

ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL

**DESIGN PROCESS, MANUFACTURING AND MATERIAL
CHARACTERIZATION OF A PROSTHETIC POLYMER AORTIC HEART
VALVE**



M.Sc. THESIS

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Department of Computational Science and Engineering

Computational Science and Engineering Programme

FEBRUARY 2024

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**PROTEZ POLİMER AORT KALP KAPAĞININ TASARIM SÜRECİ,
ÜRETİMİ VE MALZEME KARAKTERİZASYONU**

YÜKSEK LİSANS TEZİ

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To my family



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ABBREVIATIONS

3D	: 3 Dimensional
ALE	: Arbitrary Lagrangian-Eulerian
BHVs	: Bioprosthetic Heart Valves
CFD	: Computational Fluid Dynamics
CMA-ES	: Covariance Matrix Adaptation Evolution Strategy
CSA	: Coaptation Surface Area
CSAs	: Coaptation Surface Areas
DIC	: Digital Image Correlation
DICOM	: DICOM Digital Imaging and Communications in Medicine
ECM	: Extracellular Matrix
EOA	: Effective Orifice Area
FEA	: Finite Element Analysis
FEM	: Finite Element Modeling
FSI	: Fluid-Structure Interaction
GAGs	: Glycosaminoglycans
GAs	: Genetic Algorithms
GOA	: Global Orifice Area
IB	: Immersed Boundary
L-BFGS	: Limited-memory Broyden-Fletcher-Goldfarb-Shanno
LMA	: Levenberg-Marquardt Algorithm
LOA	: Leaflet Opening Area
MHVs	: Mechanical Heart Valves
MSD	: Mean Square Difference
NEWUOA	: New Unconstrained Optimization Algorithm
NMAD	: Normalized Mean Absolute Difference
OSI	: Oscillatory Shear Index
PGs	: Proteoglycans
PHV	: Polymeric Heart Valve
PHVs	: Polymeric Heart Valves
RRT	: Resident Time

SIBS	: Poly(styrene-b-isobutylene-b- styrene)
TAVR	: Transcatheter Aortic Valve Replacement
TAWSS	: Time-Averaged Wall Shear Stress
THV	: Transcatheter Heart Valve
transWSS	: Transvalvular Wall Shear Stress
UV	: Ultraviolet
VECs	: Valve Endothelial Cells
VICs	: Valvular Interstitial Cells
xSIBS	: Extended poly(styrene-b-isobutylene-b-styrene)



SYMBOLS

σ	: The Cauchy stress
$\mathbf{e}$	: Deviatoric part of the strain
Δ	: Volumetric part of the strain
$\mathbf{G}(t)$	: Shear relaxation kernel function
$\mathbf{K}(t)$	: Bulk relaxation kernel function
t	: Time
τ	: Unit tensor
N_G	: Number of Maxwell elements for the shear relaxation
n_K	: Number of Maxwell elements for the bulk relaxation
C_k	: Constant associated with the instantaneous response for shear behavior
D_k	: Constant associated with the instantaneous response for bulk behavior
G_0	: Initial shear modulus
G_∞	: Long-term shear modulus
K_0	: Initial bulk modulus
K_∞	: Final bulk modulus
λ_k^G	: Constant associated with a discrete relaxation spectrum in shear
λ_k^K	: Constant associated with a discrete relaxation spectrum in bulk
G_k	: Coefficient of the Prony Series
τ_k	: Ccoefficient of the Prony Series
T_{01}, T_{02}	: Coefficients τ_1 and τ_2
α_k	: Relative modulus
A_{01}, A_{10}	: Coefficients α_1 and α_2 are relative moduli
F	: Force
δ	: Indentation depth of a rigid sphere
R	: Radius of rigid indenter of small indentation
γ	: Shear stress
ε	: Normal stress

u	: Displacements
E	: Young's modulus
ν	: Poisson ratio
G	: Shear modulus
W	: The strain energy per unit reference volume
$\bar{I}_1$	: First deviatoric strain invariant
μ	: Initial shear modulus of the material
d	: Material incompressibility parameter
J	: Determinant of the elastic deformation gradient F
$\bar{I}_1$ and $\bar{I}_2$	: First and second deviatoric strain invariants
λ_p	: Principal stretches of the left Cauchy-Green
c_{ij}	: Material constants
C_d	: The curing depth
D_p	: Light penetration depth
$E_{\text{resin surface}}$	: Energy value at the resin surface
Φ	: Volume fraction of ceramic powder
β	: A parameter related to the ceramic particle size and laser wavelength
Δn	: Difference in refractive index between ceramic particles
E_{absolute}	: Absolute error
$E_{\text{normalized}}$	: Normalized error
σ^{trial}	: Trial stress
$\sigma^{\text{experiment}}$	: Experiment stress
Pa	: Pascal
MPa	: Megapascal
L/min	: Litre/minute
cP	: Centipoise
mm	: Milimeter
N	: Newton
f_k	: Objective function value at x_k
B_k	: Hessian matrix
R^2	: Coefficient of determination
X_i and Y_i	: Corresponding values in two sets
c_i and e_i	: Parameters specify the fiber stiffnesses
B_k	: Hessian matrix
C	: Material constant

ξ	: Material constant
τ_{base}	: Material constant
m	: Material constant
R	: Ramp function
$\dot{\gamma}_0$	: Ramp function
$\mathcal{L}^{-1}$	: Inverse of the Langevin function,
λ_L	: Limiting stretch of the network
$\overline{\lambda}^*$	: Effective distortional chain stretch
D_{bv}	: Strain rate equation
N_{bv}	: Direction of the viscoelastic flow
$\dot{\gamma}_b$	: Effective deformation
$\mathbf{F}$	: Total deformation gradient



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DESIGN PROCESS, MANUFACTURING AND MATERIAL CHARACTERIZATION OF A PROSTHETIC POLYMER AORTIC HEART VALVE

SUMMARY

Heart valve diseases can cause serious health problems due to valve dysfunction, and mortality rates associated with these diseases are high. The aortic heart valve, a vital component of the heart, can be affected by congenital or acquired disorders. Effective treatment and management of these diseases require a multidisciplinary approach that considers various factors impacting patients' quality of life. The implantation of aortic heart valve prostheses is commonly performed using mechanical or bioprosthetic heart valves.

Mechanical heart valves are known for their high durability, but they require anticoagulation due to the risk of thromboembolic formation. Bioprosthetic heart valves, which are created by fixing human or animal tissues to a stent, are widely used due to their good hemodynamic performance. However, over time, they may present complications such as deformation, tearing, and calcification. The tissues used in these bioprostheses represent a limited source. Current research in this field highlights the necessity for ongoing clinical interventions to address the limited durability and potential complications of bioprosthetic heart valves. Polymer heart valves offer an alternative solution to the challenges of traditional heart valve prostheses, addressing issues of biocompatibility and durability. Advances in tissue engineering enable these valves to possess properties more akin to biological tissues, providing better compatibility for patients.

The materials selected for producing polymer heart valves prioritize critical factors such as durability, biocompatibility, and functionality. Silicone rubber is a flexible and durable material that possesses these characteristics. Teflon®, which is known for its chemical resistance and low friction coefficient, contributes to the effective and smooth operation of valves. Different types of polyurethane provide options in terms of flexibility, durability, and biological compatibility. SIBS (poly(styrene-b-isobutylene-b-styrene)) and its extended version, xSIBS, are commonly used in the production of valve prostheses due to their resistance to oxidation and degradation. These materials offer significant advantages in terms of long-term performance and durability, potentially enhancing the effectiveness of prostheses used in the treatment of heart valve diseases.

The production of polymer heart valves involves various techniques. The extrusion method offers low cost, fast production, and extensive design flexibility, but it may have limitations in complex geometries. Injection molding is an effective method for the serial production of complex heart valves, offering high production speed and low cost, albeit with high initial investment. Three-dimensional printing technology allows for custom designs and personalized prostheses, but it may involve a slow production process and a requirement for high-quality materials. Seamless technology has the

potential to reduce the need for surgical interventions, but it faces design challenges and limitations in material selection. The electrospinning method offers advantages in producing fine fibers and ensuring biological compatibility, although process control can be challenging. Developmental processes are focused on improving these techniques to make polymer heart valve prostheses more effective, durable, and biologically compatible.

In the field of research, *in silico* studies of polymer heart valves are crucial for evaluating the design process and prosthetic performance. A 3D model is created on the computer using DICOM images based on patient medical images. The open source Slicer 3D® software version 5.4.0 is used for segmentation. The resulting 3D model provides a detailed representation of the aortic heart valve. This segmentation process enables the acquisition of significant physiological dimension information for the design of patient-specific prostheses. The model, which is based on patient information, serves as the foundation for hemodynamic analysis, the subsequent step in the process of designing durable prostheses. These studies involve detailed modeling of fundamental factors such as biomechanics, fluid dynamics, and material properties. Biomechanical models are used to analyze the behavior of prostheses inside the body by examining biomechanical properties such as force and stress distributions and deformations. Fluid dynamics simulations are used to evaluate the performance of prosthetics in blood flow, providing a detailed analysis by modeling blood flow, pressure distribution and flow rate. Material modeling and durability analysis assesses the long-term performance and durability of prostheses by evaluating the properties of polymeric materials. These studies also aim to optimise the design process by examining the effects of material selection using different models. This allows for continuous design improvements to create safer, more effective, and patient-friendly prostheses. In the transition of prostheses to clinical applications, *in silico* studies of polymer heart valves are crucial.

Various hyperelastic material models can be used to express the behavior of materials under large deformations in the modeling of heart valves. The literature has used several material models, including Arruda-Boyce, Van der Waals, Yeoh, Ogden, Mooney-Rivlin, Neo-Hookean, and Fung.

Printing experiments were conducted for polymer heart valves in this study. An initial experiment was conducted using a 3D printer due to the opportunity to work with biocompatible materials in production. However, during the initial test to determine printability, the model collapsed. To ensure successful printing, it is necessary to support the model from below with a mold, as suggested in the literature.

Experiments were conducted using the DLP (Digital Light Processing) production technique to produce polymer heart valves. DLP enables the production of high-precision products with micron-scale layering capability, allowing for prints with precise details that match the geometry of the aortic heart valve. The experiments involved the use of three different materials: Elastomer-X 43A, Flexible-X 55A, and Gingiva 81A Shore hardness resins. It was found that Elastomer-X exhibited the highest level of elasticity.

Uniaxial tensile and planar tests were conducted to characterise the mechanical properties of Elastomer-X material under DLP production conditions. The obtained data enabled the derivation of new coefficients for material models. The ANSYS® program was used to obtain constants for the Neo-Hookean, Mooney-Rivlin (2nd and 3rd degrees), and Ogden (1st, 2nd, and 3rd degrees) models. The Neo-Hookean model

coefficients obtained previously were used to perform FEM analysis again. The observed peak equivalent stress values were found to be similar to those of the previous analysis.

To ensure the accuracy of the models, the coefficients of the material models were obtained from biaxial tests performed on ascending aorta tissues in the literature. The MCalibration® program was used to process the test data. This program is powerful in modeling from test data with rich optimization techniques. Coefficients were obtained for the anisotropic hyperelastic material model (Anisotropic Hyperelastic Model: Exp), hyperelastic-linear viscoelastic material model (polynomial-prony series), and hyperelastic-nonlinear viscoelastic material model (Bergström Boyce). Obtaining these coefficients is useful for modeling the viscoelastic and hyperelastic properties of the heart valve.

Realistic computer simulations can aid in the development of polymeric heart valves, reducing production costs and advancing personalized medicine based on the patient's physiological information. Currently, there are no studies in the literature on the production of polymeric heart valves using DLP. This study shows that DLP can be used to produce a heart valve model. To further advance DLP production in this field, it is important to develop materials that are highly biocompatible and flexible, similar to soft tissues. Additionally, the high-resolution printing capability of DLP can enhance the production of fiber-reinforced polymeric heart valve models.



PROTEZ POLİMER AORT KALP KAPAĞININ TASARIM SÜRECİ, ÜRETİMİ VE MALZEME KARAKTERİZASYONU

ÖZET

Kalp kapakçığı hastalıkları, kalbin kapakçıklarının işlev bozukluğu nedeniyle ortaya çıkan ciddi sağlık sorunlarıdır. Bu hastalıkların ölüm oranları oldukça yüksektir ve kalp hastalıkları arasında önemli bir yer tutmaktadır. Kalp yetersizliği nedeniyle hastaneye yatırılan hastaların yaklaşık %50'sinin taburcu olduktan sonra ilk yıl içinde aynı tanı ile tekrar hastaneye yatırıldığı belirtilmektedir. Bu durum, kalp kapakçığı hastalıklarının ciddiyetini ve toplum sağlığı açısından önemini vurgular.

Kalbin en önemli bileşenlerinden biri olan aort kalp kapakçığı, sıklıkla hastalık görülen ve morbiteye neden olan rahatsızlıkları doğuştan veya sonradan edinilmiş olabilir. Doğuştan gelen hastalıklar, kişi doğmadan önce gelişen bir anormallik iken, sonradan edinilen kalp hastalıkları da mevcuttur. Aort stenozu, biküspid aort kapağı, uniküspid ve kuadriküspid aort kapakları hastalıklara örnek olarak belirtilebilir. Bu anomaliler, hafif kapak kalınlaşmasından yaprakçık hareketinin bozulduğu şiddetli kalsifikasyona kadar değişen aort darlığı gibi durumlara yol açabilir. Doğuştan hastalar, doku mühendisliği çalışmalarıyla üretilen kapakçıklardan en fazla fayda sağlayabilecek gruptur. Edinilmiş kalp kapağı hastalıkları romatizmal, yaşa bağlı dejeneratif olabilir. Bu hastalıkların tedavisi ve yönetimi, multidisipliner bir yaklaşım gerektirir ve hastaların yaşam kalitesini etkileyen birçok faktör bulunmaktadır. Hastaların tedavisi için aortik kalp kapağı protezlerinin implantasyonları her geçen gün artmaktadır. Protez olarak genellikle mekanik kalp kapakçıkları ve biyoprotez kalp kapakçıkları kullanılmaktadır.

Biyoprotezik kalp kapakçıkları daha yaşlı bireylere, hamilelik ihtimali olan bireylere, riskli işlerde çalışan bireylere tercih edilirken, orta yaşlı bireylere mekanik kalp kapakçığı tercih edilebilir. Mekanik kalp kapağı yüksek dayanıklılığa sahiptir ancak tromboembolik oluşum riskine karşı antikoagülasyon gerektirir. İnsan veya domuz, inek gibi hayvan dokularının bir stente sabitlenmesiyle oluşturulan biyoprotez kalp kapakçıkları, iyi hemodinamik performansları nedeniyle yaygın olarak kullanılmaktadır. Ancak zaman içinde deformasyon, yırtılma ve kireçlenme gibi çeşitli komplikasyonlara yol açabilmektedirler. Bu protezlerin ana bileşeni olan hayvan kaynaklı dokular sınırlı bir kaynağı temsil etmektedir. Bu alanda yapılan çalışmalar, biyoprotez kalp kapakçıklarının sınırlı dayanıklılığını ve bunlarla ilişkili potansiyel komplikasyonları ele almak için devam eden klinik müdahalelere duyulan ihtiyacı vurgulamıştır.

Polimerik kalp kapakları, kalp kapak hastalıklarının tedavisinde önemli bir inovasyon sunan tıbbi bir gelişmedir. Bu teknoloji, geleneksel biyomalzemelerin yerine genellikle sentetik polimerlerin kullanılmasını içerir. Bu protezler, doku mühendisliği prensiplerini kullanarak biyolojik dokulara daha yakın özelliklere sahip olabilir, böylece hastaların vücutlarına daha iyi adapte olabilirler. Doku mühendisliği

alanındaki ilerlemeler, bu kapakların biyolojik dokulara daha yakın özelliklere sahip olmasını sağlayarak, hastalara daha iyi uyum sağlamalarına olanak tanır.

Malzeme teknolojisinin gelişimi, polimerik kalp kapaklarının tasarım ve performansını iyileştirir. Daha dayanıklı, hafif ve esnek polimer malzemelerin kullanılması, kapakların uzun vadeli etkinliğini artırabilir. Bu gelişmeler, kalp kapak hastalıklarının tedavisinde daha güvenilir ve etkili seçenekler sunma potansiyeline işaret etmektedir. Polimerik kapaklar, cerrahi müdahalelerde esneklik sağlama ihtiyacına cevap verebilir. Minimal invaziv cerrahi girişimlere uyum sağlamaları, hastaların daha hızlı bir iyileşme sürecine girmelerini ve cerrahi müdahalelere bağlı komplikasyon riskini azaltmalarını sağlayabilir. Bu nedenle, polimerik kalp kapaklarının ihtiyacı ve gelişimi, biyo-uyumluluk, malzeme teknolojisinin ilerlemesi ve cerrahi kolaylık gibi temel faktörlerin etkileşimiyle şekillenmektedir.

Polimerik kalp kapakçıkları, genellikle sentetik polimerlerin kullanıldığı inovatif tıbbi cihazlardır. Bu kapakçıkların üretiminde seçilen malzemeler, dayanıklılık, biyo-uyumluluk ve işlevsellik gibi kritik faktörlere odaklanır. Silikon kauçuk, bu özelliklere sahip esnek ve dayanıklı bir malzeme olarak öne çıkar. Kimyasal direnç ve düşük sürtünme katsayısı gibi avantajlarıyla bilinen Teflon® ise kapakçıkların etkili ve sorunsuz çalışmasına katkı sağlar. Poliüretan türleri, esneklik, dayanıklılık ve biyolojik uyumluluk açısından çeşitli seçenekler sunar. Özellikle oksidasyona ve bozulmaya karşı direnç gösteren SIBS (poly(styrene-b-isobutylene-b-styrene)) ve genişletilmiş versiyonu olan xSIBS (Extended poly(styrene-b-isobutylene-b-styrene)), kalp kapakçıkları için geliştirilen kapak protezlerinin üretiminde önemli bir rol oynar. Bu malzemeler, uzun vadeli performans ve dayanıklılık açısından önemli avantajlar sunarak kalp kapakçığı hastalıklarının tedavisinde kullanılan protezlerin etkinliğini artırabilir. Bu bağlamda, malzeme seçimi, kalp kapakçıkları alanında yapılan araştırma ve geliştirme çalışmalarında temel bir odak noktası olmaya devam etmektedir.

