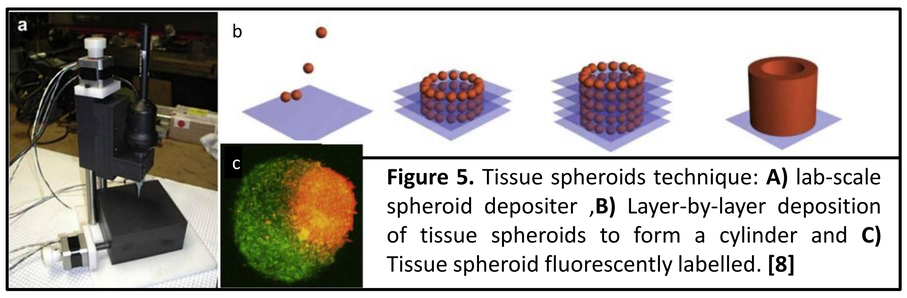

Figure 5. Tissue spheroids technique: **A)** lab-scale spheroid deposiiter ,**B)** Layer-by-layer deposition of tissue spheroids to form a cylinder and **C)** Tissue spheroid fluorescently labelled. **[8]**

Tissue spheroids are clusters of cells used for direct bioprinting. After their **encapsulation in an hydrogel**, they are deposited **layer-by-layer** and finally **self-assembled**.

5. Tissue Spheroids

Direct Cell printing

Scaffold formation for cell seeding

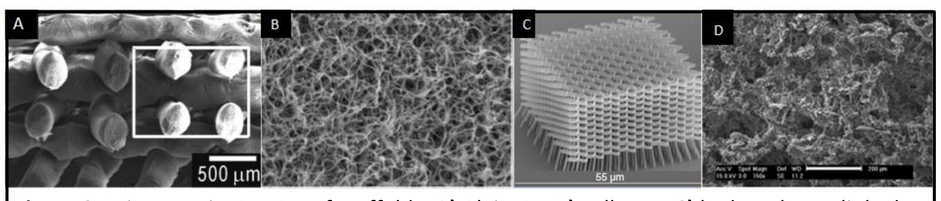

Figure 9. Microscopic structer of scaffolds: **A)** Alginate, **B)** collagen, **C)** hydrogel crosslinked by Multiphoton processing techniques, **D)** Polymer-based scaffold. **[9][10][11][12]**

Scaffolds serve as temporal support for the 3d cultured cells and helps in the **processes of cell adhesion, growth, migration, orientation and signalling.**

6. Scaffold formation

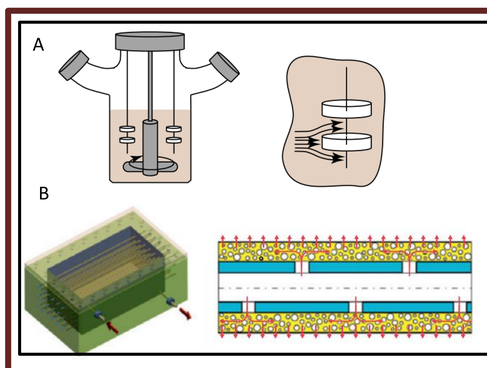

Figure 10. Bioreactor culture: **B)** Spinner flask bioreactor,

C) Irrigation dripping tripled perfusion bioreactor .

[13][14]

Different types of **Stem Cells** can be obtained depending on the approach. **Cell seeding** is enhanced by an **homogenous cell distribution** inside the scaffold. For an enhanced tissue formation, there is a need to have **high cell densities**. In addition, the **diffusion of media inside the tissue** is essential for the distribution of cells inside the scaffold.

7. Cell seeding

3. Image post-processing

Several post-processing tools are used in order to improve the quality of the images collected and form the surfaces and volumes of the 3D object .

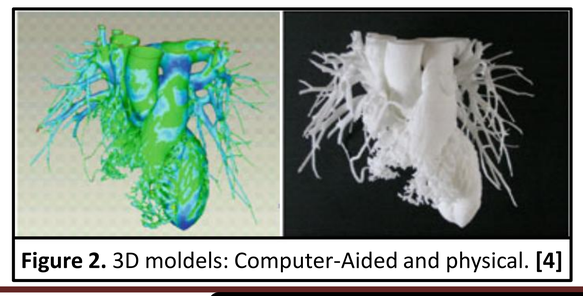

Figure 2. 3D moldels: Computer-Aided and physical. **[4]**

3D model is produced by:

- **Segmentation evaluation.**
- **Surface and volume rendering.**
- **Maximal intensity projection.**
- **Multiplanar reformation**

