

## Modeling cell-mediated compaction and collagen remodeling in tissue-engineered heart valves

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# Modeling cell-mediated compaction and collagen remodeling in tissue-engineered heart valves

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## Introduction

When tissue-engineered heart valves (TEHVs) are implanted in the pulmonary position, the in vivo functionality is compromised by cell-mediated leaflet compaction/retraction (Fig. 1), which leads to valvular insufficiency if the blood pressure is too low to cancel out retraction. It is hypothesized that the diastolic aortic pressure is sufficiently high to counteract the cell-mediated leaflet retraction.

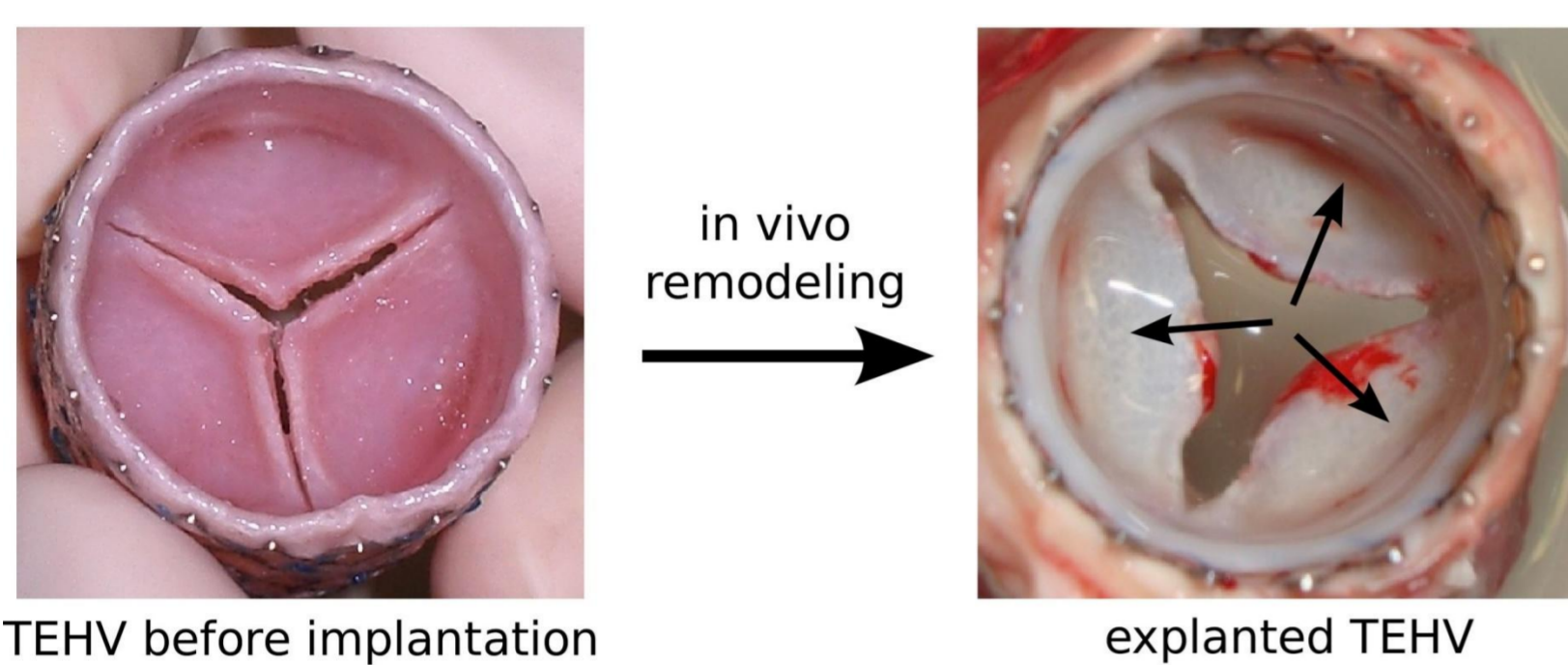


Fig. 1: TEHVs remodel after implantation such that severe leaflet retraction occurs (indicated by the arrows).