Polimerik kalp kapakçığı üretimi, çeşitli teknikleri içermekte olup her biri belirli avantajlar ve dezavantajlar sunmaktadır. Ekstrüzyon yöntemi, düşük maliyeti, hızlı üretim imkanını ve geniş tasarım esnekliğini beraberinde getirir. Ancak, karmaşık geometriye parçaların üretiminde sınırlamalara sahiptir. Bu noktada, gelişim süreçleri, daha karmaşık tasarımların başarıyla üretilmesine yönelik malzeme özelliklerinin ve üretim tekniklerinin geliştirilmesine odaklanmaktadır. Enjeksiyon kalıplama, karmaşık şekillere sahip kalp kapakçıklarının seri üretimi için etkili bir yöntemdir. Yüksek üretim hızı, düşük maliyet ve kaliteli sonuçlar sağlar. Ancak, kalıp maliyetleri ve tasarım karmaşıklığına bağlı olarak başlangıç yatırım maliyeti yüksek olabilir. Gelişim süreçleri, daha dayanıklı malzemelerin keşfi ve kalıp tasarımındaki inovasyonları içermektedir. Üç boyutlu baskı teknolojisi, özel tasarımlara ve kişiselleştirilmiş protezlere olanak tanır. Tasarım esnekliği, hızlı prototipleme ve düşük atık üretimi gibi avantajları vardır. Ancak, üretim süreci bazen yavaş olabilir ve yüksek kalitede malzeme gerektirebilir. Gelişim süreçleri, daha hızlı baskı hızları, çeşitli malzemelerin entegrasyonu ve biyolojik uyumlu polimerlerin kullanımı üzerine odaklanmaktadır. Dikişsiz teknoloji, cerrahi müdahaleyi azaltma ve enfeksiyon riskini düşürme potansiyeli sunar. Ancak, belirli tasarım zorlukları ve malzeme seçimiyle ilgili kısıtlamalar içerir. Bu bağlamda, gelişim süreçleri, dikişsiz teknolojinin daha karmaşık kardiyovasküler yapılarla uyumlu hale getirilmesi ve biyomalzeme entegrasyonunun iyileştirilmesi üzerine odaklanmaktadır. Elektrospinning yöntemi, nanolif malzeme yapısının avantajlarından yararlanabilir. İnce lif üretimi, yüksek yüzey alanı ve biyolojik uyum, bu yöntemin öne çıkan avantajlarıdır. Ancak, süreç kontrolü zor olabilir ve özel ekipman gerektirebilir. Gelişim süreçleri, elektrospinning

yönteminin daha ölçeklenebilir hale getirilmesi ve lif yapılarının özelliklerinin iyileştirilmesi üzerine odaklanmaktadır. Her bir üretim tekniğinin avantajları ve dezavantajları göz önüne alınarak, polimerik kalp kapakçığı protezlerinin daha etkili, dayanıklı ve biyolojik uyumlu hale getirilmesine yönelik gelişim süreçleri, malzeme bilimi, mühendislik ve tıp alanlarındaki ilerlemelerle birlikte devam etmektedir.

Polimerik kalp kapaklarının in silico çalışmaları, tasarım sürecinin ve protezlerin performansının önceden değerlendirilmesini sağlamak amacıyla kritik bir araştırma alanını oluşturur. Bu çalışmalar, kalp kapakçığı protezlerinin biyomekanik, akışkan dinamik ve malzeme özellikleri gibi temel faktörlerin detaylı bir şekilde modellenmesini içermektedir.

PHV tasarımının güçlendirilmesi aşamaları bilgisayar ortamında gerçekleştirilmektedir. Hasta tıbbi görüntülerine dayanarak, DICOM görüntüleri kullanılarak bilgisayar ortamında 3 boyutlu model oluşturulur. Bu amaçla, açık kaynaklı Slicer 3D® yazılımının 5.4.0 sürümü segmentasyon için kullanılır. Oluşturulan 3 boyutlu model, aort kalp kapağını detaylı bir şekilde temsil eder. Bu segmentasyon işlemi, hastaya özel tasarım yapılması için önemli fizyolojik boyut bilgisi elde etmemizi sağlar. Hasta bilgilerine dayalı olarak oluşturulan bu model, dayanıklı protez tasarım sürecinin bir sonraki adımı olan hemodinamik analizin temelini oluşturur.

Biyomekanik modellerle yapılan değerlendirmeler, bilgisayar modellemesi kullanılarak kalp kapakçığı protezlerinin vücut içindeki davranışını analiz etmeyi amaçlar. Bu analiz, protezin açılma ve kapanma süreçlerinin, kuvvet ve stres dağılımlarının, deformasyonunun ve diğer biyomekanik özelliklerin ayrıntılı bir şekilde incelenmesini içerir. Akışkan dinamik simülasyonları, protezlerin kan akışı içindeki performansını değerlendirmek ve optimize etmek için kullanılır. Bu simülasyonlar, protezin kan akışını, basınç dağılımını ve akış hızını modelleyerek hemostatik ve hemodinamik etkilerini incelemeye yönelik detaylı bir analiz sunar.

Malzeme modelleme ve dayanıklılık analizi, polimerik malzemelerin özelliklerini belirleyerek protezin dayanıklılığını, deformasyon özelliklerini ve uzun vadeli performansını değerlendirir. Bu çalışmalar, farklı malzeme modellerini kullanarak protezin malzeme seçimindeki etkilerini incelemeyi amaçlar. Optimizasyon ve tasarım geliştirme çalışmaları, in silico yöntemlerin tasarım parametrelerini ve malzeme seçimini optimize etmek için nasıl kullanılabileceğini araştırır. Bu, daha iyi bir performans, biyolojik uyumluluk ve dayanıklılık sağlamak amacıyla tasarım sürecinin sürekli olarak iyileştirilmesini içerir. In silico çalışmalar, polimerik kalp kapakçığı protezlerinin klinik uygulamaya geçiş sürecinde önemli bir rol oynar. Bu çalışmalar sayesinde, protezlerin daha güvenli, etkili ve hasta dostu olması için tasarım geliştirmeleri yapılabilir.

Kalp kapakçığı modellenmesinde farklı hiperelastik malzeme modelleri kullanılabilir ve bunlar, malzemenin büyük deformasyonlar altındaki davranışını matematiksel olarak ifade etmek için tasarlanmıştır. Malzemenin gerilme-deformasyon ilişkisini matematiksel olarak ifade eder ve tasarım sürecinde malzemenin performansını anlamak için önemlidir. Literatürde Arruda-Boyce ve Van der Waals, Yeoh, Ogden, Mooney-Rivlin, Neo-Hookean ve Fung malzeme modelleri kullanılmıştır.

Bu çalışmada, polimerik kalp kapakçığı baskı denemeleri gerçekleştirilmiştir. Üç boyutlu yazıcı ile yapılan üretimde biyoyumlu malzemelerle çalışma imkanından dolayı öncelikle baskı denemesi bu teknikte denenmiştir. Ancak tasarımın basılıp basılamayacağını görmek için yapılan ilk testte model çökmüştür. Modelin hassasiyeti

nedeniyle, literatürde önerildiği gibi modelin basılabilmesi için bir kalıp ile alttan desteklenmesi gereklidir. Üretim denemeleri, DLP üretim tekniği kullanılarak devam etmiştir. DLP, mikron ölçekte katmanlama yeteneği ile yüksek hassasiyetli ürünlerin üretimine olanak tanır. Aortik kalp kapakçığının geometrisinin hassas yapısını karşılamak için yeterli ayrıntıda baskı yapılmıştır. Baskı denemeleri DentaModel, Flexible-X, Gingiva, Elastomer-X reçineleri ile gerçekleştirilmiştir. Malzemeler arasında Elastomer-X 43A, Flexible-X 55A, Gingiva 81A Shore sertliğine sahiptir. Bu nedenle, elastikiyeti en yüksek olan ürün, Elastomer-X ile üretilen model olmuştur. DLP üretim tekniğinin avantajlarından biri de numunenin bir kalıp üzerine basılmasına gerek olmamasıdır, bu da maliyeti düşürüp kişiye özel tedavi için farklı boyutlarda üretim kabiliyetini artırır.

DLP üretim koşullarında Elastomer-X malzemesinin mekanik özelliklerini karakterize etmek için tek eksenli çekme ve düzlemsel testler gerçekleştirilmiştir. Bu testler, malzeme modelleri için yeni katsayıların türetilmesine olanak sağlamaktadır. Mekanik testlerden elde edilen veriler ANSYS® programına yüklenmiş ve Neo-Hookean, Mooney-Rivlin (2. ve 3. dereceden), Ogden (1., 2. ve 3. dereceden) modelleri için sabitler elde edilmiştir. Elde edilen kat sayılardan Neo-Hookean modeli kat sayıları ile tekrar FEM analiz yapıldı. Gözlemlenen en yüksek eşdeğer gerilim değerleri, önceki analizde modellenen Neo-Hookean modeline büyük ölçüde benzer olduğu gözlemlendi.

Bu bağlamda modellerin gerçekliğini desteklemek amacıyla literatürde ascending aorta dokuları üzerinde yapılan çift eksenli testlerin verileri kullanılarak malzeme modellerinin katsayıları elde edilmiştir. Test verileri MCalibration® programında işlendi. MCalibration® programı zengin optimizasyon teknikleri ile test verisinden model etme konusunda güçlüdür. Test verileri ile the anisotropic hyperelastic material model (Anisotropic Hyperelastic Model: Exp), hyperelastic-linear viscoelastic material model (Polynomial-Prony Series), and hyperelastic-nonlinear viscoelastic material model (Bergström Boyce) için katsayılar elde edildi. Bu aşama MCalibration programı kullanılarak gerçekleştirildi. Kalp kapakçığının hiperelastik özelliğiyle birlikte viskoelastik özelliklerini de modelleyebilmek için bu katsayıların elde edilmesi fayda sağlamaktadır.

Polimerik kalp kapağı geliştirme sürecinde gerçekçi bilgisayarlı simülasyonların kullanılması, üretim maliyetlerini azaltacak ve hastanın fizyolojik bilgilerine göre uyarlanmış kişiselleştirilmiş tıbbın ilerlemesine katkı sağlayacaktır. Literatürde, polimerik kalp kapakçığının DLP ile üretim çalışması yoktur. Bu çalışma, kalp kapakçığı modelinin DLP ile üretebileceğini ortaya koymaktadır. DLP üretiminin bu alanda ilerleyebilmesi için biyouyumluluğu ve yumuşak doku benzeri esnekliği yüksek malzemelerin geliştirilmesi önemlidir. Ayrıca, DLP'nin yüksek çözünürlüklü baskısı, fiber katkılı polimerik kalp kapakçığı modellerinin üretilebilirliğini artırabilir.

1. INTRODUCTION

1.1 Motivation

Heart valve diseases can cause serious health problems due to the malfunction of the heart valves. These diseases have high mortality rates and are a significant concern among heart conditions. The aortic heart valve, which is an essential component of the heart, can lead to congenital or acquired disorders that frequently result in diseases causing morbidity. Anomalies such as aortic stenosis, bicuspid aortic valve, unicuspid, and quadricuspid aortic valves can lead to conditions ranging from mild valve thickening to severe aortic constriction where leaflet motion is impaired. Heart valve diseases can be acquired through rheumatic or age-related degenerative conditions. Effective treatment and management of these diseases require a multidisciplinary approach, considering various factors that affect the patient's quality of life. The use of aortic heart valve prostheses in patient treatment is becoming increasingly common. Two types of prostheses are typically used: mechanical heart valves (MHVs) and bioprosthetic heart valves (BHV).

BHVs are preferred for older individuals, those who may become pregnant, and individuals in high-risk occupations. In contrast, mechanical heart valves may be preferred for middle-aged individuals. MHVs are durable but require anticoagulation due to the risk of thromboembolic formations. BHVs, which are created by fixing human or animal tissues such as pig and cow to a stent, are widely used due to their good hemodynamic performance. However, over time, they may lead to various complications such as deformation, tearing, and calcification. The main component of these prostheses is animal-sourced tissues, which represent a limited source. Research in this area highlights the importance of continuous clinical interventions to tackle the limited longevity of BHVs and the potential complications that come with them.

Polymeric heart valves (PHVs) are an innovative treatment for heart valve diseases. They aim to overcome the bio-compatibility and durability issues of traditional valve prostheses by using polymeric materials. These prostheses leverage tissue engineering

principles to have properties closer to biological tissues, enabling better adaptation to patients' bodies. Advances in tissue engineering have enabled the development of heart valve prostheses with properties more similar to biological tissues, improving their compatibility with patients.

The study aims to enhance the durability and production processes of polymeric heart valve prostheses used to treat heart valve diseases. The ultimate goal is to produce patient-specific heart valve prostheses with mechanical properties comparable to those of natural heart valves.

Polymeric heart valve production involves various techniques, each with specific advantages and disadvantages. Molding is an effective method for mass-producing heart valves with complex shapes due to its high production speed, low cost, and quality results. However, the initial investment cost can be high depending on mold costs and design complexity. Ongoing development processes aim to discover more durable materials and innovate mold design. Three-dimensional printing technology enables the production of custom designs and personalized prostheses. It offers advantages such as design flexibility, rapid prototyping, and low-waste production. However, the production process may sometimes be slow and require high-quality materials. Development processes focus on improving printing speeds, integrating various materials, and using biocompatible polymers. Seamless technology has the potential to reduce surgical interventions and lower infection risks. However, it comes with specific design challenges and limitations in material selection. Therefore, development processes aim to make seamless technology more compatible with complex cardiovascular structures and enhance biomaterial integration. The electrospinning method can benefit from the advantages of nanofiber material structure. The electrospinning method offers prominent advantages such as the production of fine fibers, high surface area, and biological compatibility. However, process control may be challenging and may require specialized equipment. Therefore, development processes are focused on making the electrospinning method more scalable and improving the properties of fiber structures.

Three-dimensional printing technologies will be used to achieve personalized valve production. Traditional mold production methods often hinder scalability and customization of production. Rapid prototyping can be achieved using 3D printers or Digital Light Processing (DLP) technology, which is known for its high-resolution

capabilities. Currently, there are no studies in the literature on the production of polymeric heart valves using DLP. This study aims to investigate the feasibility of producing a heart valve model using DLP. Furthermore, the research aims to demonstrate that high-resolution printing of DLP can enhance the producibility of fiber-reinforced polymeric heart valve models.

The study seeks to show that the required precision for the detailed and precise design of the aortic heart valve model can be achieved using this production technique. Mechanical tests will be conducted in laboratory settings to collect data. This data will be used to evaluate the mechanical properties of the material sample used in this production technique. The coefficients of the material model used in the analysis will be updated based on the tensile test data. The material model coefficients will be revised and integrated back into the model, resulting in an artificial heart valve prosthesis model with superior mechanical resistance and optimum material compatibility.

Realistic computer simulations will reduce production costs. This research will also advance personalized medicine by customizing the prosthesis according to the patient's physiological information. The aim of this research is to enhance polymeric heart valve prostheses by improving their durability, production process, and promoting personalized medicine to benefit patients with heart valve diseases.

1.2 Literature Review

Valvular heart diseases can cause disability and premature death, and reduce the well-being and life satisfaction of individuals [1]. The aortic valve is a crucial component for the proper functioning of the heart and maintaining cardiovascular health. Aortic valve diseases, such as aortic stenosis, can have significant consequences for patients. The prevalence of aortic valve anomalies is highest in the bicuspid valve, although unicuspid and quadricuspid valves are observed in rare instances. These anomalies can result in conditions such as aortic stenosis, which can range from mild valve thickening to severe calcification with impaired leaflet movement [2]. The number of therapeutic aortic heart valve prosthesis implantations is increasing daily. MHVS and BHVs are used for treatment [3]. When selecting a suitable prosthetic valve, it is important to consider the patient's information, such as age and suitability for anticoagulation therapy [4]. MHVS and BHVs are used for treatment. Mechanical heart valves (MHVs)

have high durability but require anticoagulation to prevent the risk of thromboembolic formation [5]. MHVs have high durability but require anticoagulation against the risk of thromboembolic formation.

The treatment of aortic stenosis has been revolutionized by the introduction of transcatheter aortic valve replacement (TAVR), which has become the new standard of care for individuals diagnosed with severe aortic stenosis who are considered high-risk candidates for traditional surgical aortic valve replacement or are deemed inoperable [6]. Transcatheter aortic valve replacement (TAVR) is being considered as a viable treatment option for patients who face increased risks associated with surgical aortic valve replacement or those with inoperable mixed aortic valve disease [7].

BHVs are created by affixing tissue from humans or animals, such as pigs and cattle, to the stent. BHVs imitate natural heart valves more closely than mechanical valves. However, they can cause various complications in the body, including deformations, tears, and calcifications due to movement within the stent [8]. This may reduce the lifespan of the valve, potentially necessitating a repeat operation for replacement.

PHVs are a promising option because they do not require lifelong anticoagulation therapy, unlike mechanical valves, or repeated heart valve replacement within 7-9 years, as is the case with bioprosthetic heart valves. These attributes can enhance the patient's quality of life. The use of biocompatible and durable polymers, instead of biological tissues in bioprosthetic heart valves, makes the prostheses superior. The selection of biocompatible and biostable materials for PHVs, along with the reinforcement of the valve design, can provide superior mechanical strength and fatigue resistance [9].

PHVs have had limited success due to calcification, oxidation, thrombosis formation, deficiencies in valve designs to increase strength, and deformations resulting from dynamic stresses imposed on the material. The production of PHVs has utilized polymers such as silicone rubber, Teflon®, and segmented polyurethanes. The studies continued by eliminating the disadvantages of the materials used and further strengthening their properties. It was observed that poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS) and xSIBS materials have resistance to oxidation and degradation [10].

Physiologically, heart valves are subjected to complex loads. Therefore, it is recommended to analyze the prosthetic heart valves (PHVs) using finite element

analysis (FEA) before manufacturing to ensure their strength. Additionally, printing prototypes with proven mechanical strength through calculation methods can prevent material and time loss. Whiting et al. demonstrated that Finite Element Analysis (FEA) can provide information on both the structural and hemodynamic performance of aortic valve designs, aiding in the development of prostheses [11].

Studies have been conducted to enhance valve design through various geometric applications. Claiborne et al. conducted an experiment on the aortic heart valve by implementing a tapered thickness design for the leaflets. Their findings indicated similar transvalvular energy loss to native valve platelet activation rates, transvalvular energy loss similar to tissue valves, and low regurgitant flow [12]. Gulbulak et al. (year) conducted a study on the effects of the hub curve, free edge formation, and binding curve of PHVs on geometric orifice and coaptation areas [13]. Frías et al. added extra padding to the connection between the pillars and leaflets in the design of the PHVs. They demonstrated that this padding reduces the maximum stress in the leaflets [14]. Liua et al. investigated the impact of single-ply and double-ply fiber mesh reinforcements on PHVs, as well as the effect of mesh orientation on valve function. The study found that stress was reduced with a double-layered fiber mesh, and that orienting the fibers perpendicular to each other and to the stent interface further improved stress reduction [15]. In addition, the authors investigated how to make the design's behavior prediction more realistic. Mawan et al. demonstrated that using the hysteresis model in their analysis of the PHV produces more accurate deformation behaviors for the valves [16].