Pre-processing

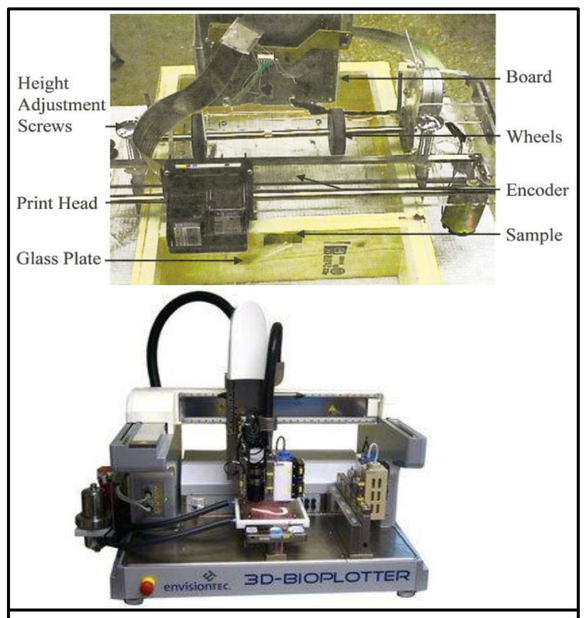

Figure 3. Different Bioprinters: Mechanical structure of the first cell printer and Robotic bioprinter (3D-Bioplotter, EnvisionTEC). **[5][6]**

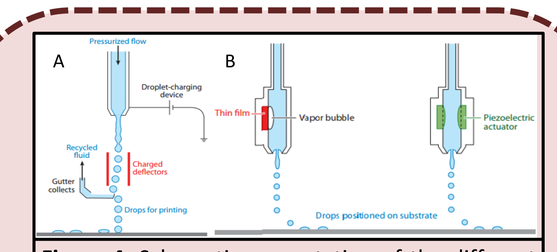

Figure 4. Schematic presentation of the different types of dropping: **A)** Continuous inkjet and **E)** Dropping-on-demand inkjet printing. **[7]**

Printers have nozzles which can be moved and placed in three-dimensional positions to accurately **generate the droplets** which will be implanted on the scaffold. They are ejected by **pressure, heat or a piezoelectric transducer**.

Thomas Boland and Cris Wilson were the f**irst to design a cell printer** by modifying a printer firstly designed for ink printing. Nowadays **Bioplotters** can automatically **create a 3d scaffold from CAD models**. It could be done within hours while working with a wide **variety of materials.**

4. Bioprinting

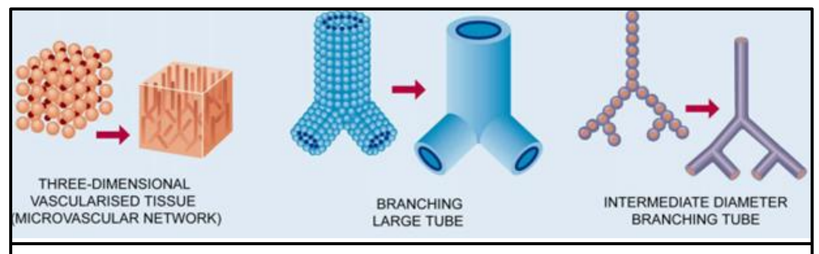

Figure 11. Schematic process for branched production of the circulatory system. **[8]**

Vascularization is vital for the whole organ to be **correctly irrigated** for the obtention of all the **indispensable nutrients**.

Processing

8. Tissue Maturation

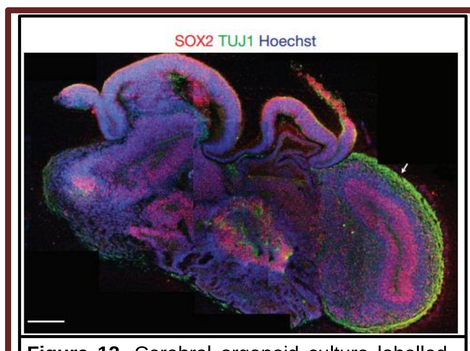

Figure 12. Cerebral organoid culture labelled with neural progenitor markers.**[15]**

A **model of human brain** was created for drug testing in **matrigel spheroids** in a **spinning bioreactor**.

Moreover, it showed the crucial steps of the process such as the **tissue maduration** and the **organ monitoring** after the creation.

9. Cerebral organoids

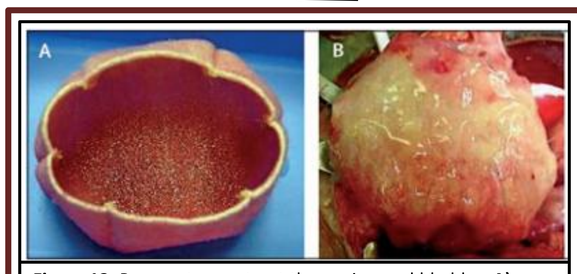

Figure 13. Process to construct the engineered bladder: **A)** Scaffold cell-seeded and **B)** engineered bladder connected by anastamoses to native bladder. **[16]**

Succesful transplants has been done with an **engineered bladder** with a **polyglicolic acid-based scaffold**.

10. Autologous Bladders

Post-processing

Conclusions

Althought 3D bioprinting is a fast-evolving technique with great potential to solve the problem of the shortage of organs donated, some limitations have appeared. More effort is needed to be done in order to increase the resolution of 3D models and improve the challenging process of vascularization. On the other hand, several objectives have been fulfilled during the past decades such as the generation of robotic bioprinters or the use of multiphoton techniques in the design of scaffolds. Future investigations will be focused on the scalability of the process and the bioprinting of heart and kidney among others.

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