

## Validation of Material Parameters of Collagen Compositions for the Application as a Bioink

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**Abstract** The novel approach of an individualized medicine affects nowadays various areas of therapeutic treatment. Primarily, these include the application of pharmaceuticals, private point-of-care solutions, surgical procedures as well as steps of rehabilitation. However, beside these existing strategies the development of patient specific models for the training of clinical personal is currently insufficient. Such models are essential to prepare a personalized approach of medical care. One possible solution to address this problem could be the adaption of the established 3d printing technology for the processing of suitable biopolymers.

The presented work is focused on the development of a printing system utilizing collagen. Therefore, it is intended to design multiple extrusion heads in accordance with the material parameters. In order to achieve the aspired physiological properties of the final model, a first set of experiments will be performed with several compositions of collagen to validate the fundamental mechanical characteristics. Hereby, the elasticity, thermal stability, force resistance as well as the haptic behaviour are of most interest.

Afterwards, these obtained experimental results should be used to simulate the extrusion process and to validate the extruder concepts. In case of a positive evaluation these concepts are realized by using rapid prototyping technologies. Finally, this novel 3d printer will be used to print first organic test structures with collagen.

### Introduction

The development in the field of medicine and the political stability had a strong effect on the life of humans in Europe within the last century. Newest inventions of antibiotics, vaccines and other medical products as well as the progress in the surgical field doubled the average human lifespan. At the very beginning of the 20<sup>th</sup> century the average age at death for female was 45.84 years and for males 43.65 years, whereas in 2008 the average ages were increases up to 79.79 for females and 73.58 for males [1]. This leads to a permanent increase of age related diseases, such as diabetes, cancer and similar medical conditions. In order to treat such diseases, a variety of treatments needs to be performed to the patients, which influences the physical and psychological conditions of the patient.

One of the biggest problems is the high increase of occurrences of cancer. Within the years of 1999 to 2015, for example, the number of patients developing a liver carcinoma radically increased. In 1999, 2199 female and 3875 male patients were diagnosed with a liver carcinoma, whereas in 2015 the number of women increased to 2709 and of men to 6374 [2]. Those numbers even ascended, while the technology and procedures to cure cancer became even further advanced. As the technology advances, the clinical personal needs to be taught to perform new treatments and surgical procedures.

At the moment, the most applied therapies are the resection of the carcinoma or transplantation. For both methods, the survival rates are nearly the same (about 50 %) [3]. In order to increase the survival rates, the surgeons need special training. Such training could be performed via artificial organ-like models. Therefore, the models need to have the same haptic and optical properties as the original organ. In this case, the most important characteristics are the solidity and coloring of various tissues. Similar organ-like models are already produced through casting [4]. However, using this technique, the models become expensive while the production is time-consuming and not individualized based on the patient data. A novel approach for the production of those models would be the adaption of a 3d printing system using a bioink.

## Requirements

This work is focused on the development of a 3d printing system utilizing different collagen compositions as bioinks. 3d printing is an additive production method where several layers of material are stacked up to create a product out of a computer-generated model. Collagen is a reliable material for the simulation of the consistency of the multiple kinds of tissues. This protein is the major structural protein inside the extracellular matrix of vertebrates [5]. Furthermore, the consistency can be determined by different compositions of collagen and crosslinking agents, whereas the colour is based on the added pigments. This implies that the designed systems should extrude several mixtures within a short period of time. To achieve such a functionality, either multiple inlets or reservoirs for pre-mixed compositions are required.

The processing of the collagen correlates to the wanted haptical characteristics, whereby the printing system needs to be adaptable. Possible designs of extruder should be constructed to eject the collagen at the gel point, where the collagen polymerizes. The total weight of the extruders also should not exceed 2 kg to ensure a high stability of the printing system.