To enhance the properties of PHVs and facilitate their use as a treatment method, it is essential to ensure that their mechanical design is hemodynamically resistant, prevents deformation formation, and that the materials used are biocompatible.

1.3 Novelty

We printed PHV's model, which was the result of hemodynamic and structural mechanics analyzes carried out in a computer environment, in accordance with the design. This is an important feature in the development process of prosthetics. Because sometimes, when developing a prosthesis, it is produced by compromising the actual geometry of the natural heart valve. Geometric properties are an important element affecting mechanical strength.

After the geometry that emerged in the design was successfully produced with the DLP manufacturing technique, uniaxial and planar tests were performed for mechanical characterization. Its strength was checked. Coefficient numbers were obtained for both Neo Hookean, Mooney Rivlin, and Ogden hyperelastic material models from the mechanical test data. The FEM model was rebuilt specifically for the material produced. Thus, we customized the in silico analysis of the model specific to the material produced. Incorporating the coefficients of material models into the existing literature will allow researchers, especially those using this manufacturing technique, to develop more realistic designs for PHVs.

It is important to thoroughly evaluate the manufacturing process of prosthetic aortic heart valves. Working together, taking into account in silico analyzes of materials and production technologies from start to finish, contributes to the production of high-strength, biocompatible prostheses suitable for patients.

We obtained coefficient numbers for various material models from the equibiaxial test results performed on the ascending aorta of a 54-year-old person. We optimized the coefficients of the anisotropic hyperelastic (Exponential), polynomial-Prony Series and Bergström Boyce models from the test data. We obtained USERMAT subroutine codes to perform analysis with these coefficients in the ANSYS program.

2. AORTIC HEART VALVE PROSTHESIS DESIGN METHODOLOGY

Designing an aortic heart valve prosthesis involves several significant considerations. Firstly, it is imperative to have a comprehensive understanding of the anatomy of the heart and the heart valve. Additionally, knowledge about the various heart valve diseases encountered is essential. The valve intended for therapeutic purposes should be free from any factors that could induce diseases post-implantation.

When developing the in silico model of the heart valve, it is important to pay close attention to the design parameters related to geometry, including shape and dimensions. Additionally, it is crucial to carefully consider the fiber orientations within the valve structure and select an appropriate material model to accurately predict material behavior. This chapter aims to provide insights into the issues related to the design of an aortic heart valve.

2.1 The Heart and Aortic Valve Anatomy

The structure of the heart in human anatomy consists of four chambers and four valves. These chambers are the right atrium, right ventricle, left atrium, and left ventricle. The valves include the tricuspid and pulmonary valves, as well as the mitral and aortic valves [17]. On average, these valves undergo around 40 million cycles of opening and closing per year, totalling over 3 billion times in a lifetime [18]. The circulatory process begins as blood moves from the right atrium to the right ventricle through the tricuspid valve. It is then propelled through the pulmonary valve into the lungs, where it becomes enriched with oxygen. Subsequently, the oxygenated blood returns to the left atrium. From there, it flows into the left ventricle through the mitral valve. Finally, the oxygenated blood is distributed throughout the body via the aortic valve [17]. The aortic valve is situated at the base of the aorta, connecting to the left ventricular outflow tract. It allows blood flow from the left ventricle into the body during systole and prevents the backflow of blood into the left ventricle during diastole [19].

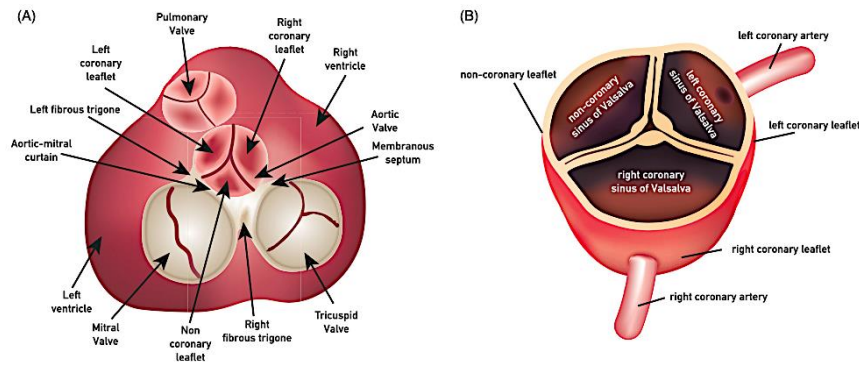


Figure 2.1 : View of the human heart and the aortic valve. A) Top view of the human heart, excluding the atria and great vessels. The image reveals the anatomical relationships between the four heart valves and the fibrous structures surrounding the aortic, mitral, and tricuspid valves. (B) The closed view of the aortic valve reveals the leaflets, sinuses of Valsalva, and coronary arteries [18].

When viewed from above, the aortic valve is located at the center of the chamber, as shown in Figure 2.1 (A). The valves are stabilized and supported by the heart's fibrous skeleton. The aortic valve's anatomy comprises three sinuses of Valsalva, three aortic leaflets, and three fibrous triangles between the leaflets. The sinuses of Valsalva project outward, creating spaces between the leaflets and the luminal surface of the aortic root wall (refer to Figure 2.1 (B)). The sinotubular junction is a ring of thickened aortic wall that marks the point of exit from the aortic root and passage into the aorta.

The leaflets are one of the pivotal components of the aortic valve in terms of its functionality. They expand during systole and are named according to the sinus of Valsalva they support: right, left, and non-coronary leaflets. The leaflets of the aortic valve consist primarily of the free margin, hub, closing margin attached to the aortic root, lunulae, and leaflet attachments or hinges. During valve closure, the free edge of the leaflets fuses with that of the neighboring leaflets.

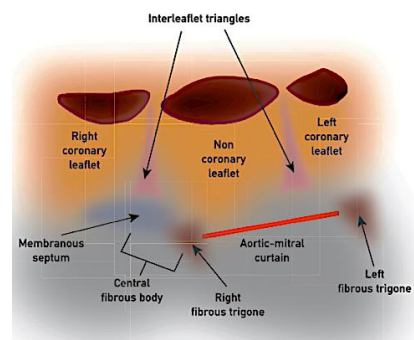


Figure 2.1 : The drawing showing the aortic valve leaflets, inter-leaflet triangles, and the fibrous continuity surrounding them, observed from the left ventricular outflow tract, is shown [18].

The lunula is the crescent-shaped area on the ventricular surfaces of the leaflets where two adjacent leaflets meet during valve closure. The area below the lunula is referred to as the belly. The belly of the aortic valve represents the non-adhesive cover part during movements. The connection point between the aortic valve and the aortic root is known as the semilunar-shaped connection or hinge. The hinges of adjacent leaflets meet at the sinotubular junction, initially running parallel for a short distance before progressing to form a fibrous region called the commissure. Therefore, the aortic valve has three commissures.

The leaflets are arranged in a semilunar pattern, creating three triangles between the adjacent leaflets and the sinuses of Valsalva (refer to Figure 2.2). The interleaflet triangle, which is located between the right and left coronary leaflets, is oriented towards the pulmonary valve. A triangle, located between the left and non-coronary leaflets, along with parts of the non-coronary and left coronary leaflets, establishes fibrous continuity with the anterior leaflet of the mitral valve through the aortic-mitral curtain. This formation contributes to the creation of the right and left fibrous trigones by thickening their edges. The third triangle, which faces the right atrium, is located between the right and non-coronary sinus. It combines with the membranous septum to form the fibrous central body of the heart, which is the strongest part of the heart. Together with the right fibrous trigone, it provides shape to the heart [18].

The leaflets form a ring in the shape of a half-moon with three points along the root. The narrowest diameter in the blood pathway connecting the left ventricle and the aorta is called the annulus. Additionally, the circular connection between the structures of the left ventricle and the sinuses of Valsalva is referred to as the anatomical aorta-ventricular connection [18].

2.1.1 Tissue contents

The aortic valve develops a complex microstructure as it works billions of times throughout a person's life and is exposed to complex mechanical forces. The leaflets contain highly specialized cells and a functionally adapted extracellular matrix. The mechanical characteristics of the aortic valve leaflet are closely associated with its anisotropic nature.

The aortic valve leaflets can be histologically classified into three layers (Figure 2.3). The aortic valve is composed of three distinct layers: an intertwined collagen layer

near the aortic surface, a spongiosa layer containing an abundance of glucosamine, and a ventricularis layer close to the ventricular surface that is rich in elastin. It is important to note that this description is free from subjective evaluations and uses clear, objective language with precise word choice. The text also adheres to conventional structure and formal register, while maintaining grammatical correctness and a logical flow of information. These layers are primarily made up of collagen, elastin, and glycosaminoglycans (GAGs), which form the extracellular matrix (ECM). Valvular interstitial cells (VIC) are also an important component. Furthermore, the leaflet has an endothelial cell layer on both surfaces that enhances resistance to thrombosis when in contact with blood [20].

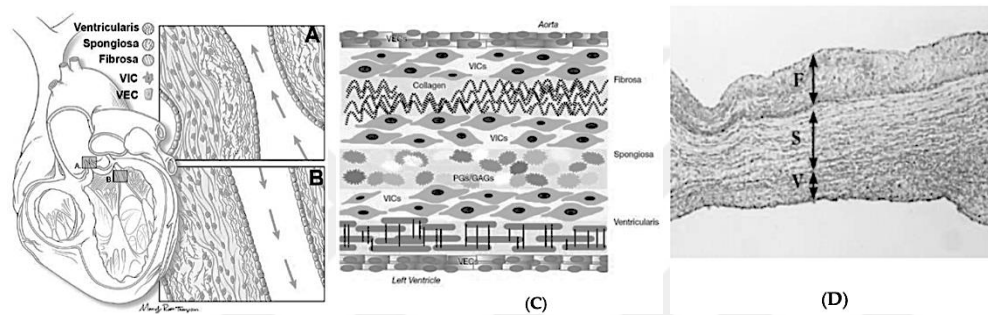


Figure 2.2 : The structures of the heart valves. A) Depicts the aortic valve, B) The mitral valve, showcasing the three layers of the extracellular matrix: ventricularis, spongiosa, and fibrosa. The red arrows indicate blood flow, with the ventricularis layer positioned closest to the direction of blood flow. VECs and VICs are also depicted. On the right side, the representation of the aortic valve highlights the coordinated rearrangement of ECM fibers and elongation of VICs during systole and diastole. C) Detailed view of the heart valve structure. The outer layer is formed by VECs. D) Tissue image of the trilayered structure of an aortic leaflet in sheep, with the three layers identified as fibrosa, spongiosa, and ventricularis [21].

The function of valves is closely linked to the various connective tissue elements and their configurations found throughout the leaflets and supporting structures. These mechanical stimuli ultimately trigger molecular changes, which protect the valve's structural integrity and ensure its mobility [14]. The valve's main stress-bearing structure consists primarily of collagen bundles located in the fibrosa layer (Figure 2.3).

The layer of spongiosa, which is situated between the ventricular and fibrous layers, contains a high concentration of proteoglycans. It typically undergoes fibrosis and is exposed to ventricular preload before being subjected to pressure under specific loading conditions. The fibrosa then assists in transferring the load of the leaflets to

the aortic wall. During diastole, the elastin found in ventricles stretches and rewinds in systole, allowing the valve to maintain its shape (Figure 2.4) [10].

Spongiosa contains hydrophilic glycosaminoglycans (GAGs) that bind with proteins to form proteoglycans (PGs) in the structural composition of the valve leaflets and supporting tissues. GAGs act as a buffer to reduce friction and stress-induced damage. The observed continuous transmural strain distribution from the fibrosa towards the ventricles is noteworthy. In such cases, the spongiosa is considered a transition zone between the two outer layers that resists delamination. This shear function reduces the stresses caused by leaf deflection, allowing collagen fibers to move around each other without fatigue caused by wear and tear. Additionally, GAGs assist in maintaining compressive forces and reducing calcification by binding calcium ions and preventing hydroxyapatite nucleation.

Elastin applies tensile tension during valve unloading, enhancing the pre-stretched formation of the fibrosa and ventricularis. The valve allows for significant radial and circumferential extensibility in the leaflets and walls of the aortic sinus and ascending aorta, facilitating leaflet coaptation and reducing diastolic regurgitation [8].

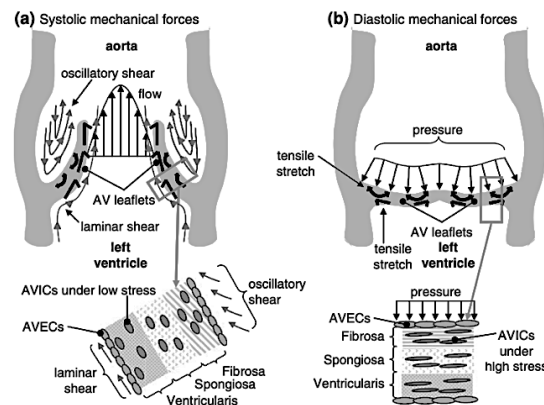


Figure 2.3 : Visual representation depicting the distinct mechanical stimuli encountered by aortic valve endothelial and interstitial cells throughout a cardiac cycle: (a) Mechanical forces during systole and (b) Mechanical forces during diastole [20].

2.2 Aortic Valve Diseases

Heart valve diseases are prevalent globally, with the aortic valve being the most commonly affected site, leading to morbidity. Valve disease can be congenital or acquired (Figure 2.5). Congenital valve disease is an anomaly that arises before birth,

resulting in the aortic valve having two leaflets instead of the normal three. Congenital valve disease is an anomaly that arises before birth, resulting in the aortic valve having two leaflets instead of the normal three. Congenital valve disease is an anomaly that arises before birth, resulting in the aortic valve having two leaflets instead of the normal three. This can cause inappropriate valve sizes, malformations of the leaflets, and improper attachment irregularities. Valves generated through tissue engineering research can provide the greatest advantage to individuals with congenital conditions. Heart valve diseases can be acquired through various means such as rheumatic or age-related degenerative conditions [22]. In order to prevent deformation, heart valves must grow sufficiently with physiological development and maintain resistance to changing blood pressure while preserving the properties of their tissue. Disturbances to this balance can lead to various pathological conditions.

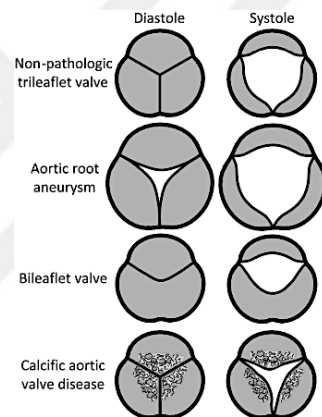


Figure 2.4 : Diagrammatic comparison between non-pathologic trileaflet aortic valve, aortic root aneurysm, bileaflet and calcified valves [10].

The causes of abnormal heart valve function are as follows. Aortic stenosis, the most common condition, is an incomplete opening of the aortic valve. The most common pathology is aortic root aneurysm. This condition causes aortic regurgitation. As a result of the inadequate central closure of the valve during diastole, blood is pushed back into the left ventricle [23]. Water retention occurs when high concentrations of glycosaminoglycan or cholesterol bind to elastin. This leads to dehydration of the elastin and stiffening of the aorta.

2.3 Artificial Aortic Heart Valves

MHV, BHV, and PHV are being studied as artificial aortic heart valves. This chapter will provide information about these valve types.

2.3.1 Mechanical valves

Pioneered as the first prosthetic heart valve, the MHV was designed with durability and hemodynamic acceptability in mind [24]. Developed from hard and durable materials, MHVs were a significant advance in heart valve surgery [25]. The first heart valve surgery was performed in 1952, and by 1957 the first commercially available valve prosthesis was available—a ball-and-cage mechanical valve, a collaboration between surgeon Albert Starr and engineer Lowell Edwards. Subsequently, the development of mechanical valves positioned them as the preferred choice for surgical procedures, particularly in the treatment of young patients.

However, MHVs, which are made from materials much harder than human soft tissue, lack physiological valve geometry (Figure 2.6). Considered a foreign body in the body, these valves increase the risk of thrombosis in patients, mainly due to factors such as increased shear stress and backflow jets, especially around the hinge points. The presence of backflow jets is associated with red blood cell damage and increased platelet activation [26].

To reduce the risk of thrombosis, people with mechanical valves require lifelong anticoagulant therapy. However, this treatment increases their susceptibility to bleeding, ranging from minor to severe injury. This prolonged use of anticoagulants has been associated with fetal loss and congenital malformations in pregnant women. Therefore, mechanical valves are not recommended for women and athletes planning to become pregnant. In addition, the audible closing sound of the valve, which some patients may find annoying, has been attributed to the stiffness of the valve material [25].

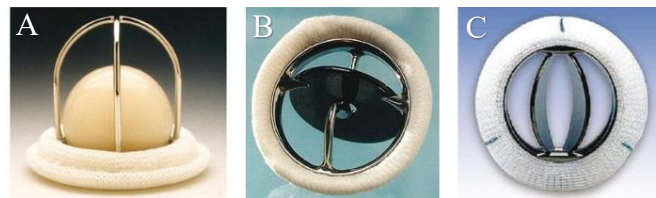


Figure 2.5 : The three fundamental types of MHVs are illustrated as follows: A) Ball and cage valve, B) Tilting disk valve, C) Bileaflet valve [27].

There are some considerations for mechanical or bioprosthetic aortic valve implantation depending on patient characteristics. Individuals over 70 years of age, those who are likely to become pregnant, those with renal failure, those who work in

hazardous occupations, and those who are unsuitable for anticoagulation therapy are considered suitable for bioprosthetic heart valves, while MHV may be preferred in individuals with hyperparathyroidism, metabolic syndrome, and small aortic annulus [14].

2.3.2 Bioprosthetic valves

BHVs offer more hemodynamic benefits than mechanical valves. They offer better patient outcomes. They have reduced platelet adhesion, which reduces the risk of thrombogenicity compared to mechanical valves. Patients do not require long-term anticoagulant therapy, which reduces the risk of internal bleeding and stroke. BHVs are categorized as autografts and xenografts. Autografts (homografts) are taken from humans, while xenografts (heterografts) are taken from animals (pigs, cattle, etc.). Autografts obtained from cadavers may not only be insufficient to meet the patient's needs, but may also result in size incompatibility. They are therefore less favoured. Patients usually receive stented porcine and bovine valves. Medtronic and Edwards Lifesciences aortic heart valves are generally preferred commercially [8].