## Objective

The goal of this study was to develop a theoretical framework and finite element (FE) model to predict tissue compaction/retraction and collagen remodeling in TEHVs, to answer the following question:

**Are the pulmonary (2 kPa) and aortic (10 kPa) diastolic pressure high enough to counteract leaflet retraction in TEHVs?**

## Methods

Compaction was modeled by including contractile stresses exerted by the cells [1] and cell-mediated crimp of the collagen fibers (Fig. 2). Collagen remodeling consisted of strain-dependent degradation and oriented production [2].

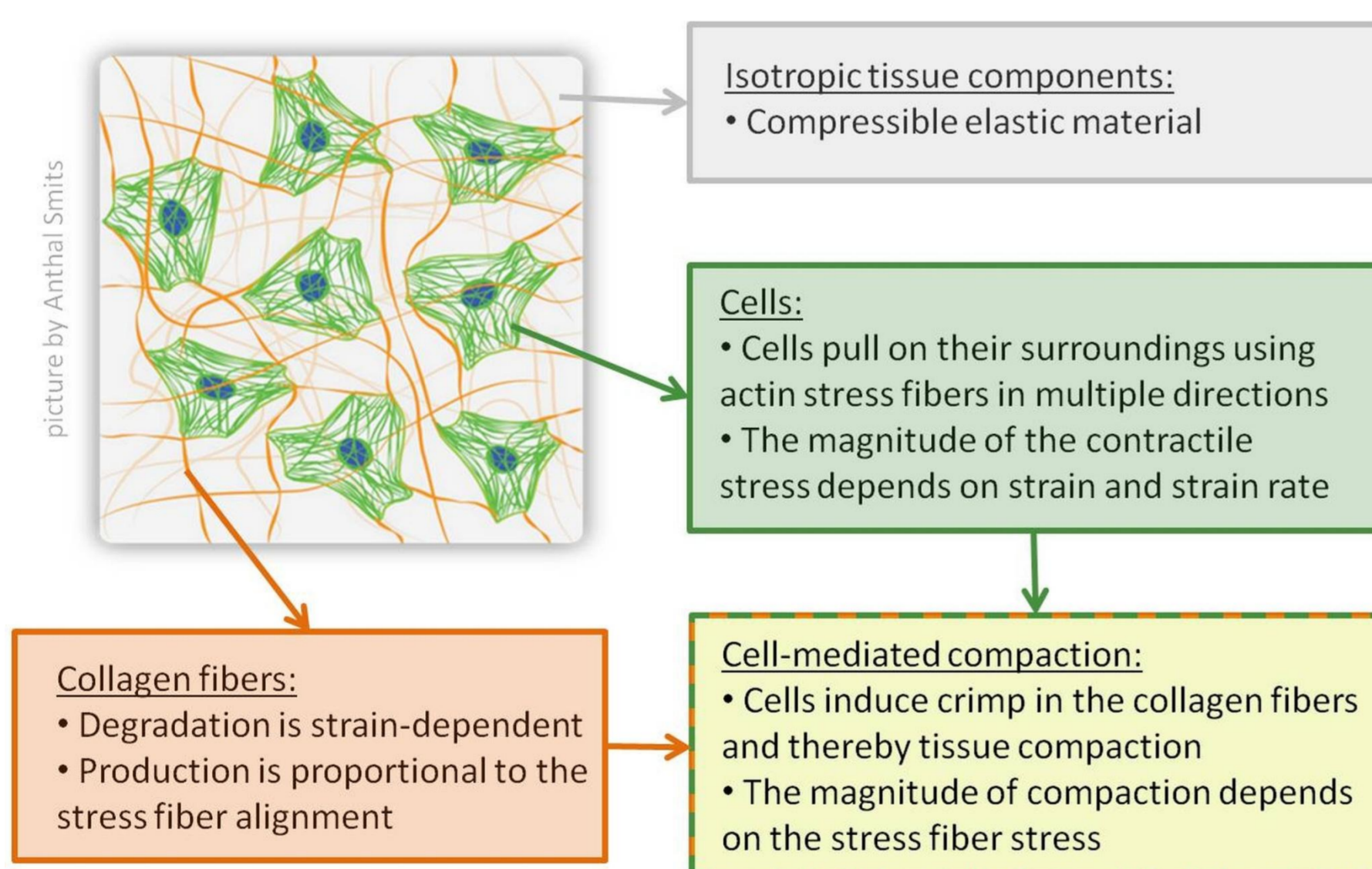


Fig. 2: Overview of the computational model.

