# Controlling the adaption behaviour of next-generation tissue-engineered cardiovascular implants via computational modelling

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# Controlling the adaption behaviour of next-generation tissue-engineered cardiovascular implants via computational modelling

## Will computational modelling help to expedite clinical translation of next-generation bioengineered implants?

## Introduction and clinical problem

Structural and congenital heart diseases represent a major cause of death around the world. Although current therapy strategies have rapidly evolved over the past decades, the currently used artificial prostheses (i.e. vascular grafts, heart valve prostheses) to treat affected patients are still suboptimal as they do not promote regeneration, functional remodelling, or growth (which is particularly important in children).

For instance, while transcatheter aortic valve implantation (TAVI) techniques have truly revolutionized the therapy options for valvular heart disease and are now becoming first-line therapy for the majority of patients, the currently available bioprostheses for TAVI are all based on glutaraldehyde-fixed xenogenic material and are, therefore, prone to continuous degeneration. This is particularly accelerated in younger patients and may, therefore, require multiple re-interventions throughout a patient's lifetime. Besides that, the currently used artificial prostheses also carry the permanent risk for significant adverse events (i.e. thrombosis, infection) throughout the patient's lifetime, thereby increasing the overall morbidity and mortality of affected patients. Furthermore, the lack of growth capacity of current cardiovascular implants put children that are affected by congenital heart disease on a long and burdensome journey of repetitive and risky surgeries and interventions for their entire life.

Driven by the urgent quest for next-generation cardiovascular implants with regeneration, remodelling, and growth capacity, comparable to native cardiovascular tissues, the concept of tissue engineering (TE) has been repeatedly proposed as a promising strategy, which may be particularly beneficial for younger patients and children.

However, despite promising data from pre-clinical and first clinical pilot trials, the translation and clinical relevance of such technologies are still very limited. The reasons for that are multifaceted and comprise of scientific, logistical, infrastructural, and regulatory challenges that need to be systematically addressed in order to facilitate clinical translation of these next-generation cardiovascular implants. In particular, most of the TE concepts are technically and logistically still too complex. To address that, optimized and clinically more relevant 'off-the-shelf' strategies were established and are currently under pre-clinical and first clinical investigation. Accordingly, the so-called *in situ* concepts, either based on cell-free fully synthetic bioresorbable scaffolds or TE matrices depleted of cells, which rely on the recipient's body to regenerate and remodel the implant, currently represent the most advanced and clinically relevant methodology.

However, despite these advances, and even more importantly, long-term proof of such next-generation implants is still pending. For instance, almost universally and independently of the methodology used, most of the TE valves demonstrated in pre-clinical models that they still continuously lose their functionality within a few months due to uncontrolled (adverse) tissue remodelling phenomena which translate into valvular leaflet shortening (retraction) or thickening resulting in valvular dysfunction and failure (*Figure 1*).

Therefore, the understanding and, importantly, guidance of the adaptive remodelling processes (thereby avoiding maladaptive remodelling) remain a major challenge in current TE approaches to enable safe and effective clinical translation.

To improve and accelerate that, computational modelling of tissue biomechanics and mechanobiology in the context of tissue adaptation has been suggested as a strong approach to understand and predict the *in vivo* remodelling process and its consequences for the overall outcome. In a recent proof-of-concept study, we tested the hypothesis whether integration of a computationally inspired heart valve design into our TE methodologies can guide tissue remodelling towards long-term functionality in TE valves. Using a clinically and regulatory relevant sheep model, computationally designed TE valves implanted minimally invasively as pulmonary valve replacements exhibited a preserved and good long-term *in vivo* performance as predicted by and consistent with our computational simulations (*Figure 2*). Additionally, the remodelling characteristics were comparable to native heart valves. These findings indicate the high relevance and potential of computational modelling as an integral part of future TE and bioengineering approaches to deliver next-generation cardiovascular implants with regeneration, remodelling, and growth capacity.

Here, we review the relevance and potential of computational modelling as an opportunity to understand, predict, and ultimately control cardiovascular tissue development and adaptation, and thereby a promising tool to accelerate the clinical translation of these next-generation cardiovascular implants.