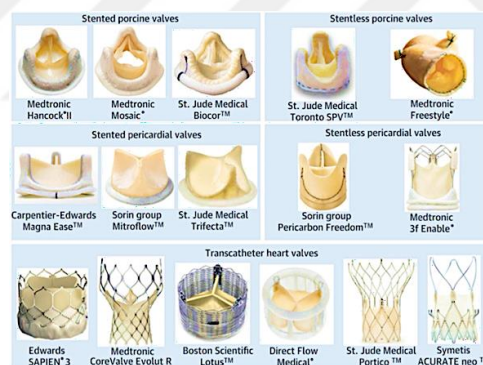


Figure 2.1 : Various categories of heart valves are employed in both surgical and transcatheter procedures [23].

These valves are implanted with a stent, which can lead to various complications in the body. For example, the use of glutaraldehyde bovine pericardium as a heart valve in one patient for 5 years had resulted in some deformations caused by movement within the stent, leading to leaflet rupture and aortic insufficiency.

Various models have been developed, including stentless porcine valves, which are made by modifying the aortic roots with a suture ring or changing the technique of suturing the pericardium to a stent (Figure 2.7). Stentless porcine valves, which consist of aortic roots connected by a suture loop, can be implanted in place of or within the

patient's aortic root. This increases the opening area, but the technique is more complicated than the stented version and there is insufficient understanding of its long-term durability. Placement within the root changes the shape of the valve and can lead to valve insufficiency in patients with a calcified aorta. However, complete placement of the root requires specific surgical expertise and prolongs implantation time. A high incidence of perioperative aortic insufficiency may result from structural incompatibilities [8].

However, bioprosthetic valves have several drawbacks, including inadequate mechanical strength and susceptibility to structural deterioration and extensive calcification. The latter is thought to occur due to the inability of non-viable cells to repair the damaged extracellular matrix, ultimately leading to calcification through the accumulation of deceased phosphate-rich cells. When combined with calcium-containing plasma, calcium phosphate is formed. This happens because it acts as a nucleus for the process. Chemical fixation increases the flexural strength of the caps.

2.3.3 Polymeric heart valves

Significant progress has been made with BHVs, but there is a continuing need for research and development of PHVs to overcome the limitations associated with the use of bioprosthetic valves. The biomaterials used to make these heart valves should mimic the natural mechanical properties of the valve. PHVs must have essential properties, including flexibility for adequate strength, high hemodynamic performance, resistance to calcification and fatigue resistance. In addition, they should be applicable to different age groups of patients. PHVs offer the advantage of long-term valve use without the need for lifelong anticoagulation therapy. It also eliminates the need for valve replacement every 7-9 years [28]. With these features, PHVs improve patients' quality of life. PHV production patterns ensure reproducibility and low cost.

The choice of polymer material allows PHVs to be designed to more closely mimic the properties of natural tissue. Critical properties sought include the material's ability to withstand the dynamic pressure changes of the heart and its biocompatibility, with the aim of eliminating the need for anticoagulation. The valve material must be biocompatible so that the body does not perceive foreign substances. This material property will help reduce the body's immune response. Over time, structural valve

degeneration is inhibited by the valve material. The valve material promotes integration with the tissue and stimulates natural tissue regeneration and endothelialisation after implantation in the body [29].

Silicone rubber, which is a flexible and durable material; Teflon®, which has chemical resistance and a low coefficient of friction; various types of polyurethane in terms of flexibility, durability and biological compatibility; SIBS (poly(styrene-b-isobutylene-b-styrene)), which was developed for heart valves that are resistant to oxidation and degradation; and xSIBS (extended poly(styrene-b-isobutylene-b-styrene)), which is an extended version of SIBS and more resistant) are used in the manufacture of valves [30].

The quality of PHVs cannot be attributed solely to the choice of material. Other critical factors that have a significant impact on the quality of these valves include their design, the way they are transferred into the body and their biocompatibility. For example, replicating the anisotropic properties of the natural tissue components of a heart valve in a polymer heart valve results in valves with greater durability.

2.3.3.1 Sources of failure of the polymeric heart valves

Various failures occur due to both the design and the preferred materials used in the construction of PHVs. These failures can be listed as follows: mechanical degeneration, degradation, calcification, thrombotic complications, pannus formation. The following sections describe the failures that can occur.

Mechanical degeneration

If the material of the PHV does not have the required mechanical properties or is not resistant to mechanical fatigue, long-term overpressure can lead to mechanical degeneration of the prosthesis.

Aortic heart valves are exposed to pressures of up to 1 MPa. They can withstand a stress of 1.74 ± 0.29 MPa in the circumferential direction. The mechanical strength of PHVs should be comparable to or exceed that of biological tissue. The molecular weight of the polymers, their polydispersity and the manufacturing method should also be considered. PHVs should not invert the leaflets under blood flow. To prevent this, the material must be moderately stiff and flexible, as the valve must be moderately stiff to prevent blood flow reversal when opening and moderately stiff to close.

In addition, the prosthesis must be able to maintain the shape of the valve during both systole and diastole. Rapid valve cycling may limit the ability of the prosthesis to return to its original shape, as the impact of a new load may occur before the material has fully recovered. These conditions can lead to elongation, localized thinning, increased stress, stress accumulation and a reduction in fatigue strength. Adding functional groups to the polymer to increase its creep resistance increases its molecular weight and consequently its stiffness, but reduces its hysteresis [9].

Degradation

Another concern is the structural deterioration of the PHV due to chemical changes caused by foreign substances in the body. A significant risk is the development of fibrosis within the valve. Various components such as lipids, blood proteins, proteins, water and ions can be absorbed from the valve surface, causing plasticisation and consequently affecting the mechanical properties of the valve. Blood proteins have properties that initiate oxidation and/or hydrolysis. This results in the rapid formation of fibrous material in the valve, a situation exacerbated by the porous nature of the material.

In addition, the large surface area, amorphous nature and hydrophilic functional groups of the polymer accelerate hydrolysis and oxidation. Despite these limitations, some measures can be taken to mitigate these effects. For example, hydrophobic functional groups can be added to the polymer. The orientation of the macromolecules and the degree of crystallisation can be increased by thermal annealing. To reduce the overall surface area, it is better to use manufacturing techniques such as casting rather than those that increase the surface area, such as electrospinning [9].

Calcification

Calcification of aortic valves can lead to loss of elasticity and even fracture, highlighting the need for effective preventive measures. Calcification has been observed in certain materials, such as segmented polyurethane, and is attributed to the stretching of the soft segments when the valve is loaded. In this condition, structures such as blood proteins and phospholipids can accumulate in the prosthesis. The aggregation attracts calcium ions to these areas [9].

Thrombotic complications

Blood clot formation and subsequent thrombosis can occur in the PHV due to excessive stiffness of the materials or flaws in the valve design, resulting in non-physiological blood flow and consequent shear stresses. Platelet activation may be observed in such scenarios. Hemodynamic performance can be improved by selecting a more appropriate valve design and materials with higher elasticity, thereby reducing platelet activation and minimising red blood cell damage [9].

Several factors contribute to the thrombogenic potential of heart valves, including flow-induced stress, prosthesis design and kinematics. The factors that trigger flow-induced thrombogenicity are as follows (i) Leakage around the valve into the left ventricle during diastole may induce high shear stress, contributing to thrombus formation and thromboembolism. (ii) Stagnation zones may develop in the neo-sinuses of the valve, potentially leading to thrombus formation on the leaflets. It is important to address these factors in valve design and optimization to minimise the risk of thrombosis. (iii) Disturbance of blood flow through the valve during systole could trigger platelet activation and thromboembolism. Prosthetic implants over the valves may increase the natural constriction of the valve, further accelerating blood flow and increasing stress [31].

Pannus formation

Pannus is a tissue that grows in PHV as an inflammatory response to calcification. Hemodynamic changes may contribute to the development of this condition. Once stimulated, it activates leukocytes and causes the release of inflammatory molecules, as well as activating lymphocyte monocytes. In addition, polymer surfaces are known to activate various inflammatory complement systems, namely factors D, H and C3b [9].

2.4 The Aortic Valve In Silico Model Design

In silico models, experiments and analyses are of great value to researchers in the development of a product. Carrying out the stages of the project in vitro means wasting raw materials, money and time on unsuccessful experiments. The ideal is to use in silico methods. Based on the analysis, the physical experiments are organised. In this way, success can be achieved quickly and with more robust arguments. As mentioned,

the PHV manufacturing process begins with in silico studies. Geometric design, haemodynamic and structural mechanical analysis are performed in silico. The manufacturing process is then initiated based on the most ideal model. The following sections highlight the requirements for the design of the model.

2.4.1 Geometry design parameters

During the design phase, it is important to consider certain factors to mitigate the failures observed in PHVs: (i) The large effective orifice area (EOA) in the PHV should be comparable in size to the natural valve. (ii) The transvalvular pressure should have a minimal mean decrease. (iii) The risk of regurgitation, bleeding and thrombogenicity should be minimised.

With these requirements in mind, the design process is divided into two main steps: (i) proposing the initial design with design parameters focused on maximising EOA and minimising regurgitation and transvalvular pressure drop; (ii) optimising the initial design to improve stress distribution to minimise stress concentration in the leaflets during systolic and diastolic cardiac phases [32]. Figure 2.12 shows the symbols for the dimensions found on aortic heart valve models.

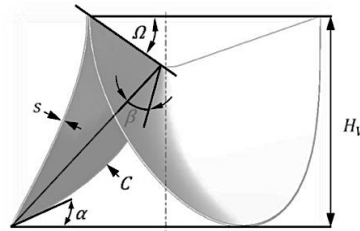


Figure 2.2 : The symbols for the dimensions found in aortic heart valve models A) Side view of heart valve model: H_V valve height, Ω lunula angle, α commissure angle, β coaptation angle, C curvature of the belly, s leaflet thickness [33].

Leaflet Opening Area (LOA) refers to the projection of blood flow through the valve onto an imaginary plane perpendicular to the direction of flow. In particular, variations in the angle of the lunula have resulted in significant changes in the LOA.

There are three leaflets in a heart valve model. Each leaflet is in contact with its neighbouring leaflets. The leaflet coaptation surface areas (CSA) of the three contact pairs in the valve are each combined into an average coaptation surface area (CSA).

In 2019, Pfensig et al. investigated the developments that occur in the valve with varying lunula angles. They compared different models with lunula angles of 0° , 20° ,

35°, 42° and 50°. They achieved the highest CSA with a 0° lunula angle and the highest LOA with a 50° lunula angle [33].

Sarrafzadeh-Ghadimi et al in 2022 studied different models using the parameters of commissure length and leaflet eccentricity. They observed that in their asymmetric design, one small and two large, the leaflets closed faster during closure. They concluded that the polymer should be thicker to reduce stress in the junction areas near the commissure where stress is concentrated. They emphasized that the radial curvature of the leaflets is a crucial parameter for the coaptation zones [34].

In 2023, Zhou et al. investigated the material properties and leaflet thickness of PHVs. They found that the low Young's modulus of Carbothane PC-3585A allows the production of valves thicker than 0.3 mm. On the other hand, high modulus materials such as xSIBS allow the production of valves thinner than 0.2 mm. The study suggests that if the elastic modulus exceeds 23.9 MPa, the recommended leaflet thickness for the prosthesis should be between 0.1 and 0.15 mm. Materials with a higher elastic modulus can withstand greater stresses, and reducing the thickness of such materials may be a strategy to prevent regurgitatio [35].

2.4.2 Fiber orientation

In 2019, Coulter et al employed fiber reinforcement to replicate the anisotropic texture of the heart valve. They used a biocompatible soft, medium-hard silicone (Shore 43 A) to mimic the elastic structure of the ventricular layer, while a harder silicone (Shore 73 A) was used to represent the high-strength structure of the fibrosa. Strips of harder silicone were incorporated into the prosthesis for reinforcement, with the researchers experimenting with different fiber orientations. A thinner leaflet design was also analysed in the study [36].

The stresses generated during the cycle of valve operation differ at different stages, i.e. stress accumulates in a different region during systole and in a different region during diastole. However, the stresses along the leaflet were much greater in diastole than in systole. According to the researchers, reducing the stresses in the prosthetic valve design, particularly during diastole, has the potential to prolong the life of the prosthesis. Fiber reinforcement in diastolic stress zones will help prolong prosthesis life

In 2007, Liu et al. analysed single and double layer fiber orientation (Figure 2.9) and volume density in a heart valve model. The aim of this study was to investigate how fiber reinforcement induces changes in mechanical analysis. The fibers were modelled as embedded in a polymer matrix (Figure 2.10). The highest stress was measured in the unreinforced model. While the stress reduction in the single layer model was 64%, a stress reduction of 84% was observed in the double layer model [15].

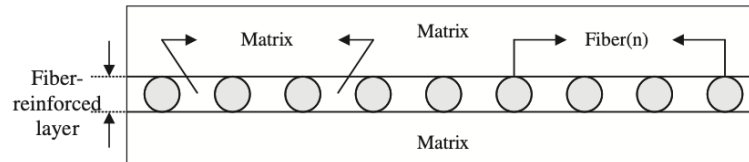


Figure 2.3 : Cross section of parallel fiber reinforced polymer embedded between homogeneous polymer matrix laminates [15].

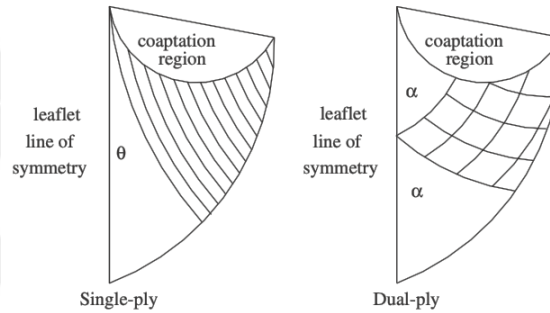


Figure 2.4 : Illustration of fiber orientation in the leaflet. Fiber structures are designed as single-ply and double-ply along geodesic lines on the global surface [15].

The study showed that stress levels were lower when the fiber angle was 30 degrees in the monolayer model and 45 degrees in the bilayer model. Conclusions from the study include: a double-layered fiber network structure contributes to stress reduction, and optimal fiber orientation perpendicular to the stent and to each other results in reduced stress.

Heart valves need to be flexible to allow full opening when open, but also stiff enough to be durable and prevent blood backflow when closed. In polymer-designed valves, fiber reinforcement, which reduces stress and has a higher strength than other areas of the polymer, strengthens the design.

2.4.3 Material models

Different materials have different mechanical properties. There are constitutive equations that predict the behavior of materials under external loads. The material

properties that are most relevant to heart valve technology are discussed first, followed by a description of material models.

2.4.3.1 Isotropic material

Materials with the same mechanical and physical properties in all directions are called isotropic materials. They exhibit uniform behavior and symmetry in all directions. In isotropic soft tissues, the response to mechanical loading is the same in all directions, regardless of the direction [37]. Materials with the same mechanical and physical properties in all directions are called isotropic materials. They exhibit uniform behavior and symmetry in all directions. In isotropic soft tissues, the response to mechanical loading is the same in all directions, regardless of the direction.

Although isotropic models are rare in biological tissues, they are often used to approximate the behavior of soft tissues that have relatively uniform properties, such as certain types of biological gels.

In heart valves, isotropic materials can be used to represent specific components, such as the isotropic core of the leaflets. In soft tissue mechanics, isotropic materials exhibit consistent mechanical properties regardless of the direction of force application. They are characterized by a uniform response to mechanical loading regardless of the direction of measurement. Although true isotropic behavior is rare in biological tissues, isotropic models are often used to approximate the behavior of soft tissues that have relatively uniform properties, such as certain types of biological gels [38].

It's important to note that heart valve leaflets are typically non-isotropic due to the directional arrangement of collagen fibers. However, isotropic hyperelastic material models are currently used in computational modeling [39].

2.4.3.2 Anisotropic material

Materials with - are called anisotropic materials. This means that their properties change depending on the direction of measurement [40].

Anisotropic soft tissues vary according to the direction of their response to mechanical loading. In soft tissue mechanics, anisotropic materials are often used to model and analyse biological tissues with preferentially oriented structural components, such as tendons, ligaments and blood vessels. In heart valves, anisotropic materials are

essential to capture the complex behavior of the leaflets, which are composed of layers of collagen fibers oriented in specific directions [38].

Anisotropic materials are crucial for modeling heart valve leaflets because they accurately capture the complex mechanical behavior of collagen fibers. Leaflets have anisotropic properties due to the arrangement of layers of collagen fibers oriented in specific directions. Modeling leaflets as anisotropic materials allows a more realistic representation of their mechanical response to dynamic forces applied during the cardiac cycle [39].

2.4.3.3 Orthotropic material

Orthotropic materials have three mutually perpendicular planes of symmetry, each with different material properties along the corresponding orthogonal axis. In soft tissue mechanics, orthotropic materials are used to represent tissues with complex fiber arrangements, such as the myocardium of the heart or the layers of the arterial wall. In heart valves, orthotropic materials can be used to capture the anisotropic behavior of leaflets with different fiber orientations in different layers [42].

Viscoelastic material

Orthotropic materials have three mutually perpendicular planes of symmetry, each with different material properties along the corresponding orthogonal axis. In soft tissue mechanics, orthotropic materials are used to represent tissues with complex fiber arrangements, such as the myocardium of the heart or the layers of the arterial wall. In heart valves, orthotropic materials can be used to capture the anisotropic behavior of leaflets with different fiber orientations in different layers.

Viscoelastic materials have both viscous properties, with time-dependent deformation, and elastic properties, with instantaneous deformation and recovery. These materials exhibit time-dependent mechanical behavior, meaning that their response to an applied load depends not only on the magnitude and direction, but also on the rate and duration of loading. The viscoelastic properties of a material are usually described by parameters such as stiffness, damping and relaxation time [38].

Viscoelasticity in soft tissue mechanics plays a crucial role in understanding the mechanical behavior of biological tissues. Soft tissues such as tendons, ligaments and muscles exhibit viscoelastic properties due to the presence of various structural

components such as collagen and elastin fibers, proteoglycans and water content. These tissues undergo time-dependent deformation and exhibit stress relaxation, creep (time-dependent deformation under a constant load) and hysteresis (energy dissipation during loading and unloading).