For validation, the model was first applied to simulate compaction and collagen remodeling in engineered strips, where compaction and collagen alignment have been quantified. Next, remodeling of TEHVs was simulated under applied pressures of 0, 2, and 10 kPa.

## Results

### Tissue-engineered strips (validation)

Rectangular tissue-engineered constructs compact half in width and show a strong collagen alignment in the constrained direction (Fig. 3) [3, 4]. The model results correspond with the experimental results.

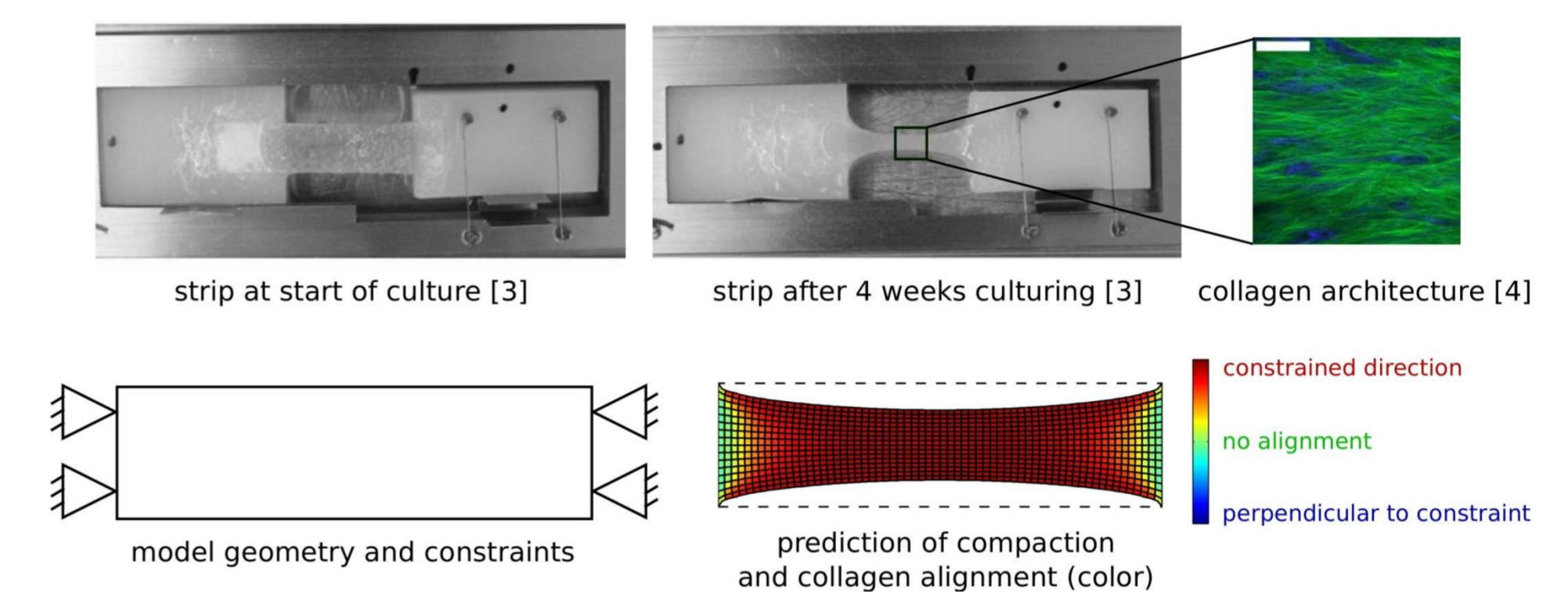


Fig. 3: Tissue compaction and collagen alignment in strips observed from experiments (top) and predicted by the FE model (bottom).

### TEHVs remodeling at different pressure levels

At pulmonary pressure, the model indeed predicts that cell traction and collagen remodeling result in valvular insufficiency (Fig. 4). At aortic pressure, retraction is sufficiently counteracted by the blood pressure to ensure full closure of the valve.