## Computational modelling to understand the *in vivo* evolution of tissue form and function

One of the major reasons for developing computational models in the context of cardiovascular TE is to describe experimentally observed

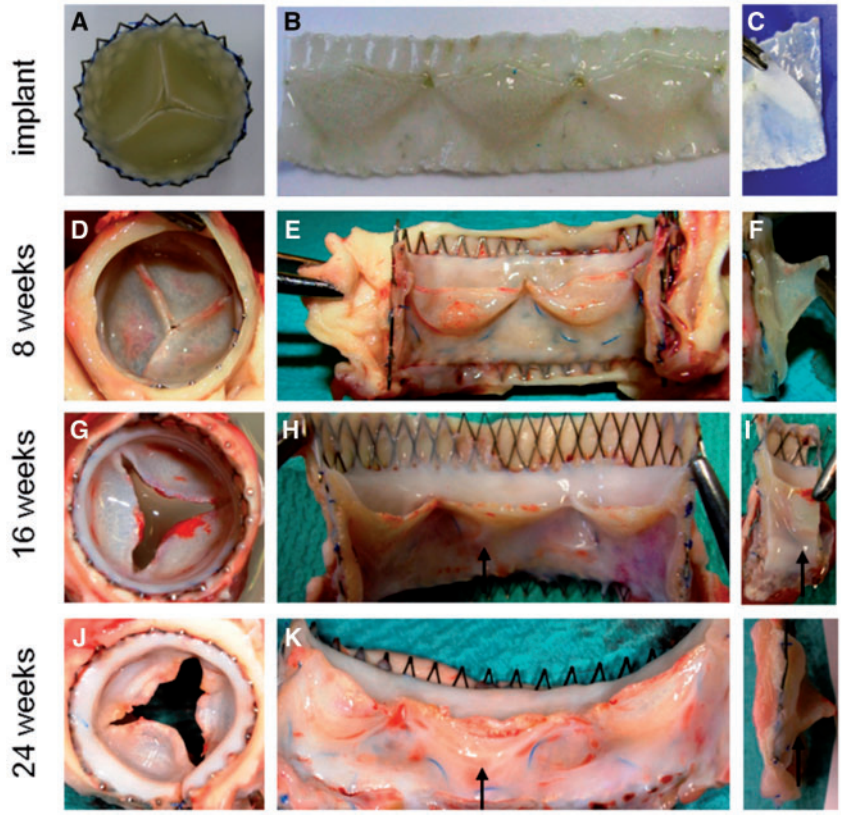


**Figure 1** Macroscopic appearance of an implanted (*A–C*) and explanted (*D–L*) 'tissue-engineered' heart valve in a sheep model. In this study, the valves displayed unremarkable functionality (no regurgitation) for 8 weeks but then started to become leaky with moderate regurgitation at 24 weeks due to merging of the leaflets with the valvular wall (at the hinge area) and the occurrence of a single leaflet prolapse in some animals (reproduced with permission from Driessen-Mol *et al.*, *JACC* 2014).

tissue adaptation in terms of growth (i.e. changes in mass and volume) and remodelling (i.e. changes in tissue structure and properties), in order to (i) unravel the underlying adaptation mechanisms of engineered tissues, and (ii) uncover why certain TE approaches are more successful than others. Importantly, integrating model development with experimental research (both *in vitro* and *in vivo*) is essential for accurately modelling the relevant biological phenomena as well as validating model predictions across various experimental observations (*Figure 3*).

Computational simulations of the *in vivo* evolution of TE vascular grafts have, for example, been able to explain the development of inter-animal variations in ultimate graft stiffness, the differential remodelling and performance of venous and arterial vascular grafts, and the (relative) roles of inflammatory-driven and mechano-mediated tissue formation in neovessel development. Similarly, via retrospectively simulating TE heart valve remodelling using experimentally derived valve-specific tissue properties as model input, we recently demonstrated that differences in valve remodelling and function can be explained by inter-animal variations in tissue properties.