The viscoelastic behavior of soft tissues is influenced by various factors such as tissue composition, structural organisation and loading conditions. Understanding and measuring the viscoelastic properties of soft tissues is essential for accurate modeling of their mechanical response. Various mathematical models such as Kelvin-Voigt and Prony series have been used to capture the viscoelastic behavior of soft tissues.

Viscoelasticity also plays an important role in the mechanical behavior of heart valves. Heart valve leaflets are composed of connective tissue that exhibits viscoelastic properties due to the presence of collagen, elastin and proteoglycans. The viscoelastic behavior of heart valve leaflets affects their opening and closing dynamics and their response to forces applied during blood flow [41].

The viscoelastic properties of heart valve leaflets influence their stress relaxation, creep and hysteresis behavior. These properties are important in maintaining proper valve function, ensuring efficient blood flow and minimising wear and fatigue. Accurate modeling of the viscoelastic behavior of heart valve leaflets can assist in the design and development of prosthetic heart valves and tissue engineering structures [39].

The strain function for a viscoelastic material model is generally expressed in integral form. The small strain equation for isotropic materials is shown.

$$\sigma = \int_0^t 2G(t - \tau) \frac{de}{d\tau} d\tau + I \int_0^t K(t - \tau) \frac{d\Delta}{d\tau} d\tau \quad (2.1)$$

The Cauchy stress is represented as σ , the deviatoric part of the strain as e , the volumetric part of the strain as Δ , the shear relaxation kernel function as $G(t)$, the bulk relaxation kernel function as $K(t)$, the current time as t , the past time as τ , and the unit tensor as I .

In finite element solutions, the kernel function of a function is anyone that is related to the domain. The integral form of the kernel functions of Maxwell elements is given below.

$$G(t) = G_{\infty} + \sum_{k=1}^N G_k e^{-\frac{t}{\tau_k}} \quad (2.2)$$

$$K(t) = K_{\infty} + \sum_{k=1}^N K_k e^{-\frac{t}{\tau_k}} \quad (2.3)$$

$$K(t) = K_{\infty} + \sum_{k=1}^n K_k e^{-\frac{t}{\lambda_k^K}} \quad (2.4)$$

$$G_k = C_k(G_0 - G_{\infty}) \quad (2.5)$$

$$K_k = D_k(K_0 - K_{\infty}) \quad (2.6)$$

The pseudo or reduced time is represented as t , the shear relaxation kernel function as $G(t)$, the bulk relaxation kernel function as $K(t)$, number of Maxwell elements used to approximate the shear relaxation as n_G , number of Maxwell elements used to approximate the bulk relaxation as n_K , constant associated with the instantaneous response for shear behavior as C_k , constant associated with the instantaneous response for bulk behavior as D_k , initial shear modulus as G_0 , final shear modulus as G_{∞} , initial bulk modulus as K_0 , final bulk modulus as K_{∞} , constant associated with a discrete relaxation spectrum in shear as λ_k^G , constant associated with a discrete relaxation spectrum in bulk as λ_k^K .

Prony series viscoelastic model

As a Prony series, the shear relaxation function ($G(t)$) of viscoelastic materials is shown.

$$G(t) = G_{\infty} + \sum_{k=1}^N G_k e^{-\frac{t}{\tau_k}} \quad (2.7)$$

The long-term shear modulus is represented as G_{∞} , shear elastic moduli, the coefficient of the Prony Series as G_k , relaxation times for each Prony component, and the other coefficient of the Prony Series as τ_k .

The equation for the two-term Prony series used in ANSYS® is given.

$$G(t) = G_0 \left[\alpha_{\infty} + \sum_{k=1}^2 \alpha_k e^{-\frac{t}{\tau_k}} \right] \quad (2.8)$$

The coefficients τ_1 and τ_2 are represented as T_{01} and T_{02} , also the coefficients α_1 and α_2 are relative moduli and represented as A_{01} and A_{10} ANSYS® Parametric Design Language (APDL) in the optimization and results sections.

From the experimental force relaxation data and using small deformation assumptions, the following equation is established.

$$G = \frac{3F}{16\delta\sqrt{R\delta}} \quad (2.9)$$

The force is represented as F , indentation depth of a rigid sphere as δ , radius of rigid indenter of small indentation as R .

2.4.3.4 Linear elastic material model

The linear elastic material model is a fundamental and widely used model in solid mechanics to describe the mechanical behavior of materials. This model assumes that the relationship between stress and strain in a material is linear and follows Hooke's law. According to Hooke's law, the stress (force per unit area) applied to a material is directly proportional to the strain (deformation) it undergoes within its elastic limit. In mathematical terms, this relationship is expressed as follows. The linear elastic material model assumes that when the applied load is removed, the material returns to its original shape and size and exhibits full elastic recovery. This means that the stress is reversible and there is no permanent deformation or loss of energy in the material.

The linear elastic material model is valid as long as the applied stress remains within the point beyond which the material exhibits permanent deformation. If the stress exceeds this limit, the material may exhibit non-linear behavior such as plastic deformation or failure. While the linear elastic material model provides a useful approximation for many engineering applications, it is important to recognise that there are materials that do not follow this model exactly. For example, some materials may exhibit time-dependent behavior (viscoelasticity) or irreversible deformation (plasticity). In such cases, more advanced material models are used to accurately describe the material behavior [43].

The normal stress (ε) elements are located in the x , y , and z axes as shown below.

$$\varepsilon_x = \frac{\partial u}{\partial x}, \quad \varepsilon_y = \frac{\partial v}{\partial y}, \quad \varepsilon_z = \frac{\partial w}{\partial z} \quad (2.10)$$

The displacements are represented as follows. u for x -axis, v for y -axis and w for z -axis. The components of shear stress (γ) are found as shown below.

$$\gamma_{xy} = \frac{\partial u}{\partial y} + \frac{\partial v}{\partial x}, \gamma_{yz} = \frac{\partial v}{\partial z} + \frac{\partial w}{\partial y}, \quad \gamma_{zx} = \frac{\partial w}{\partial x} + \frac{\partial u}{\partial z} \quad (2.11)$$

Generalized Hooke's Law defines linearity between stress and strain as shown in the following equations.

$$\varepsilon_x = \frac{1}{E} [\sigma_x - \nu(\sigma_y + \sigma_z)] \quad (2.12)$$

$$\varepsilon_y = \frac{1}{E} [\sigma_y - \nu(\sigma_x + \sigma_z)] \quad (2.13)$$

$$\varepsilon_z = \frac{1}{E} [\sigma_z - \nu(\sigma_x + \sigma_y)] \quad (2.14)$$

$$\gamma_{xy} = \frac{\tau_{xy}}{G}, \quad \gamma_{yz} = \frac{\tau_{yz}}{G}, \quad \gamma_{zx} = \frac{\tau_{zx}}{G} \quad (2.15)$$

The stress is represented as σ , Young's modulus as E , Poisson ratio as ν , and shear modulus G . Young's modulus, also known as the modulus of elasticity, represents the stiffness of the material and measures its resistance to deformation under an applied load [44].

2.4.3.5 Non-linear elastic material models

The non-linear elastic material model is an advanced and realistic approach to characterising the mechanical response of materials that exhibit non-linear stress-strain relationships. This model shows that the response of the material deviates from linearity, particularly at higher levels of stress or strain. A nonlinear constitutive equation is used to describe the relationship between stress and strain, taking into account the behavior of the material.

Nonlinear elastic materials can exhibit different types of nonlinear behavior, such as strain hardening or strain softening. In strain-hardening materials, the stiffness increases as the material is further deformed, leading to an increase in stress with increasing strain. This behavior is commonly seen in metals and some composites. In contrast, strain-softening materials experience a reduction in stiffness and stress with increasing strain. This behavior is typical of materials such as rubber or certain types of foam. To simulate the non-linear elastic properties of materials, it is usually necessary to collect experimental data or perform material tests to determine the stress-strain relationship under various loading conditions. These data can then be used to formulate constitutive equations or material models that effectively represent the nonlinear behavior. Nonlinear elastic material models are required in engineering practice such as structural analysis, FEA and simulations of complex mechanical

systems where the deformation of materials exceeds the linear elastic limit or where accurate predictions of stress and strain are required [38].

Hyperelastic material models

Hyperelastic material models are useful for describing the behavior of materials that undergo large deformations. Examples of such materials include elastomers. Hyperelastic material models are available in many finite element software packages.

The models generate the stress-strain relationship based on the strain energy density function (W). Figure 2.11 shows the stress-strain relationships for elastic and hyperelastic materials..

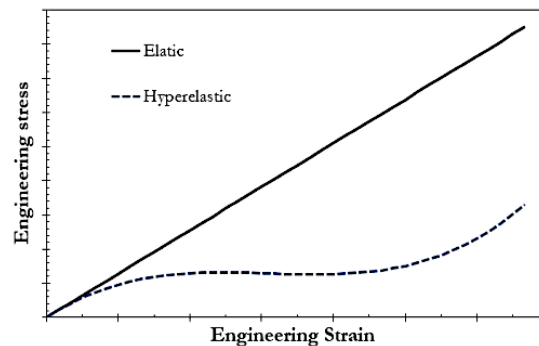


Figure 2.5 : Engineering stress-strain curves of elastic and hyperelastic materials [45].

For hyperelastic materials undergoing significant deformations, models in the form of polynomials or exponentials involving components of the strain tensor or strain invariants are used. Examples of these strain energy functions are Arruda-Boyce, and Van der Waals, Yeoh, Ogden, Mooney-Rivlin, Neo-Hookean, and Fung [46]. Figure 2.12 illustrates the material models applicable to various tissues in vascular applications.

In contemporary times, particularly with the surge in tissue engineering research, the ability to model the mechanical behavior of biological tissues holds significant importance. Biological tissues show viscoelastic properties. However, as proposed by Fung in 2013, pseudo-hyperelastic materials find application in modeling the mechanical characteristics of biological tissues.

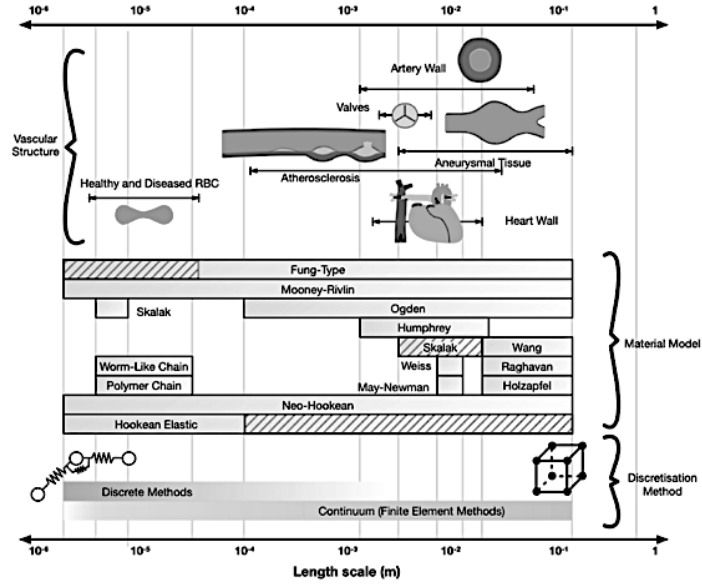


Figure 2.6 : Popular material models and discretization methods used to model vascular tissues of different sizes are shown. Lined boxes indicate that the model is not widely used [47].

The strain-energy function based on the deformation gradient tensor of the hyperelastic material is used to model the behavior of biological tissues.

$$P = \frac{\partial \psi(F)}{\partial F} \quad (2.16)$$

The Piola-Kirchoff stress tensor measures the force per undeformed unit. For the stress-energy function, the Green-Lagrange strain tensor is constructed with 'E'. It is shown in Eq 2.17.

$$S = \frac{\partial \psi(E)}{\partial E} \quad (2.17)$$

The second Piola-Kirchhoff voltage tensor can be defined alternatively using a different approach.

$$S = JF^{-1}\sigma F^{-T} \quad (2.18)$$

The Cauchy stress tensor σ represents σ and $J = \det(F)$ corresponds to the Jacobian of the deformation. The Cauchy stress is also known as the real stress.

The hyperelastic material model is extensively employed for exploring the stress-strain behavior of soft biological tissues. In this model, it is postulated that the constitutive equations are entirely determined by an elastic potential. The tensor ' σ ' corresponds to the Jacobian of deformation ($J = \det(F)$).

Soft tissues are minimally permeable as they are predominantly composed of water. For materials with constant volume as they deform, the incompressibility constraint is denoted as $J=1$ [48].

Neo-Hookean model

The Neo-Hookean model is described by Hooke's law. It is used to predict the nonlinear stress-strain of highly deformed materials (such as rubber) [45]. The Neo-Hookean strain energy potential is given.

$$W = \frac{\mu}{2}(\bar{I}_1 - 3) + \frac{1}{d}(J - 1)^2 \quad (2.19)$$

The strain energy per unit reference volume is denoted as W , first deviatoric strain invariant as $\bar{I}_1$, initial shear modulus of the material as μ , material incompressibility parameter as d , determinant of the elastic deformation gradient F as J .

The initial bulk modulus is defined by:

$$K = \frac{2}{d} \quad (2.20)$$

Neo-Hookean cannot accurately predict the modulus increase of the material under large stresses. It is generally reliable for stresses less than 20%. In addition, the model is not suitable for biaxial stress scenarios. Yet, the outcome of the relationship between stress and strain in the model is initially linear and deviates from linearity after a certain point [49].

Fung-Elastic material model

Fung model accurately analyzes the nonlinear mechanical responses of biological soft tissues [48]. The Fung strain-energy function, introduced over thirty years ago, has been proven to accurately capture the nonlinear mechanical responses of numerous biological soft tissues. The Fung model has a full expansion of the quadratic terms of Q to account for in-plane shear strains.

$$W = \frac{c}{2}[e^Q - 1] \quad (2.21)$$

where

$$Q = A_1 E_{11}^2 + A_2 E_{22}^2 + 2A_3 E_{11} E_{22} + A_4 E_{12}^2 + 2A_5 E_{11} E_{12} + 2A_6 E_{22} E_{12} \quad (2.22)$$

The c and A_i in the equations are material constants. As mentioned earlier, due to the incompressibility of biological tissues, $J=1$. Based on this, Fung and Tong proposed the following modified constitutive equation in 2001.

$$S = p' C^{-1} + \frac{\partial S}{\partial E} \quad (2.23)$$

In this context, p' acts as a Lagrangian multiplier that allows the incompressibility constraint to be applied. In equation 2.21, the value of W is preserved and replaced by $W+g(J-1)$. But in this case, the derivative of W with respect to E undergoes a change and the constitutive equation is formed.

$$S = p' C^{-1} + \frac{\partial W}{\partial E} + \frac{\partial g(J-1)}{\partial J} J C^{-1} \quad (2.24)$$

$$\bar{S} = S - \frac{1}{3}(S:C)C^{-1} = \frac{\partial W}{\partial E} - \frac{1}{3}\left(\frac{\partial W}{\partial E}:C\right)C^{-1} \quad (2.25)$$

The reformulation of the above equation according to deviatoric stress is given below.

$$S = p' C^{-1} + \bar{S} = p' C^{-1} + \frac{\partial W}{\partial E} - \frac{1}{3}\left(\frac{\partial W}{\partial E}:C\right)C^{-1} \quad (2.26)$$

where

$$p = p' + \frac{1}{3}\left(\frac{\partial W}{\partial E}:C\right) \quad (2.27)$$

In the case of planar and homogeneous deformations occurring in a biaxial test, $S_{13} = S_{23} = S_{33} = 0$.

$$S_{33} = p C_{33}^{-1} + \frac{\partial W}{\partial E_{33}} - \frac{1}{3}\left(\frac{\partial W}{\partial E}:C\right)C_{33}^{-1} = 0 \quad (2.28)$$

Given that $\partial W / \partial E_{33} = 0$ according to Equation 2, we can derive.

$$p = \frac{1}{3}\left(\frac{\partial W}{\partial E}:C\right) \text{ and } p' = 0 \quad (2.29)$$

Note that with $p=0$, Equation 2.28 is reduced to

$$S = \frac{\partial W}{\partial E} \quad (2.30)$$

This follows the same format as the constitutive equation for a compressible material. Additionally, the fourth-order elasticity tensor C is provided below.

$$C = \frac{\partial S}{\partial E} \quad (2.31)$$

The matrix form of the elasticity tensor C is given below.

$$D = \frac{c}{2} e^Q \begin{bmatrix} 2A_1 + \xi_1^2 & 2A_3 + \xi_1\xi_2 & 2A_5 + \xi_1\xi_3 \\ & 2A_2 + \xi_2^2 & 2A_6 + \xi_2\xi_3 \\ \text{sym} & & 2A_4 + \xi_3^2 \end{bmatrix} \quad (2.32)$$

where

$$\xi_1 = 2A_1E_{11} + 2A_3E_{22} + 2A_5E_{12} \quad (2.33)$$

$$\xi_2 = 2A_2E_{22} + 2A_3E_{11} + 2A_6E_{12} \quad (2.34)$$

$$\xi_3 = 2A_4E_{12} + 2A_5E_{11} + 2A_6E_{22} \quad (2.35)$$

The Cauchy stress and elasticity tensor can be derived using forward push operations.

Mooney-Rivlin model

An alternative polynomial strain energy function is the Mooney-Rivlin model, which was initially developed by Mooney in 1940 and subsequently expressed in terms of the invariants of the Cauchy-Green deformation tensor [50].

The representation of strain energy per unit reference volume is W , first and second deviatoric strain invariants are represented as $\bar{I}_1$ and $\bar{I}_2$ and material incompressibility parameter is represented as d .

The initial shear modulus is defined as:

$$\mu = 2(C_{01} + C_{10}) \quad (2.36)$$

The initial bulk modulus is defined by:

$$K = \frac{2}{d} \quad (2.37)$$

where:

$$d = (1 - 2 * \nu) / (C_{01} + C_{10}) \quad (2.38)$$

2 Parameter Mooney-Rivlin Model is defined by:

$$W = c_{10}(\bar{I}_1 - 3) + c_{01}(\bar{I}_2 - 3) + \frac{1}{d}(J - 1)^2 \quad (2.39)$$

The constants c_{10} , c_{01} , and d are defined by C1, C2, and C3 in ANSYS®.