## Results

The resulting designs are shown in fig. 1 and fig. 2. Displayed are two different designs as multi-component systems in full and cut view. The pictures A and B in fig. 1 illustrate a screw extruder. This version consists of two different parts: the screw and the cylinder. The cylinder possesses two inlets, one for the collagen and one for the crosslinking agent, whereas the outlet is located in the tip. Three notches provide an opportunity to attach thermal devices to achieve three temperature areas. The cylinder itself should be manufactured out of a material holding a high thermal conductivity, such as brass or aluminium. The screw consists of a hexagonal top, a conical stem with a straight thread and a tip at the end of the cylinder. Depending on the composition, the collagen and crosslinking agents can be dosed via the inlets. The screw blends the compartment and transports them through the temperature areas to the tip of the cylinder, where the extrusion process proceeds. The supply of the inlets can be accomplished via peristaltic pumps. In order to generate the required forces for the extrusion and polymerisation processes, the number of windings, the distance of the stem to the cylinder as well as the diameter of the nozzle need to be optimized.

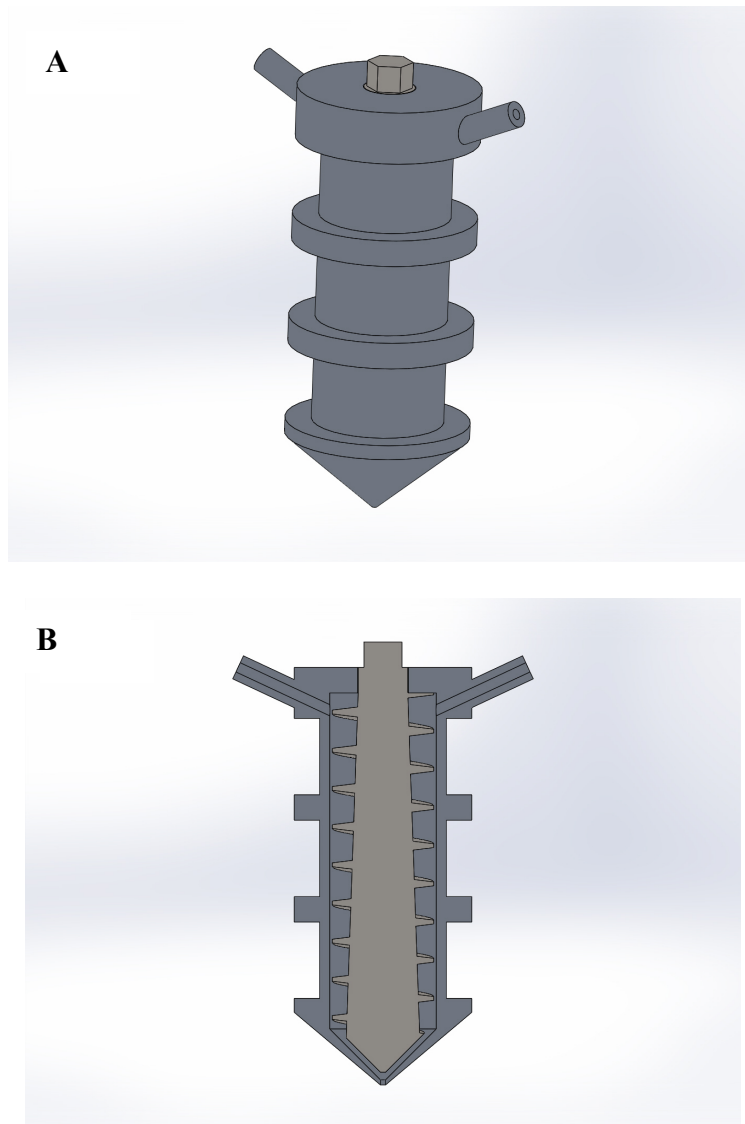


Figure 1: Possible screw extruder, A – closed view, B – cut view

The illustrations A and B of Fig. 2 show a syringe extruder using a revolver-like construction to achieve a high variability of compositions. The syringe revolver consists of different main parts. At first, a rotatable revolver-like structure, which mounts the syringes. Those are filled with the already mixed and heated compositions of collagen and crosslinking agent. A base plate is located at the bottom of the revolver, which is unmovable and carries the nozzle. The revolver itself can rotate via a tooth belt as well as a stepper motor to align with the correct syringe. Hereby, the axis is surrounded by a heating module, which adjusts the temperature of the syringes to a pre-set value. In order to push the syringes for the extrusion, a stamp is moved down via a motor.