Computational modelling has also made important contributions to understanding native cardiovascular development, function, and adaptation in health and disease. This knowledge can provide important guidelines for achieving native-like form and function in TE implants. In the context of human heart valve development, for example, we have shown that growth and remodelling ensure that aortic and pulmonary valves maintain a homeostatic stretch state throughout life, where growth is the dominant mechanism to preserve stretch early in life and remodelling takes over this role later in life (*Figure 4*). Moreover, simulations of collagen remodelling before and after birth revealed that cells play a major role in establishing the native-like collagen architecture in human semilunar heart valves. With regard to arterial function and adaptation, computational studies have been essential for understanding the important role of the tissue microstructure on arterial functionality in health and disease, as well as for unravelling the mechanisms responsible for pathological adaptation in conditions such as hypertension, fibrosis, and aneurysm formation.

## Leveraging the predictive power of computational modelling to rationally design implants for tissue engineering

An even stronger reason to adopt computational models to advance cardiovascular TE is the fact that they can predict the *in vivo* evolution

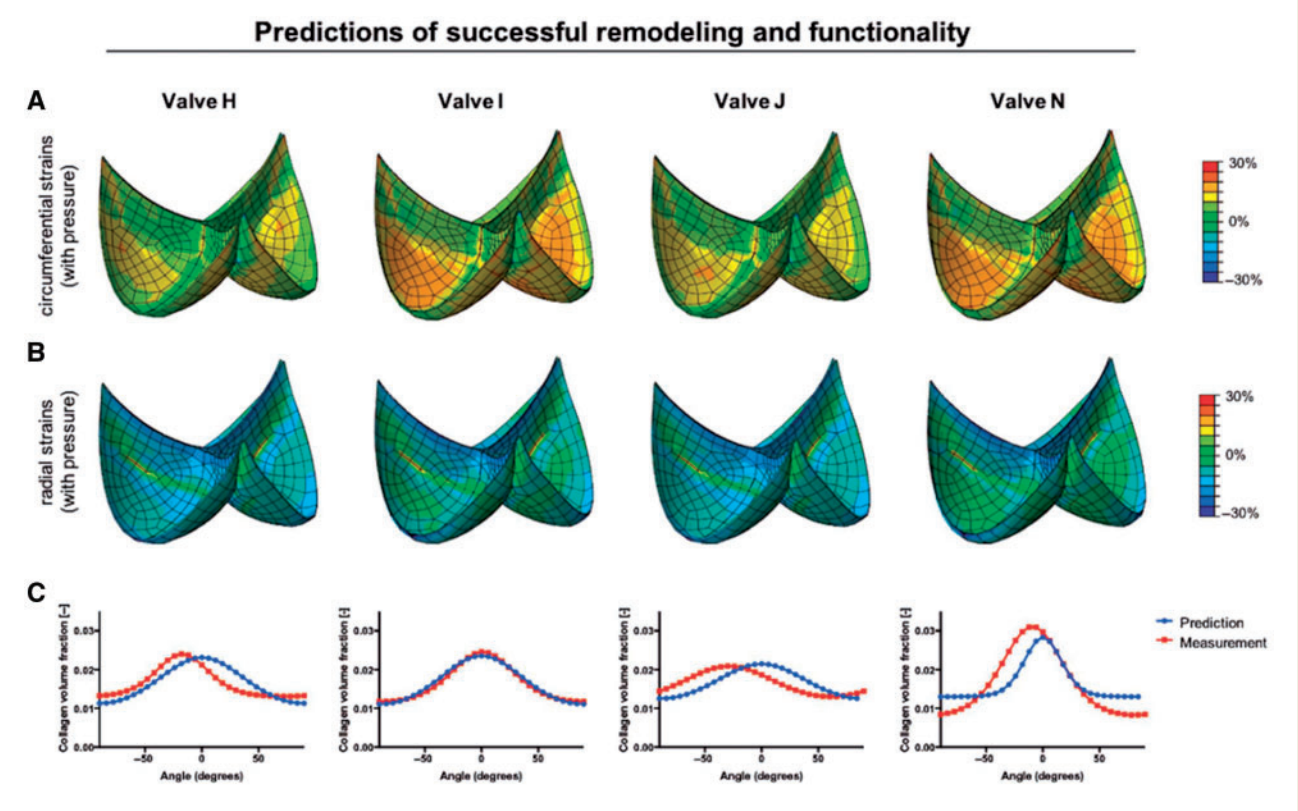


**Figure 2** Computational predictions of *in vivo* remodelling of tissue-engineered heart valves in terms of circumferential (*A*) and radial (*B*) strains and collagen structure (*C*) (reproduced with permission from Emmert *et al.*, *Sci Transl Med* 2018).