3 Parameter Mooney-Rivlin Model is defined by:

$$W = c_{10}(\bar{I}_1 - 3) + c_{01}(\bar{I}_2 - 3) + c_{11}(\bar{I}_1 - 3)(\bar{I}_2 - 3) + \frac{1}{d}(J - 1)^2 \quad (2.40)$$

5 Parameter Mooney-Rivlin Model is defined by:

$$W = c_{10}(\bar{I}_1 - 3) + c_{01}(\bar{I}_2 - 3) + c_{20}(\bar{I}_1 - 3)^2 + c_{11}(\bar{I}_1 - 3)(\bar{I}_2 - 3) + c_{02}(\bar{I}_2 - 3)^2 + \frac{1}{d}(J - 1)^2 \quad (2.41)$$

9 Parameter Mooney-Rivlin Model is defined by:

$$W = c_{10}(\bar{I}_1 - 3) + c_{01}(\bar{I}_2 - 3) + c_{20}(\bar{I}_1 - 3)^2 + c_{11}(\bar{I}_1 - 3)(\bar{I}_2 - 3) + c_{02}(\bar{I}_2 - 3)^2 + c_{30}(\bar{I}_1 - 3)^3 + c_{21}(\bar{I}_1 - 3)^2(\bar{I}_2 - 3) + c_{12}(\bar{I}_1 - 3)(\bar{I}_2 - 3)^2 + c_{03}(\bar{I}_2 - 3)^3 + \frac{1}{d}(J - 1)^2 \quad (2.42)$$

$c_{10}, c_{01}, c_{20}, c_{11}, c_{02}, c_{30}, c_{21}, c_{12}, c_{03}$, and d are material constants [51]. Although it has limitations in accurately describing some stress states, the Mooney-Rivlin model is practical for local strain values up to approximately 200%.

The Mooney-Rivlin material model has been used to model various biological tissues. Examples include porcine liver, kidney, spleen, muscle and brain tissue, human brain tissue, aortic heart valve and rat lung. This material model provides efficiency for computer simulations. It is consistent, computationally efficient and has fewer parameters.

Ogden hyperelastic model

The Ogden hyperelastic material model, described by Ogden in 1972, can be used to predict the stress-strain behavior for nonlinear materials such as rubber. The model is expressed below [49].

$$W = \sum_{i=1}^N \frac{\mu_i}{\alpha_i} (\bar{\lambda}_1^{\alpha_i} + \bar{\lambda}_2^{\alpha_i} + \bar{\lambda}_3^{\alpha_i} - 3) + \sum_{i=1}^N \frac{1}{d_i} (J - 1)^{2i} \quad (2.43)$$

$\bar{\lambda}_p (p = 1, 2, 3)$ = deviatoric principal stretches, defined as $\bar{\lambda}_p = J^{-\frac{1}{3}} \lambda_p$

The strain energy potential is represented as W , principal stretches of the left Cauchy-Green as λ_p , determinant of the elastic deformation gradient as J , material constants as N, μ_p, α_p and d_p . The higher the N value, the closer the result is to reality. But then the determination of material constants will become difficult.

The initial shear modulus μ is defined by:

$$\mu_i = \frac{1}{2} \sum_{i=1}^N \alpha_i \mu_i \quad (2.44)$$

The initial bulk modulus K is defined by:

$$K = \frac{2}{d_1} \quad (2.45)$$

For $N = 1$ and $\alpha_1 = 2$, the Ogden option is equivalent to the Neo-Hookean option. For $N = 2$, $\alpha_1 = 2$, and $\alpha_2 = -2$, the Ogden option is equivalent to the 2-parameter Mooney-Rivlin option.

By changing the N and α options in the Ogden model, it can be made equivalent to different models. While $N = 1$ and $\alpha_1 = 2$ can be taken for the Neo-Hookean model, $N = 2$, $\alpha_1 = 2$, and $\alpha_2 = -2$ can be taken for the 2-parameter model.

Polynomial Form hyperelastic model

Polynomial form expresses the hyperelastic model strain energy in polynomial form. It is expressed below.

$$W = \sum_{i+j=1}^N C_{ij} (\bar{I}_1 - 3)^i (\bar{I}_2 - 3)^j + \sum_{k=1}^N \frac{1}{d_k} (J - 1)^{2k} \quad (2.46)$$

Strain energy per unit reference volume is represented as W , first and second deviatoric strain invariants are represented as $\bar{I}_1$ and $\bar{I}_2$, determinant of the elastic deformation gradient F as J , material constants as N , c_{ij} , and d .

The value of N can be chosen as desired. The higher it is chosen, the closer to reality. However, fitting the material constants can make the calculation difficult. In addition, the model requires as much data as the deformation range.

The initial shear modulus μ is defined by:

$$\mu = 2(C_{10} + C_{01}) \quad (2.47)$$

and the initial bulk modulus is defined as:

$$K = \frac{2}{d_1} \quad (2.48)$$

By changing the N 's in the polynomial form options, Neo-Hookean and Mooney-Rivlin equivalent models are formed.

Bergström-Boyce model

Hyperelastic models do not account for changes in the strain rate of the material, while viscoelastic models do not account for sudden load changes and large deformations. It

addresses the limitations of the hyperelastic and viscoelastic models. The Bergström-Boyce model is a generalisation of non-linear viscoelastic behavior that can model both large and small deformations and can be used for both elastomers and biomaterials. The Bergström-Boyce model is represented by two parallel meshes. The eight chain model was introduced by Arruda and Boyce in 1993. The networks used are eight-chain macromolecular networks. One of the networks is hyperelastic for equilibrium requirements and the second is for time response.

Assume that the total deformation gradient (F) has an equal effect on both networks in the model ($F = F_a = F_b$). The network b represents the time dependence of the model. The deformation gradient can be decomposed into elastic e , and viscoelastic v components.

$$F_b = F_e F_v \quad (2.49)$$

The total stress of the model is the sum of the elastic stresses in the two networks ($\sigma = \sigma_a + \sigma_b$).

$$\sigma_a = \frac{\mu}{J\lambda^*} \frac{\mathcal{L}^{-1}(\bar{\lambda}^*/\lambda_L)}{\mathcal{L}^{-1}(1/\lambda_L)} \text{dev}[B^*] + k(J - 1)I \quad (2.50)$$

$$\sigma_b = \frac{s}{J_{be}\lambda_{be}^*} \frac{\mathcal{L}^{-1}(\bar{\lambda}_{be}^*/\lambda_{Lb})}{\mathcal{L}^{-1}(1/\lambda_{Lb})} \text{dev}[B_{be}^*] + k(J_{be} - 1)I \quad (2.51)$$

$$J = \det(F) \quad (2.52)$$

$\mathcal{L}^{-1}$ is the inverse of the Langevin function. B^* is the distortional part of the left Cauchy–Green tensor. The initial shear modulus is represented as μ , bulk modulus as k , the limiting stretch of the network as λ_L , the effective distortional chain stretch as $\bar{\lambda}^*$, $\bar{\lambda}^* = \sqrt{\text{tr}(B^*)/3}$, and the unit matrix as I . The strain rate equation of the model is given below.

$$D_{bv} = \dot{\gamma}_b N_{bv} \quad (2.53)$$

The direction of the viscoelastic flow is represented as N_{bv} , the effective deformation as $\dot{\gamma}_b$.

$$\dot{\gamma}_b = \dot{\gamma}_0 (\bar{\lambda}_{bv} - 1 + \xi)^C \left[R \left(\frac{\tau}{f_v \tau_{base}} - \hat{\tau}_{cut} \right) \right]^m \quad (2.54)$$

ξ , C , τ_{base} , and m are material constants. The constant introduced for dimensional consistency is $\dot{\gamma}_0$ and R is the ramp function.

The term $(\overline{\lambda_{bv}} - 1 + \xi)$ captures the rate-dependent behavior. $\tau = \|\text{dev}(\sigma_b)\|$, being $\|\cdot\|$ the Frobenius norm.

f_v is a network interaction factor that captures behavior. This behavior results from having different strain rate dependence during loading than unloading [95].

ANSYS Anisotropic Hyperelastic: Exponential

Anisotropic material models are useful in modeling materials such as fiber-reinforced rubbers and biomaterials. ANSYS Mechanics supports the following exponential function based anisotropic hyperelastic material model energy function.

$$W = \sum_{i=1}^3 a_i (\bar{I}_1 - 3)^i + \sum_{j=1}^3 b_j (\bar{I}_2 - 3)^j + \frac{c_1}{2c_2} (\exp[c_2 (\bar{I}_4 - 2)^2] - 1) + \frac{e_1}{2e_2} (\exp[e_2 (\bar{I}_6 - 2)^2] - 1) - \frac{1}{d} (J - 1)^2 \quad (2.55)$$

It is often difficult to separate the I_2 dependence from the fiber response. Therefore, simplification was made.

$$W = \sum_{i=1}^3 a_i (\bar{I}_1 - 3)^i + \frac{c_1}{2c_2} (\exp[c_2 (\bar{I}_4 - 2)^2] - 1) + \frac{e_1}{2e_2} (\exp[e_2 (\bar{I}_6 - 2)^2] - 1) - \frac{1}{d} (J - 1)^2 \quad (2.56)$$

The c_i and e_i parameters specify the fiber stiffnesses [96].

3. HEMODYNAMIC ANALYSIS

The stages of strengthening the design of the PHV are carried out in the computer environment. A 3D model must be created on the computer based on the patient's medical images. DICOM (Digital Imaging and Communications in Medicine) images were imported into Slicer 3D® version 5.4.0 for segmentation. This software is open source. It is used for medical image processing. After importing the DICOM images, four different screenshots of the Slicer 3D® interface can be examined (Figure 3.1). Axial slices are surrounded by a red border, coronal slices are surrounded by a green border and sagittal slices are surrounded by a yellow border. In the top right-hand corner is the window for viewing the 3D model derived from the imported images.

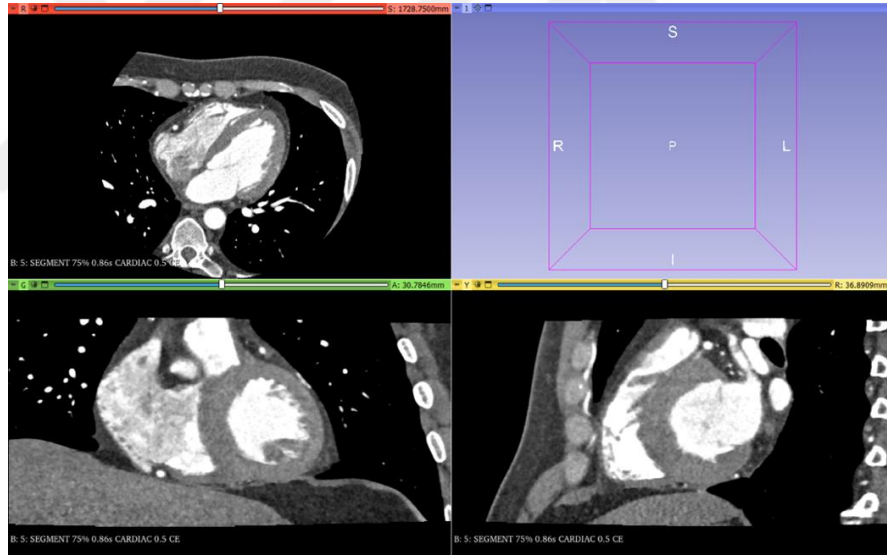


Figure 3.1 : After importing the DICOM images, the Slicer 3D® interface displays four different screenshots. Image taken with special permission from Hacer Duzman, member of İTÜ Informatics Institute Computational Biomechanics Group.

The segmentation performed here can be used to create a 3D model of the aortic valve. The physiological dimensional information obtained here is important for creating a patient-specific design. The next step in the process of designing a durable prosthesis, based on the 3D model created according to the patient's information, is the hemodynamic analysis. Hemodynamic analysis can be performed using different methods and models. There are three basic approaches to this analysis: Structural

mechanics analysis, computational fluid dynamics (CFD) modeling and fluid-structure interaction analysis. In structural mechanics analysis, the flow pressure is set as a specific boundary condition and the deformation and stress distribution of the blades are obtained. CFD models are used to study hemodynamics during the cardiac cycle. Fluid-structure interaction analysis is a method that combines blood flow with the structural mechanics of the leaflets. The following sections provide information on the CFD model and fluid-structure interaction analysis.

3.1 Computational Fluid Dynamics

CFD analysis of aortic heart valves covers a number of critical aspects that are essential for evaluating valve performance and identifying potential problems. These analyses are critical for understanding valve performance, optimising design and assessing the impact of surgical interventions [52]. The main areas of CFD analysis for aortic heart valves include flow dynamics, stress and durability analysis, geometric optimization, problem identification and solution proposals, and innovation and development [53]. Flow dynamics involves modeling parameters such as velocity, pressure and density of the flow in both the open and closed states of the valve, as well as determining whether the flow is laminar or turbulent [54]. This is essential to understand the behavior of blood flow through the valve and its effect on valve function. Stress and durability analysis focuses on the simulation of mechanical stress and durability during the opening and closing of the valve, as well as the analysis of material properties, stress and deformation [55]. Geometric optimization involves evaluating the impact of design changes on valve performance and using geometric optimization techniques to achieve better flow characteristics and lower pressure losses [56]. Problem identification and solution proposals revolve around identifying abnormal flow conditions, proposing solutions to these problems and identifying abnormalities in valve function, assessing the need for surgical intervention [57]. Finally, innovation and development use CFD analysis as a tool to develop new valve designs or surgical procedures [58]. While CFD simulations are critical, real-world data and clinical studies also play an important role in medical applications, highlighting the need for a comprehensive approach that integrates computational modeling with empirical evidence [59].

In summary, CFD analysis of aortic heart valves is a multifaceted and interdisciplinary endeavour involving flow dynamics, stress and durability analysis, geometric optimization, problem identification and solution proposals, and innovation and development. It plays a critical role in understanding valve performance, optimising design and assessing the impact of surgical interventions, and is complemented by real-world data and clinical studies to provide comprehensive insight into the behavior and functionality of aortic heart valves.

3.2 Fluid-Structure Interaction

Fluid-Structure Interaction (FSI) analyses of aortic heart valves are essential for the comprehensive study of the interactions between fluid flow and the structural components of the valves. These analyses take into account the dynamic interplay between blood flow and the mechanical behavior of the valve tissue, providing valuable insights into the complex fluid dynamics and structural response of aortic valves during the cardiac cycle.

FSI simulations have been used to assess the dynamics of various types of heart valves, including BHVs [60]. These simulations have been instrumental in understanding the behavior of artificial heart valves under different conditions, such as during the cardiac cycle, exercise and in vitro testing, and have provided insights into the optimization of valve designs and the assessment of potential complications associated with different types of heart valves. FSI simulations have been used to study the fluid dynamics, hemodynamics and stress distribution on the leaflets of bioprosthetic heart valves, providing valuable information for the design and analysis of these devices [61].

In summary, FSI plays a crucial role in the study of artificial heart valves, allowing comprehensive assessments of their dynamics, fluid mechanics and structural behavior. The use of FSI simulations has contributed significantly to the understanding and optimization of artificial heart valve designs, providing valuable insights into their performance and potential complications. Arbitrary Lagrangian-Eulerian and the immersed boundary methods are used in FSI analysis. The following sections provide information about these methods.

3.2.1 Arbitrary Lagrangian-Eulerian method

One of the methods used to analyse the aortic valve is the Arbitrary Lagrangian-Eulerian (ALE) method. This is a computational technique used to simulate fluid-structure interactions in heart valves. The ALE method involves several steps to accurately model the behavior of the aortic valve and to evaluate the success of the procedure. The use of advanced imaging techniques such as three-dimensional computed tomography and magnetic resonance imaging is recommended in the analysis of heart valves. These imaging modalities provide detailed anatomical and functional information about the heart valves, which is essential for the ALE method to accurately simulate valve dynamics [5].

It emphasises the importance of considering thromboembolic complications and durability when analysing polymer and tissue valves. The ALE method should consider flow-induced platelet activation and the potential for thrombosis in different types of heart valves to assess their long-term performance [62]. Numerical strength comparison analyses of aortic valve prostheses were performed to evaluate their performance under varying mechanical loads. These analyses are necessary to validate the ability of the ALE method to predict the structural behavior of aortic valves under physiological conditions [63].

In addition, TAVR has shown promising results in the treatment of aortic valve disease, and the ALE method can be used to simulate hemodynamic changes and valve function before and after these procedures [64]. The concept of "lifetime management" of aortic valve disease is also discussed, highlighting the importance of optimising hemodynamics and endurance in the management of structural valve degeneration. Surgical techniques such as aortic valve neocuspidation with autologous pericardium are highlighted as additional options to consider in aortic valve disease [65]. The ALE method can help to assess the long-term performance of such innovative surgical approaches.

In summary, the ALE method for aortic valve analysis is a comprehensive approach that integrates advanced imaging, fluid dynamics, biomechanics and structural analysis. By combining data from transcatheter procedures, mechanical analysis, personalized modeling and innovative surgical techniques, the ALE method can

provide valuable insights into the behavior of the aortic valve and contribute to the development of more effective and durable valve prostheses.

3.2.2 Immersed boundary method

The Immersed Boundary (IB) method has proven to be a valuable approach for modeling fluid-structure interaction in the context of aortic heart valve dynamics. Originally introduced to study blood flow through heart valves, this method has been extended to simulate heart valve dynamics and model fluid-structure interaction in the heart and its valves [66]. The IB method provides an alternative approach to modeling interactions between blood and the aortic valve and root, and provides a framework for simulating complex fluid-structure interactions in the cardiovascular system [67].

Recent research has focused on the construction of anatomically and physiologically realistic IB models of the dynamics of the aortic root and ascending aorta, reflecting advances in the creation of detailed and accurate representations of the cardiovascular system [68]. In addition, the IB method has been used to simulate fluid-structure interaction in aortic valve models, providing insights into the hemodynamics and mechanics of aortic valve function [69].

The development of immersed boundary models that reproduce the material properties of real aortic valves and sinuses remains an area of ongoing research, highlighting the continuing efforts to produce accurate and reliable representations of aortic valve dynamics [70]. In addition, the IB method has been used to study the effect of the implantation orientation of a mechanical bileaflet heart valve on the kinematics and hemodynamics in an anatomical aorta, demonstrating its applicability to the study of prosthetic valve performance [71]. The IB method has also been integrated with large-scale kinematic models to animate the left ventricular wall and drive fluid-structure interactions between blood flow and mechanical heart valve prostheses, demonstrating its potential to simulate complex physiological conditions and interactions within the cardiovascular system [72].

Overall, recent studies have demonstrated the versatility and applicability of the Immersed Boundary Method in simulating the fluid dynamics and mechanics of natural and prosthetic heart valves, particularly in the context of aortic valve dynamics. These advances underscore the importance of the IB method in advancing our understanding of aortic valve function and its impact on cardiovascular health.

