Developing Biomimetic alveolar scaffolds through computer-based additive manufacturing technologies

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Introduction

Nowadays an increasing necessity to investigate the lung is due to a rising in the air pollution leading to increasing occurrence of disorders that affect the respiratory system [1]. To overcome this issue a major bottleneck in the development of new drugs for lung diseases is identified by the shortage of preclinical models that can reliably predict a clinical outcome [2-4]. In particular, there is clear need to improve the biomimicry of the currently available in vitro models of lung diseases to refine the solutions discovered and to reduce the current amount of animal models needed in research. Here, a transwell-based system has been designed and developed in order to support a co-culture on both sides of an elecrospun membrane, mimicking the pulmonary basement membrane and enabling an air-liquid interface (ALI) cell culture. In order to achieve this purpose of biomimicry more effectively, the Voronoi pattern has been identified as a descripting tool for modelling the relative positioning of alveoli, in particular representing the contact points between adjacent alveoli. This principle was integrated into the model ' s design through a biomimetic compartmentalization approach, obtained by developing a scaffold via additive manufacturing techniques. The production of the scaffold has been conducted relying on two extrusion-based technologies, melt electro writing (MEW) and fusion deposition modelling (FDM). In this context, the pattern reproduction encounters difficulties through the common slicing softwares, for this reason a software to design a pathway suitable for these techniques has been developed.

Materials and Methods

The Voronoi structure was produced by MEW and FDM developing an ad-hoc design software using Python as programming language. The software is composed by 4 main consecutive blocks which aim is to generate, analyse and translate in machine-language the pattern with the desired parameter. The first block is a graphic user-friendly interface to set the parameters such as the number of seeds that generates the pattern, the expected fiber diameter and the total diameter of the design. The second block generates the pattern though the scipy.spatial library. The pattern here generated is then analyzed in terms of porosity, calculating the area of each voronoi cell, influenced by the fiber dimension expected which is subtracted by the theorical area. The third block instead translates the pattern into a graph, this passage is used to find a pathway that follows the entire pattern correctly. In particular, since the MEW is a continuous technology, a continuous pathway has been found exploiting the chinese postman path.
The final block instead translates the pathway in gcode, distinguishing two different approaches for the two techniques. Then, the pattern is then converted in STL. For what concerns the printing of the pattern obtained with the software, the Novaspider v9 has been used for the MEW,

while the 3D Bioplotter has been used for the FDM. employing PCL (Mw 42kDa for MEW and 50kDa for FDM) . Lastly, a membrane has been incorporated in the model using solution electrospinning of PCL and gelatin directly on the constructs [3].
A preliminary biological validation has been conducted using lung epithelial and endothelial cell lines (A549 and HUVECs).

Results
The development of the files though the software has been successfully conducted, hence it was employed through the two selected technologies MEW and FDM. After a printing parameters optimization process, several scaffolds with different designs and porosities have been produced with a high printing fidelity. Moreover the inclusion of the electrospun membrane in the model completed the construct in order to be employed in cell cultures, fixing it on transwells. During the cell culture, the construct demonstrated to be suitable to perform ALI culture.

Discussion and conclusion
The present work successfully obtained the generation of a pathway for extrusion based technologies with an innovative approach of a complex pattern such as the Voronoi one. Moreover the final construct with the membrane demonstrated to be suitable for cell culture and ALI culture, which is a fundamental for the alveolar tissue.

Visualization of the grafic user interface of the software; additionally, a visualization af the extruder paths generated for MEW and FDM

Produced scaffold with the employment of the software. on the left produced with MEW, on the right with FDM.

References

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