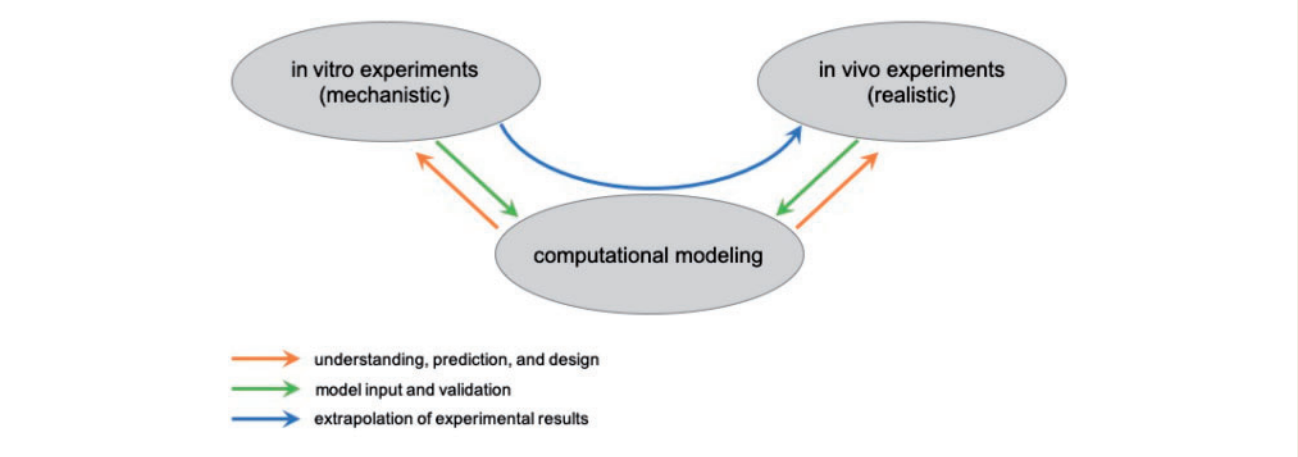


**Figure 3** Conceptual figure illustrating the benefits of integrating computational modelling and experimental research to advance the field of cardiovascular tissue engineering.

of implant properties and function. The ability to predict how implants will grow and remodel inside the body as a function of the initial implant properties and *in vivo* (patient-specific) conditions enables the evaluation of whether certain TE strategies will lead to physiological adaptation and long-term function on the one hand, or maladaptation and failure on the other hand. This potential to predict success and failure is conditional for developing safe and robust TE technologies. Moreover, as the ultimate form and function of engineered tissues depend to a large extent on the initial implant properties, the predictive power of computational models should be leveraged to identify promising implant designs based on their expected growth and remodelling profiles. In this way, only a small subset of potential designs needs