3.3 Design Parameters

The design of prosthetic heart valves takes into account various hemodynamic parameters to ensure optimal performance and compatibility with the cardiovascular system. Hemodynamics is the study of blood flow and the forces involved in its circulation. Here are some of the key hemodynamic parameters considered in the design of prosthetic heart valves.

The rate at which blood flows through the prosthetic valve is a critical parameter. It should match physiological flow rates to ensure adequate cardiac output and systemic perfusion. Another parameter is the pressure drop. The pressure drop across the prosthetic valve during systole and diastole is important. Excessive pressure gradients can lead to problems such as haemolysis or inadequate forward flow. It is also important to minimise regurgitation or backflow of blood through the closed valve. Prosthetic valves aim to replicate the natural valve's ability to prevent leakage. In addition, EOA represents the cross-sectional area available for blood flow through the valve. A larger EOA generally allows for better hemodynamics by reducing pressure gradients. Another parameter, shear stress on the blood cells and valve surface, should be within physiological ranges. Excessive shear stress can damage blood cells and activate coagulation pathways. Another design parameter is the velocity profile. Examining the velocity distribution across the valve orifice helps to assess the smoothness of the blood flow. Turbulent flow can lead to increased shear stress and energy loss. Minimising energy loss during blood flow through the prosthetic valve is important for maintaining efficient cardiac function. The speed and efficiency of valve opening and closing affect haemodynamics. Slow or incomplete valve closure can lead to regurgitation, while rapid closure can lead to excessive pressure gradients. The other important parameter is the risk of cavitation. Monitoring the potential for cavitation, the formation and collapse of vapour bubbles in the blood, can lead to tissue damage and affect valve durability. Design features that minimise the risk of blood clots forming on or around the valve are also essential to prevent thromboembolic complications [73].

Successful prosthetic valve design requires a balance between these hemodynamic parameters to ensure optimal performance, longevity and biocompatibility in the dynamic cardiovascular system. Computational modeling is often used to simulate and

optimise these parameters during the design process. In addition, in vitro testing and clinical trials play a critical role in validating the hemodynamic performance of prosthetic heart valves.

3.3. Transvalvular Hemodynamic Indices

Transvalvular hemodynamic indices are parameters that describe the flow and pressure characteristics across a heart valve, specifically the aortic valve. These indices provide valuable information about valve performance and associated hemodynamic changes. The following are some of the most important transvalvular haemodynamic indices. The orifice area represents the opening through which blood flows across the valve. Global Orifice Area (GOA) is a measure of the effective opening size of the valve. Figure 3.2 shows the variation in GOA over time for aortic valves over a cardiac cycle for a steady inflow. The GOA is typically in the range of 2.5 to 4.0 square centimetres for a healthy aortic valve. It's important to provide enough space for blood to flow through during systole.

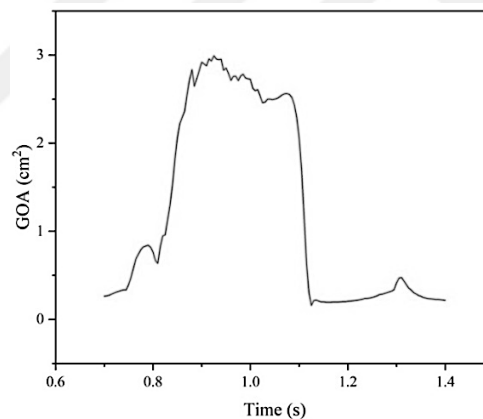


Figure 3.2 : Temporal variation of GOA for aortic valves over a cardiac cycle for uniform inflow. Image taken with special permission from Reza Daryani and Emre Cenk Ersan, members of İTÜ Informatics Institute Computational Biomechanics Group.

Maximum velocities represent the maximum speed of blood flow through the valve. The magnitude of the jet velocities is measured and an increase in calcification severity will generally result in increased jet velocities due to the reduced orifice area. Figure 3.3 shows the maximum fluid velocities through the orifice area in non-calcified conditions under uniform inflow regimes.

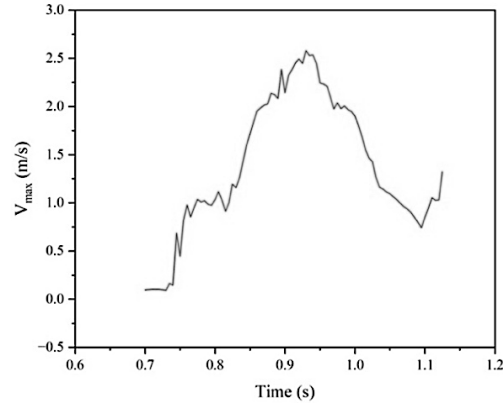


Figure 3.3 : Maximum fluid velocities through the orifice area in uncalcified conditions, under uniform inflow regimes. Velocities measured at 0.068 cm from the inlet. Image taken with special permission from Reza Daryani and Emre Cenk Ersan, members of İTÜ Informatics Institute Computational Biomechanics Group.

Kinetic energy provides information about the energy associated with blood flow. The variations in kinetic energy in the sinuses of Valsalva and the ascending aorta are analysed. Interestingly, there is an unexpected decrease in kinetic energy in conditions of severe aortic stenosis. Figure 3.4 shows the variation in kinetic energy in the sinuses of Valsalva and the ascending aorta for a uniform inflow. Kinetic energy should be within normal limits, indicating efficient movement of blood through the valve without excessive turbulence or energy loss.

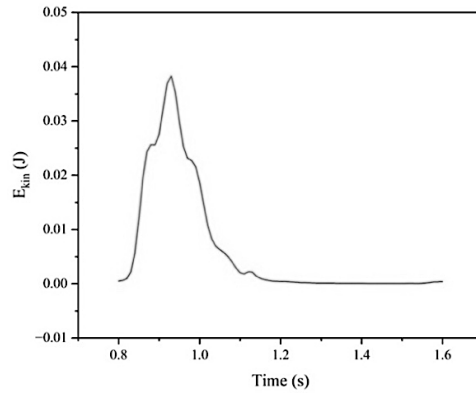


Figure 3.4 : Variation in kinetic energy in the Valsalva sinus and ascending aorta across for uniform inflow. Image taken with special permission from Reza Daryani and Emre Cenk Ersan, members of İTÜ Informatics Institute Computational Biomechanics Group.

Energy dissipation rate indicates the rate at which energy is dissipated in the flow. Higher levels of calcification are associated with increased energy dissipation, suggesting the formation of more intense vortices and greater energy loss. Figure 3.5

shows the energy dissipation rate in aortic valves under steady inflow conditions over a cardiac cycle.

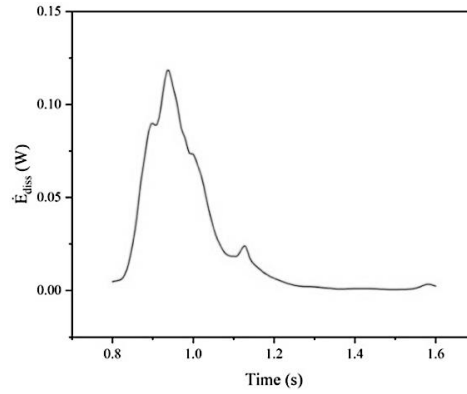


Figure 3.5 : Energy dissipation rate in aortic valves uniform inflow conditions over a cardiac cycle. Image taken with special permission from Reza Daryani and Emre Cenk Ersan, members of İTÜ Informatics Institute Computational Biomechanics Group.

The other transvalvular hemodynamic indicator is the magnitude of vorticity. Vorticity is a measure of the rotation of fluid elements. Vorticity magnitude gives an indication of the intensity of the vortices. Increasing severity of calcification is associated with the formation of more intense vortices. Figure 3.6 shows the magnitude of vorticity in aortic valves under uniform inflow during a cardiac cycle.

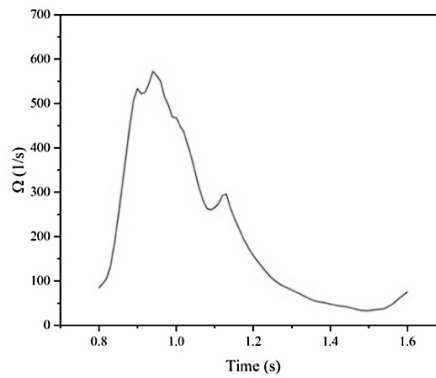


Figure 3.6 : Vorticity magnitude in aortic valves under uniform inflow during a cardiac cycle. Image taken with special permission from Reza Daryani and Emre Cenk Ersan, members of İTÜ Informatics Institute Computational Biomechanics Group.

The time averaged wall shear stress (TAWSS) is the cyclic average of the magnitudes of the instantaneous wall shear stress (WSS) vectors. It provides information about the shear forces acting on the leaflets. Figure 3.7 shows the distribution of TAWSS on the

aortic valve leaflets under uniform inflow conditions. TAWSS is expected to ensure that the shear forces on the leaflets are adequate to maintain valve health.

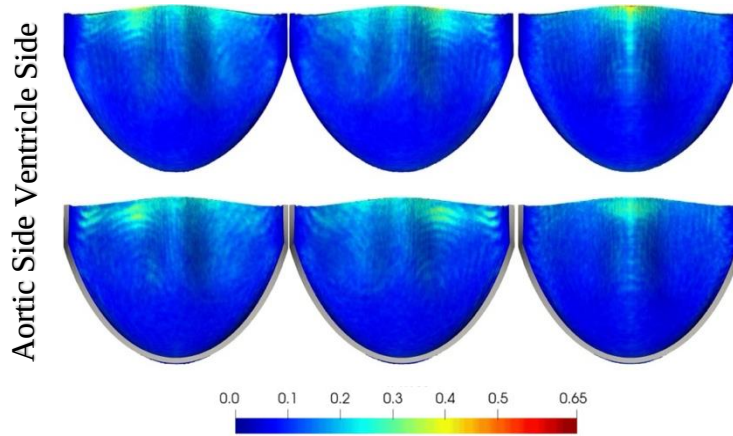


Figure 3.7 : Distribution of TAWSS [Pa] on aortic valve leaflets under uniform inflow conditions. Image taken with special permission from Reza Daryani and Emre Cenk Ersan, members of İTÜ Informatics Institute Computational Biomechanics Group.

The Oscillatory Shear Index (OSI) is an indicator of the degree of reversal of WSS direction within a cardiac cycle. Higher OSI values indicate unsteady flow and lower values are associated with more stable flow. The effect of calcification on OSI depends on factors such as the distribution and symmetry of the deposits. Figure 3.8 shows OSI contours on the aortic and ventricular sides of uniform inflow patterns. OSI values indicate predominantly unidirectional flow with minimal oscillatory components.

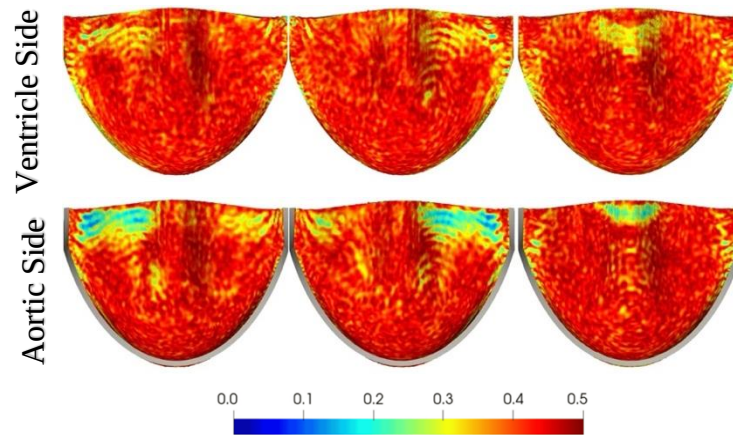


Figure 3.8 : OSI contours on aortic and ventricle sides uniform inflow patterns. Unit is dimensionless. Image taken with special permission from Reza Daryani and Emre Cenk Ersan, members of İTÜ Informatics Institute Computational Biomechanics Group.

Residence time (RRT) is the time that blood remains in the endothelium. Elevated RRT values are associated with impaired blood flow. Figure 3.9 shows the distribution of RRT across the leaflets for uniform inflow types.

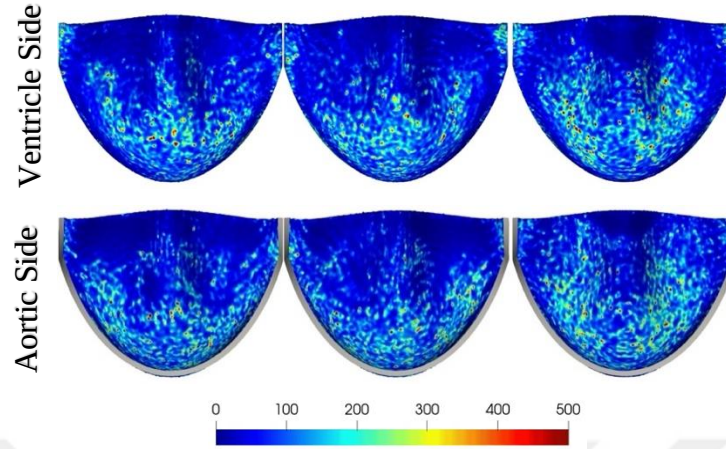


Figure 3.9 : Distribution of RRT [Pa^{-1}] across leaflets for uniform inflow types. Image taken with special permission from Reza Daryani and Emre Cenk Ersan, members of İTÜ Informatics Institute Computational Biomechanics Group.

Transvalvular wall shear stress (transWSS) measures the average of the WSS components perpendicular to the temporal mean WSS vector over a cardiac cycle. Increased calcification severity is generally associated with increased transWSS values, particularly near the leaflet tips and in the abdominal region. Figure 3.10 shows the distribution of transWSS (Pa) values across the cardiac cycle, highlighting the increased directional variation under steady flow conditions. transWSS values reflect normal variations in the shear stress components perpendicular to the main flow direction.

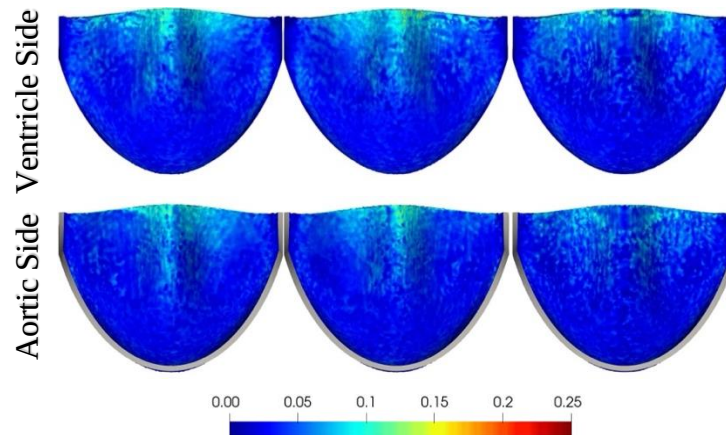


Figure 3.10 : Distribution of transWSS (Pa) values across highlighting increased directional fluctuations under uniform flow conditions. Image taken with special permission from Reza Daryani and Emre Cenk Ersan, members of İTÜ Informatics Institute Computational Biomechanics Group.

Transvalvular hemodynamic indices are parameters used to assess blood flow characteristics in heart valves. In order to increase the durability of the prosthesis, it is necessary to hemodynamically analyse the design based on patient images with respect to these indices. A hemodynamically enhanced model should be constructed using structural mechanics analysis. The design will be improved by considering both the mechanical properties of the prosthesis material and the hemodynamic loads [107].



4. MECHANICAL DESIGN

The most important factor in the performance of artificial heart valves is their design. In addition to the choice of material, a valve design that can withstand mechanical stress leads to a longer lifespan. Before computer modeling was used, valves were evaluated in in vitro and in vivo tests. The manufacturing process for a prototype could be both costly and time-consuming for the researcher. Finite element modeling (FEM) allows potentially defective prototypes to be eliminated before production. By performing mechanical tests in a computer environment, the suitability of both the design and the material for the model can be analysed. The finite element method can be used in various physical situations such as stress, heat conduction and vibration. The body is divided into finite elements and analysis is performed on each element. The solution of all elements is used for the final analysis of the body.

Computational modeling and hemodynamic and structural mechanical analysis of the aortic valve can be used to determine the factors that increase stress concentrations. These factors can be geometry, anisotropic structure and stent structure. As mentioned above, heart valves are subject to complex physical stresses. Most computational models cannot mimic physiological behavior. Typically, modeling is done by applying differential pressure to the leaflets or by stretching the leaflet classes. However, this needs to be improved to be more in line with physiology [10].

The high stress concentration zones identified by FEM allow more attention to be paid to these areas when designing the model. This makes the design more resistant to fatigue. High stress is the stress to which the material is cyclically subjected until failure occurs under load. The transfer of time-varying pressure information from the FSI analysis to the FEM analysis of the aortic valve during a systole-diastole period allows for a comprehensive and realistic structural analysis. The following sections provide information on these topics.

4.1 Transferring Data from FSI to FEM

Standard FEM analyses of heart valves are performed with a given initial pressure. However, hemodynamic changes over time create different loads at different locations on the leaflet surface. In this context, the pressure information generated by the FSI analysis at the nodes of the geometry is critical to the FEM analysis. Transferring this information to the FEM analysis helps to better simulate the physiological environmental conditions.

In the FEM analysis, the pressure values at the planned time intervals should be generated as a data file from the FSI analysis. Some intermediate programmes are used for this purpose (ParaView, VisIt, etc.). For each step, a data file is created containing a node ID, location and pressure information. For the structural analysis (dry analysis), Ansys® was preferred over commercial programs. This choice was influenced by the availability of a graphical user interface, the editability of material models, the wide range of numerical solver and material model options, the availability of an academic licence, etc. As mentioned above, hyperelastic material models are the most commonly used material models for modeling the aortic valve and exhibit realistic behavior. Using the Engineering Data module of Ansys® it is possible to use models from the program's material library or to define new models. The coefficients of the Neo-Hookean material model used in the FEM analysis are shown in Figure 4.1 and the stress-strain graph is shown in Figure 4.2.

Properties of Outline Row 3: Neo-Hookean					
	A	B	C	D	E
1	Property	Value	Unit		
2	☒ Material Field Variables	☐ Table			
3	☒ Density	1100	kg m ⁻³		
4	☒ Neo-Hookean				
5	Initial Shear Modulus Mu	200000	Pa		
6	Incompressibility Parameter D1	0	MPa ⁻¹		

Figure 4.1 : Shows the values of the Neo-Hookean material model used in the modeling entered in the engineering data module.

