PhD in Bioengineering

Final Defense

POLITECNICO MILANO 1863

PHD BIOENGINEERING – THESIS FINAL DEFENSE

PHD Student
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THESIS:

GENERATION OF ADVANCED MUSCULOSKELETAL TISSUE MODELS BY INTEGRATING BIOFABRICATION AND COMPUTATIONAL TECHNIQUES

Date: 22.04.2021
h. 15:30
Online Microsoft Teams

SCHEDULE OF THE DAY	
15:30 – 15:45	Committee Meeting
15:45 – 16:45	PhD Student VALERIO LUCA MAINARDI Thesis presentation - Discussion
16:45 - 17:00	Committee meeting
17:00	Award Ceremony

COMMITTEE MEMBERS		
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SAVE THE DATE

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PhD in Bioengineering Final Defense

POLITECNICO MILANO 1863

PhD student: MAINARDI VALERIO LUCA – XXXIII Cycle

Thesis title: GENERATION OF ADVANCED MUSCULOSKELETAL TISSUE MODELS BY INTEGRATING BIOFABRICATION AND COMPUTATIONAL TECHNIQUES

Advisor:	Prof. Gabriele Angelo Dubini
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Abstract:

The engineerization of human tissues is a very complicated process involving several steps that are strictly connected. However, to be able to study specific mechanisms of physiological and/or pathological processes it is necessary to develop models that replicate the structural and functional properties of involved tissues. The strong crosstalk occurring among musculoskeletal tissues should be considered and the integration of multiple biological components in the same device should be achieved in order to realize reliable models.
In this work, biofabrication and computational simulation techniques have been combined to optimize some phases of the whole process towards the development of advanced musculoskeletal tissue models.
One possible approach of biofabrication of biological constructs consists in seeding cells on three-dimensional (3D) scaffolds that support cell proliferation and extracellular matrix (ECM) formation during the tissue development. In this case, cell seeding outcome influences all the subsequent phases. Thus, it is clear the crucial role of this step in the whole process. In chapter 2 an easy and effective approach to improve the efficiency of cell seeding performed using dynamic systems was presented. Specifically, extrusion-based 3D printing technology was applied to produce 3D scaffolds made of polymeric fibers that are characterized by a non-circular cross-sectional shape. These multilobed scaffolds were tested using an oscillating perfusion bioreactor and the number of adhered cells was compared using scaffolds characterized by standard cylindrical fibers as control. Computational fluid dynamic (CFD) simulations were performed to analyze the influence of multilobed fiber geometry on two different aspects: first, the path followed by cells flowing through the scaffold fibers was assessed to understand how the fiber shape modifies the cell trajectories; secondly, the distribution of fluid velocity and shear stress on scaffold fibers was evaluated to analyze their effect on adhered cells. The proposed multilobed approach resulted in a higher seeding efficiency on multilobed fiber scaffolds compared to circular fiber scaffolds due to a combination of fluid dynamic parameters that increased the number of cells reaching regions of the fibers more suitable for cell adhesion. As a consequence, the obtained results suggest that the reciprocal influence of geometrical and fluid dynamic features and their combined effect on cell trajectories should be

considered to improve the dynamic seeding efficiency when designing scaffold architecture.
The growth and differentiation of several cell types are strongly dependent on environmental stimulation induced by fluid flow and/or mechanical stimuli. Thus, several types of bioreactors have been developed aiming at recreating the physiological stimulation required to obtain proper tissue maturation.
In chapter 3 the influence of fluid dynamic stimulation on bone tissue maturation was evaluated. Specifically, an extrusion-based bioprinting technology was applied to produce alginate and gelatin constructs embedding human mesenchymal stem cells (hMSCs). Bioprinted constructs were dynamically cultured using a perfusion bioreactor. The effect of flow-induced mechanical stimulation was assessed through CFD simulations, performed to evaluate the distribution of shear stress, fluid velocity and hydrostatic pressure on constructs fibers. Obtained results demonstrate that stimulating the developing constructs with adequate stimuli can improve the level of tissue maturation and promote the development of bone substitutes suitable for clinical applications.
A strategy based on biofabrication to address the integration of multiple tissues is presented in chapter 4, where a novel mesoscale perfusable device was designed as a tool for the 3D bioprinting of a multi-tissue construct. Specifically, a muscle-tendon-bone interface model with a physiological architecture was bioprinted ensuring a structural and functional connection between the tissues. The optimization of the perfusable device allowed the stimulation of the bioprinted tissues with distinctive culturing conditions that can be adapted to the specific needs of involved tissues.
Only recently, the need of multi-tissue models is being considered with the proper attention taking into account all the aspects involved in the engineerization of human tissues, such as architectural, structural and functional connection and proper fluid dynamic and/or mechanical stimulation of involved tissues. In this regard, the work presented in this thesis represents an important contribution towards the development of advanced models for the study of all those physio-pathological mechanisms that involve multiple tissues.