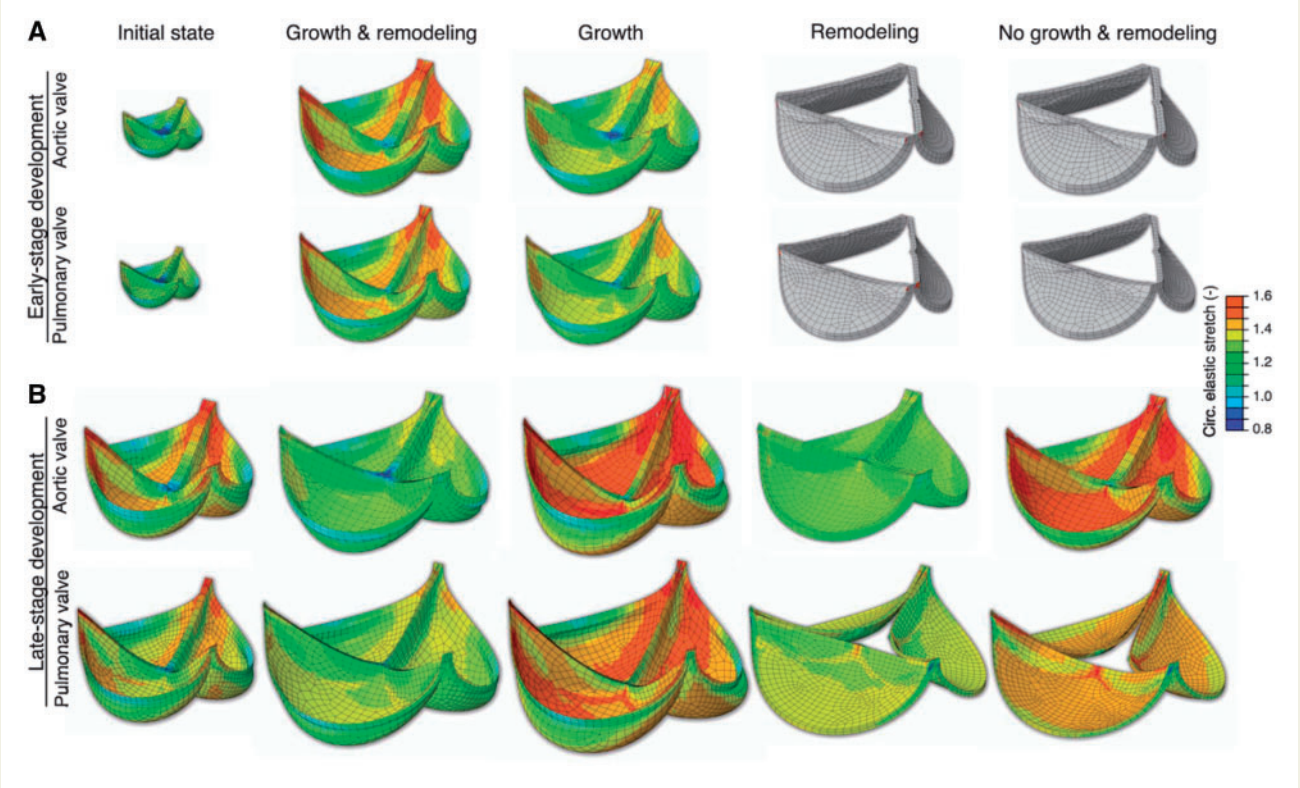


**Figure 4** The impact of growth and/or remodelling on the haemodynamically induced stretches of human aortic and pulmonary heart valves during development (reproduced with permission from Oomen *et al.*, *Sci Rep* 2018).

to be tested experimentally, which can tremendously accelerate the development and improvement of implants for cardiovascular TE.

In terms of predicting the evolution of TE vascular grafts, important advances have been made in successfully predicting their *in vivo* development as well as identifying the sensitivity of their ultimate form and function to relevant parameters and processes. In the context of TE heart valves, by comparing computational predictions of valve remodelling with experimental results of valve function and remodelling up to one year of implantation, we recently showed that in the *in vivo* remodelling of TE valves can be accurately predicted from the valve properties at implantation. Furthermore, with regard to the sensitivity of the *in vivo* valve remodelling response, systematic variations of model parameters revealed that the remodelling response is very sensitive to the contractility of the infiltrating cells. Finally, with respect to predicting success and failure, our model predicted valve maladaptation and consequently failure in case of disturbed haemodynamic loading conditions, which was corroborated by experimental observations.

As it is increasingly appreciated that the initial implant design has a large impact on the long-term implant function and adaptive capacity, computational modelling studies aimed at understanding how the initial mechanical state and function of the implant can be manipulated via modifications in implant geometry and material properties in order to achieve a more native-like situation are essential. In fact, it was one of those studies that enabled us to retrospectively explain the adverse remodelling of TE heart valves observed in previous pre-clinical studies and suggest a substantial improvement in valve geometry to achieve a more favourable remodelling response. Very recently, a computational model that can predict the *in vivo* development and adaptation response of implants for TE was even integrated with an optimization algorithm to iteratively identify optimal implant designs based on chosen functional targets. Such developments in the area of computational modelling are very promising to rationally advance the cardiovascular TE field.