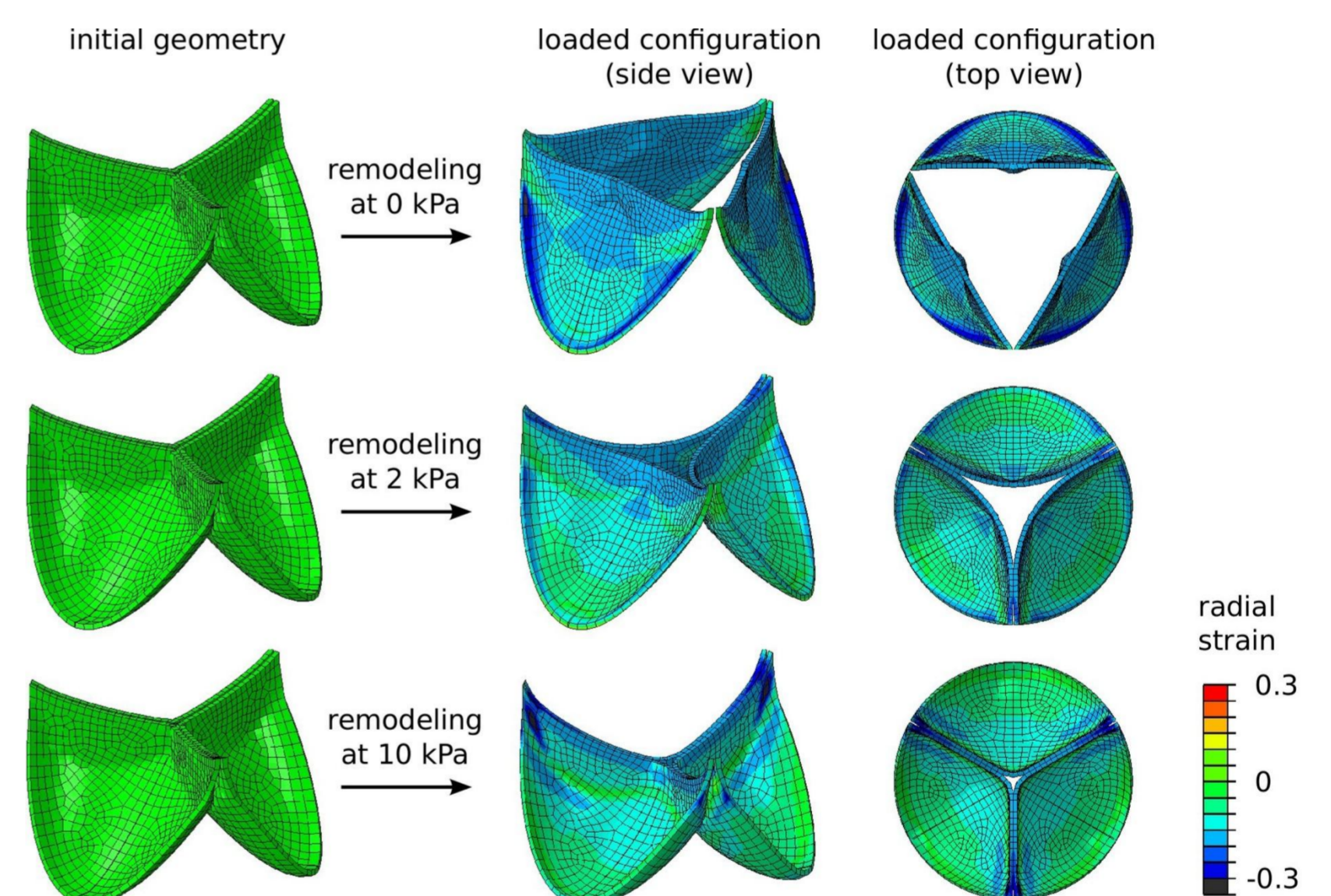


Fig. 4: Initial geometry (left) of TEHVs and their loaded configuration (middle and right) after remodeling at different pressures.

## Discussion

The FE model successfully predicted compaction and collagen remodeling in engineered strips. For TEHVs, the model predicted a decrease of the leaflet retraction with the applied pressure. However, complete valve closure was only present at aortic pressure conditions, which may explain the regurgitation issues in pre-clinical studies where TEHVs are implanted in the pulmonary position.

## References

- [1] Obbink-Huizer et al., Biomech Model Mechanobiol, 2013.
- [2] Loerakker et al., submitted.
- [3] Van Vlimmeren et al., Tissue Eng Part C, 2011.
- [4] Rubbens et al., Tissue Eng Part A, 2009.