Towards the creation of an atlas of scaffold patterns

Chapter 9

Societal impact

There is a shortage of tissues and organs for transplantation. Patients who have not received a heart transplant after 5 years on the waiting list have a survival rate of 40% [1]. This has led to a need to create tissues within a lab and was the foundation of regenerative medicine (RM). The global RM market size reached 22.24 billion dollar in 2022 and is expected to grow until 125.54 billion dollar in 2030, according to a market analyses report by Precedence Research [2]. The majority of cell therapy studies performed their research in 2D before RM became a specialization within medicine. RM promoted the investigations and creation of 3D tissues and substrates to grow cells. These substrates are better known as scaffolds. Several fabrication techniques have been applied within RM to construct 3D scaffolds. Specifically, additive manufacturing techniques such as fused deposition modeling (FDM) are commonly used in RM for this purpose. Recently, implants fabricated with FDM or FDM-derived technologies have been used for critical bone defects and articular cartilage [3][4]. Therefore, further improvements in additive manufacturing technologies can bring additional benefits to the entire RM community and ultimately to the patient.

The findings in **Chapter 3** provide a setup to create a library of patterns for other researchers to use. This could allow to design and engineer tissue specific patterns that can be used for scaffold fabrication aiming at mimicking a broad range of tissues. These patterns could also be used to guide cells to mimic specific tissue functions. One of the examples from **Chapter 4** revealed that using a hypotrochoidal design improved not only the mechanical, but also the biological outcome when envisioning scaffolds for cartilage regeneration. The only difference between the conditions was the design of the scaffold, thus highlighting how with the design of tailored scaffold structural properties it is possible to influence cell activity and tissue formation by architected biomaterials. Therefore, frequently studied biomaterials can offer additional enhanced tissue regeneration when appropriately combined with advanced architectures. The work in **Chapter 4** can serve as a biomimetic approach

blueprint for the research community. Future work could lead to a workflow that starts with a tissue of interest to then test a selection of patterns to assess the best outcome, for instance to determine which load is required for the targeted tissue of interest (e.g. bone, articular cartilage), and use the conceptual framework here developed to match loading with the correspondent architecture pattern. The next step in this endeavor is to fine-tune the chosen pattern to the patients' needs. As every patient provides a different biomechanical and tissue architecture signature, this strategy has the potential to contribute to personalized medicine. The required scaffolds can be fabricated based on medical imaging techniques and manufactured using an appropriate pattern that matches the mechanical and biological requirements.

Designing and validating a pattern for a specific tissue is potentially time-consuming. However, once the design is finalized it can be easily shared without rewriting the entire source code besides some printer specific commands. The universality of G-code allows the code to be transferred to almost any additive manufacturing equipment. This was highlighted in **Chapter 4,** where the code to create a hypotrochoidal pattern was used with FDM, bioprinting and melt electrowriting (MEW). As G-codes can be shared and transferred digitally, the proposed approach can be easily transferred to any printing facility. This is beneficial, since the production of a personalized scaffold can be done locally while specialized personnel can design the scaffolds centrally, making additive manufacturing a more cost effective process for the improvement of RM therapies, especially when applied on a global scale.

In 2019 insurance companies in the Netherlands had to pay for the cardiovascular-, urogenital, intestinal- and respiratory- system a combined 19.8 billion Euro, which translates to 1,142 Euro per inhabitant [5]. This does not reveal to total cost of these healthcare sectors, as not everything is

covered by the insurance, but any relieve for this economic burden is welcome. Currently, FDM systems are not able to reach these healthcare sectors, as tubular structures are impossible to create with classical FDM techniques. Therefore, **Chapter 5** focused on creating a system that is capable of creating scaffolds for these healthcare sectors and potentially reducing the costs. The freedom of the system allows the user to create a variety of different patterns with different mechanical properties that could mimic various tubular tissues.

Chapter 6 highlighted that it is possible to mimic the elastic properties of a coronary artery using a stiff material such as PCL [6]. This finding can have broader implications for material sciences and RM, as some materials are not deemed suitable due to their bulk material properties. **Chapter 6** contributed to the increasing know-how over architected materials, showing an example in the vascular field where mechanical properties of scaffolds can be tunable by varying the scaffolds' architecture, independently from the bulk properties of the selected biomaterials.

Chapter 7 demonstrates how a complex process such as melt spinning can be simplified to make it understandable for everyday users. As a consequence of this simplification, melt spinning can be more broadly adopted within the biofabrication community without necessarily applying electrostatic fields as in the case of melt electrowriting (MEW). In addition, the formulated equations in this chapter are universal and improve the reproducibility by already predicting what the fiber outcome will be. Also, this approach will help researchers by providing more control over the fabrication technique and reducing the time needed to optimize processing parameters, which can require a substantial amount of wasted material during optimization [7]. The developed parametric mathematical method can be applied to other more complicated techniques such as MEW, further increasing the standardization of scaffold fabrication within the RM field.

A future outlook on the impact of this thesis is already briefly discussed in **Chapter 2**, where I postulated that research should focus more on multiple aspects of biomimicry. Instead of focusing on a single pattern, **Chapter 3** and **Chapter 5** highlighted the importance to further investigate the role of architected material patterns, which can be easily available to manufacture. The expansion of such patterns can inspire fellow researchers to use them to discover new fundamental biological processes that can be triggered by more unconventional scaffolds' structural properties. The path from bench to bedside for scaffolds should also include defining a pattern for production, as shown in **Chapter 4**. More studies are required before these scaffolds will become available in the clinic, which shall aim at investigating the effect of, in this case, the hypotrochoidal architecture *in vivo*.

References

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