## Will computational modelling expedite clinical translation of tissue engineering technologies?

In contrast to standardized contemporary cardiovascular implants (i.e. mechanical or bioprosthetic heart valves, artificial vascular grafts) which come with a very established and predictable performance profile, the safety and efficacy of next-generation TE implants strongly depend on tissue adaption and remodelling characteristics which are also driven by the recipient itself. Therefore, from a clinical viewpoint, and in addition to classical *in vitro* and *in vivo* assessments, the utilization of computational models to predict and guide the complex mechano-biological processes may represent an extremely valuable tool to increase the safety margin—thereby the translational readiness—of such next-generation implants.

Traditionally, and especially from a regulatory point of view, medical device approval by the FDA was granted based on data from bench tests, animal studies, and clinical trials. Since recently, given the

increasing capabilities of computational models, digital evidence provided by computational modelling is increasingly used to complement and even partially replace data sets collected via the traditional methods. A particular example in this context is the use of '*in silico*' clinical trials. Computational models are ideally suited to efficiently simulate the clinical outcomes for thousands of 'virtual patients' under various conditions. Therefore, modelling has the potential to reduce the number of patients needed for actual clinical trials and can predict outcomes in situations that are difficult or impossible to evaluate clinically.

However, to fully leverage the predictive power of computational models in this context, there are a couple of challenges that need to be addressed. For example, there are several open challenges in modelling the evolution of implant properties and function. Understanding and predicting tissue remodelling has received vast attention over the past years, but attempts to understand and predict other important processes such as (the potential for) somatic growth and cell-mediated scaffold degradation remain rather limited. On the other hand, expansion of the current computational models towards including more, and preferably biologically inspired, phenomena related to tissue development and adaptation as well as scaffold degradation, inherently leads to an increase in model complexity. This may hamper the numerical tractability of such models, especially when it comes to simulating implant development and adaptation in complex *in vivo* conditions. In addition, the usual increase in model parameters when model complexity increases may give rise to problems related to the (unique) identification of all parameters. To address these issues, it is important to develop numerical methods that contribute to simplifying model descriptions, in order to match model complexity with the research question under investigation. Furthermore, model development should be strongly integrated with experimental research (*in vitro* and *in vivo*) to optimize parameter identification and allow for model validation. For this latter aspect, it is essential that the computational modelling field collaborates with experts in TE, medicine, cell biology, immunology, and materials science to maximize model credibility.

In summary, due to their remodelling, regeneration and growth capacity, next-generation TE implants, such as heart valves or vascular grafts carry great hope for future cardiovascular therapeutic concepts which may be particularly beneficial for the young and children. However, to ensure a safe and large-scale clinical translation, a thorough understanding of the complex biological adaptation processes in these next-generation implants is of utmost importance as it builds the basis for their long-term safety and performance. Hence, computational modelling with its strong ability to predict and guide such remodelling processes may substantially accelerate the clinical implementation of next-generation TE implants.

**Conflict of interest:** none declared.

## References

References are available as supplementary material at *European Heart Journal* online.


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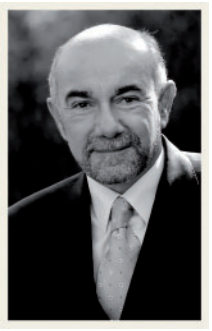
# Pedro Brugada MD



## The Spanish cardiologist who together with his brother Josep Brugada, first described the Brugada Syndrome

Pedro Brugada was born in Girona (Spain) in 1952. His primary and secondary school University of Barcelona and received his Medical Degree in 1975. After a period as a General Practitioner in the Pyrenees and Internal Medicine in Tarragona, he trained in Cardiology at the Hospital Clinic of the University of Barcelona under the mentorship of the late Professor Navarro-Lopez. He then moved to the new University of Maastricht in The Netherlands in 1979 to train in Clinical Cardiac Electrophysiology with Professor Hein Wellens. In 1982, he presented his doctoral thesis at the same university and became the Director of the Clinical Electrophysiology Laboratory and thereafter Professor of Cardiology. Most of his research activity was initially directed to understanding the cause of arrhythmias.

With better understanding of the mechanisms of arrhythmias, Pedro Brugada pioneered together with other investigators much research for curative treatment. Initially, some cardiac arrhythmias were cured by open and later, closed-heart operations. Pedro Brugada developed the technique of transcoronary chemical ablation. This 'targeted' therapy promoted the search and utilization of other techniques such as radiofrequency ablation and cryoablation. These newer