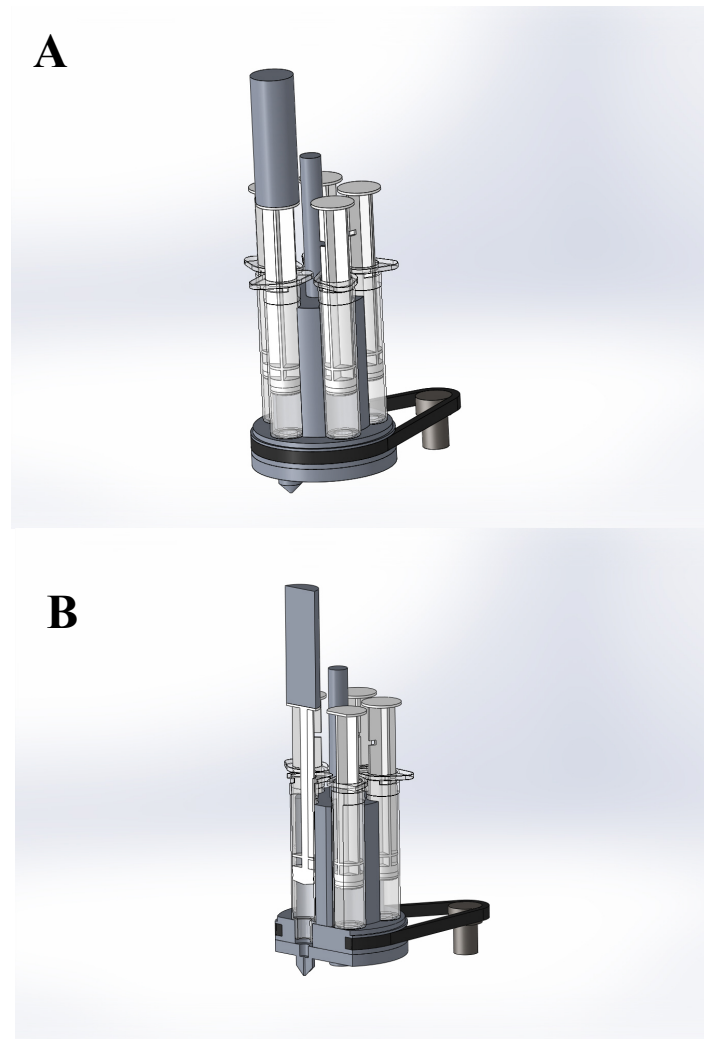


Figure 2: Possible syringe revolver extruder, A – closed view, B – cut view

The shear forces needed for the liquefaction of the composition are achieved via the design of the tip of the screw extruder as well as the tip of the syringe. Whereas the screw extruder produces the compositions while performing the extrusion, the syringe extruder is limited by the volumes of the syringes.

### Summary

The aim of the presented ongoing work is to construct multiple extruders for a printing system utilizing collagen as a bioink. Those extruders should be adapted to the parameters needed for the collagen, whereas the shear forces and temperature are of most importance for the extrusion process. The final objective is to print organic test structures, which possesses the same haptic and optical characteristics as the original organ. Eventually, two extruder designs were presented. A screw extruder with two inlets and multiple heating areas could achieve a continuous extrusion process while blending collagen with crosslinking agents. Additionally, a revolver- like syringe extruder could hold multiple syringes with pre-mixed collagen compositions. The revolver is rotated via a stepping motor, while being mounted onto a base plate, where a nozzle is attached. Currently, both concepts are realized by rapid prototyping and will be afterwards implemented in a functional laboratory setup.

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