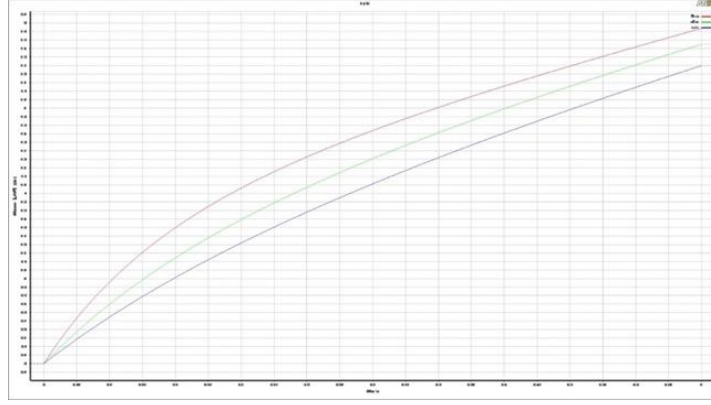


Figure 4.2 : The stress-strain curve generated by the Neo-Hookean material model.

4.1.1 Geometry transfer

To make the FEM analysis more similar to physiological conditions, time-dependent pressure information should be transferred. To ensure the integrity of this analysis process, the geometry used in the FSI analysis was also used in the FEM analysis. The view of the geometry transferred from FSI together with the aortic root is shown in Figure 4.1. The view of the leaflets to be analysed by FEM is shown in Figure 4.2 and Figure 4.3.

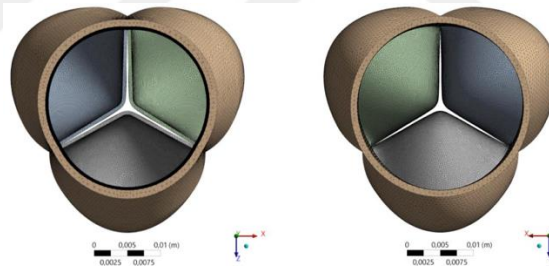


Figure 4.3 : Vascular side view (left), ventricular side view (right) of the entire transferred geometry. Image taken with special permission from Emirhan Yiğit, member of İTÜ Informatics Institute Computational Biomechanics Group and student of Mechanical Engineering Department and Mechanical Engineering Department.

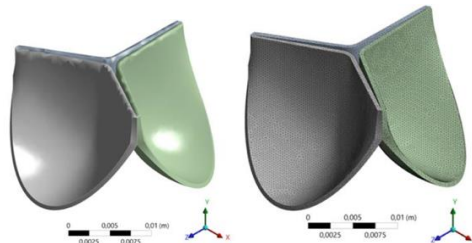


Figure 4.4 : The aortic valve and its mesh are transferred to the ANSYS® Transient Structural Module. Image taken with special permission from Emirhan Yiğit, member of İTÜ Informatics Institute Computational Biomechanics Group and Mechanical Engineering Department.

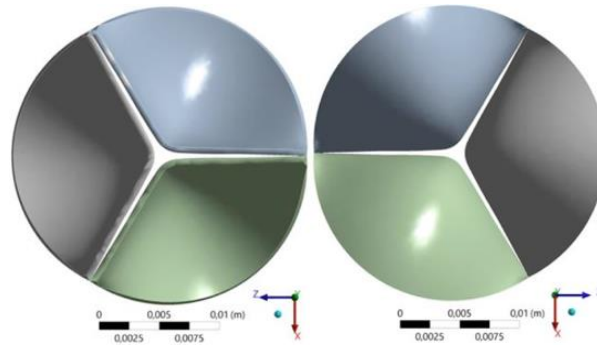


Figure 4.5 : Vascular side (left) and ventricular side (right) views of the aortic valve. Image taken with special permission from Emirhan Yigit, member of İTÜ Informatics Institute Computational Biomechanics Group and Mechanical Engineering Department.

4.1.2 Transfer of hemodynamic pressure data

Although structural mechanics calculations are performed in the FSI model, dry FEM analysis is required for detailed FEM analysis for different scenarios. For this reason, the "External Data" module in Ansys® Workbench has been used to transfer the load data. This module allows to read external data files (files with extensions such as ".txt", ".xls", ".csv"). These data can be processed on the model to be analysed. The data file loaded into the module contains the pressure values calculated by the FSI analysis corresponding to each node of the structural mesh for each time step of the simulation. Some information about the file is imported into the module. These are the methods used to separate the columns of data and which column is which data. The application of this time-varying data to the structural model takes place in the Transient Structural module.

4.1.3 Matching of data

Once the time-varying pressure data file has been read in, it is transferred to the structural model in the Transient Structural module. This transfer is done by following the path "Imported Load -> Imported Pressure". The Node ID and Pressure columns defined in External Data are read by the program. As the Node IDs identifying each node are entered directly instead of the location information of the nodes, the pressure value in this row is loaded by the program to the Node ID in the same row in the .csv file with "Direct Assignment". Note that the node point in the data file and the node point in the structural model at the same location must have the same Node ID. If a matching problem occurs, file manipulation should be performed. The data file and the

file containing the node ID and location information of the structural model taken from the Transient Structural module should be checked and updated to have a single node ID for a single location.

4.1.4 Boundary conditions

Since the parts of the aortic valve attached to the walls inside the heart must remain in a fixed position, the built-in boundary condition is assigned as shown in Figure 4.1. This is the correct approach as these parts must remain in a fixed position.

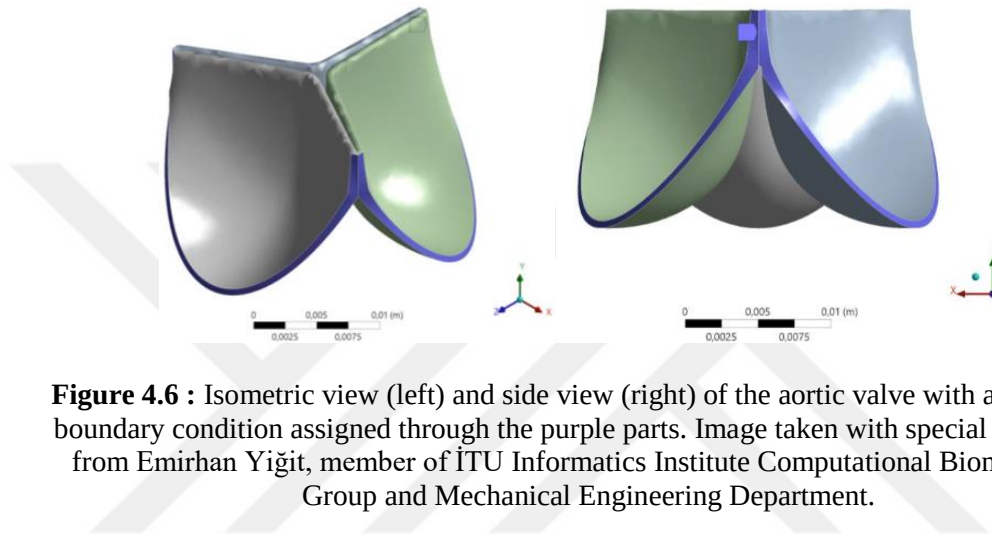


Figure 4.6 : Isometric view (left) and side view (right) of the aortic valve with an anchored boundary condition assigned through the purple parts. Image taken with special permission from Emirhan Yiğit, member of İTÜ Informatics Institute Computational Biomechanics Group and Mechanical Engineering Department.

Contact surface definition

The contact surfaces between the aortic heart valves must be identified. The definition of the contact area is very important for accurate calculations. In addition to the loads created by blood flow through the aortic valve, neighbouring leaflets also create loads on each other. If the contact surfaces are not defined in the modeling, the leaflets may overlap. This is an abnormal situation that does not actually exist. Therefore, a frictionless contact surface model can be used to prevent penetration. In the frictionless contact surfaces of the heart valves, 'symmetric' conditions are assigned to the behavior of the contact and target surfaces, so that the program can perceive both sides as having equal contact. The representation of the leaflet contact surfaces in the valve is shown in Figure 4.3.

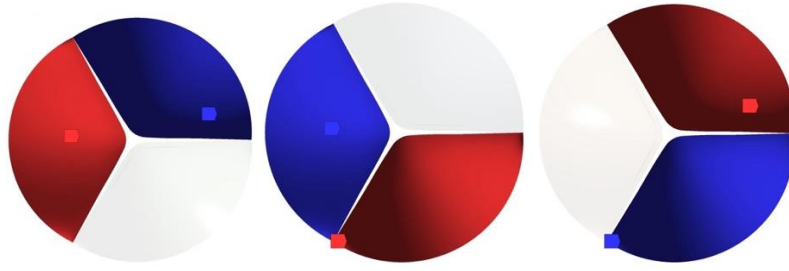


Figure 4.7 : Representation of the contact surface of the leaflets inside the valve. The contact (red) and target (blue) surfaces are identified. Image taken with special permission from Emirhan Yiğit, member of İTÜ Informatics Institute Computational Biomechanics Group and Mechanical Engineering Department.

4.1.5 Loading conditions

As mentioned above, the pressure data can be imported into the solid model by following the path "Imported Load -> Imported Pressure" in the "Transient" tab. The pressure load applied by the aortic valve during systole and diastole acts on the surfaces. These areas are defined. The pressure data that should be applied to the surfaces of the aortic valve leaflets, the parts shown in green in Figure 4.8, are plotted.



Figure 4.8 : Selection of the areas to be loaded. Image taken with special permission from Emirhan Yiğit, member of İTÜ Informatics Institute Computational Biomechanics Group and Mechanical Engineering Department.

4.1.6 Solution method

The anisotropic nature of heart valve tissue, the exposure to large deformations during physiological cycles, the contact area of the leaflets and the time-dependent loading conditions lead to the application of nonlinear FEM analysis to heart valve models. Non-linear FEM analysis is much more difficult to converge to a solution than linear FEM analysis. In addition, the calculation must be kept stable over a systole-diastole period. Figure 4.9 shows the results of calculating the equivalent von Mises stress and total deformation of the aortic valve over a systole-diastole cycle.

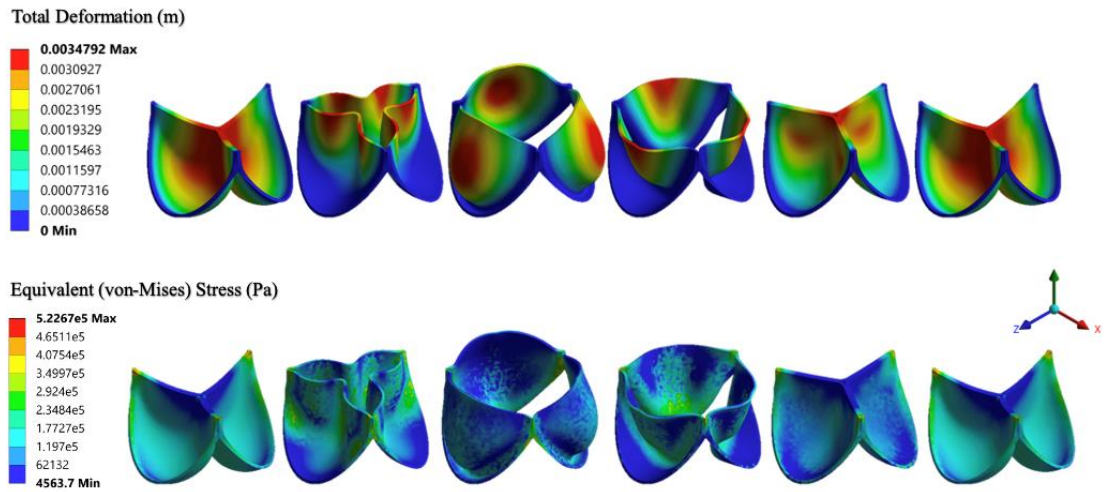


Figure 4.9 : Illustration of Equivalent von Mises Stress and Total Deformation calculation results of the aortic heart valve during one systole and diastole cycle.

Image courtesy of Emirhan Yiğit, member of İTÜ Institute of Informatics Computational Biomechanics Group and Mechanical Engineering Department.



5. PRODUCTION OF PROSTHETIC AORTIC HEART VALVE

There are several considerations in the manufacturing process of an aortic heart valve prosthesis. These are the quality standards that determine the quality of the intended product, the choice of materials and the manufacturing technique. The following sections provide detailed information on these issues.

5.1 ISO 5840 Quality Standards

The ISO standard outlines the in vitro tests that must be performed to demonstrate the reliability of the developed artificial heart valve prior to clinical evaluation. ISO 5840 defines the requirements and performance of the valve under operating conditions. All manufacturers must comply with ISO 5840-3.

There are standards for transcatheter heart valve (THV) substitutes that manufacturers should be aware of. These are discussed in this chapter. The requirements for the implantable device can be listed as follows;

1. It must be able to be safely loaded into the body delivery system.
2. It must be properly and safely deployed in the implanted area.
3. It must be able to be safely retrieved and additionally repositioned when necessary.
4. It must be able to remain fixed in the implant site throughout the lifetime of the implant, and structural and functional continuity must be ensured.
5. It should not cause anatomical distortion in the area to be implanted and should maintain integrity.
6. It should allow forward flow with an acceptable pressure difference and prevent retrograde flow with small regurgitation.

7. It should resist migration and embolization, minimize hemolysis and thrombus formation during its lifetime.

The design features required to ensure the performance of the THV can be listed as follows;

1. Comply with the requirements of ISO 10993-1 and ISO 10993.
2. The THV system should be visible on imaging modalities such as fluoroscopy and compatible with magnetic resonance imaging (MRI).
3. The system must be able to maintain its stability and functionality before and after implantation.

The manufacturer shall carry out validation tests to verify that the replacement THV system has the required design characteristics. These tests should be related to the hazards identified in the risk analysis. The biocompatibility of the materials used in the THV replacement system shall be assessed according to ISO 10993-1. In the biosafety assessment of the selected materials, the following issues should be considered in the hazard identification of the selected material. Toxicological, haematological effects. The properties of the material should be explained in relation to these issues. If there is a hazard, the toxicological risk should be expressed. Biochemical interactions that may occur in this situation, toxicokinetic information and exposure levels should be analysed. In addition, if animal tissues or derivatives are to be used, relevant standards should be consulted.

The mechanical properties of the material of all parts of the THV substitute must be appropriate to the design. Once suitable materials have been selected, they must also be characterized during the manufacturing process. Characterisation should be performed on the raw materials for the structural components, the fabricated structural component, the structural component in the catheter and the implanted structural component. Shelf life, corrosion resistance and environmental conditions should be demonstrated.

Mechanical strength testing of THV substitutes shall evaluate the processability of the valve and shall include a minimum of 200 million in vitro test cycles. If the test has not been performed, it must be scientifically validated. In the durability test, the valves

are subjected to a differential pressure. If replacement valves of the same design are to be implanted in different positions, the differential pressure conditions to be used in the test shall be for the worst case valve. The test setup should simulate the shape of the implanted valve and changes in ambient temperature. In addition, the hydrodynamics of the valves should be varied in the test rig according to their size. A different test set-up should be used for paediatric patients.

When analysing the structure of the implant in vivo, it is essential to consider all valve stresses. In addition, it is necessary to perform fatigue and durability assessments of the structural components under in vivo conditions to assess the risks associated with valve fatigue. It is also important to consider the compatibility of the implanted valve with the patient's body. The level of calcification at the implant site and the stability of the valve must be assessed and taken into account. Pulsatile testing should be used to assess the migration resistance of the THV replacement. In addition, the crush resistance of the prosthesis should be tested under a specific load. A peripheral structure that does not expand spontaneously should be present when a radial load is applied. THV substitutes must meet certain standards, including design, manufacturing and implantation processes, to protect the health of the patient. Researchers and companies should continue their work with these rules in mind.

5.2 Materials

During the production phase, ultraviolet (UV)-curable, flexible materials suitable for DLP devices were preferred.

5.2.1 DentaModel

It is a photopolymer generally used in dental studies (Figure 5.1). Compatible with DLP 3D printers.



Figure 5.1 : DentaModel resin [74].

5.2.2 Gingiva

Power Resins Gingival resin (Figure 5.2) is a flexible resin used to print soft gingival masks for model printing. It has high dimensional stability. It has high dimensional stability. Material properties of gingiva resin are given in Table 5.1.



Figure 5.2 : Gingiva resin [75].

Table 5.1 : Material properties of gingiva resin [75].

Material Properties	Value	Standart
Flexural Strength	1.1 MPa	ASTM D790-02
Elongation at Break	24.5%	-
Density	1.104 g/cm ³ (at 23°C)	ASTM D1475
Viscosity	1145 mPa.s (at 23°C)	DIN 53211-4
Shore Hardness	81	ASTM D2240

5.2.3 Flexible-X

Liqcreate Flexible-X is a black opaque photopolymer compatible with DLP, LCD, MSLA, and SLA 3D printers in the 385 - 420nm range (Figure 5.3). Flexible-X, which has a hardness of 55 Shore A, can extend up to 160%. It can be used for the production of elastic parts. Mechanical properties of Flexible-X after UV curing are given in Table 5.2. The liquid properties of Flexible-X are presented in Table 5.3.



Figure 5.3 : Flexible-X resin [76].

Table 5.2 : Mechanical properties of Flexible-X after UV curing [76].

Definition	ASTM Method	Metric
Tensile Strength	D638	1.5 MPa
Elongation at Break	D638	120 – 160%
Tear Strength	D624	14.9 kN/m
Pressure Persistence at 22°C for 24 Hours	D395	2%
Shore A Hardness	D2240	55
Water Retention	D570-98	3.3 %

Table 5.3 : The liquid properties of Flexible -X [76].

Definition	Value
Appearance	Opaque black liquid
Viscosity	25°C/de 950 cps
Intensity	1.18 g/cm ³
EC	6.87mJ/cm ²
dp	0.35 mm

5.2.4 Elastomer-X

Liqcreate Elastomer-X is a clear photopolymer resin (Figure 5.4). Liqcreate Elastomer-X can be used in clear DLP, LCD and SLA 3D printers in the 385 - 420 nm range. 3D printed parts from this material are soft at 43 Shore A and have great flexibility. Its properties simulate soft TPU (thermoplastic polyurethane) and silicone. It can be used to produce digital lattice foams, soft end of arm assemblies for robots, washers, bellows and resilient parts. The mechanical properties of Elastomer-X after UV curing are described in Table 5.4 and the fluid properties of Elastomer-X are described in Table 5.5.

**Figure 5.4 :** Liqcreate Elastomer-X resin [77].

Table 5.4 : Mechanical properties of Elastomer-X after UV curing [77].

Definition	ASTM Method	Metric ^[1]
Tensile Strength	D638	1.5 MPa
Elongation at Break (Moment of Fracture)	D638	140 – 180%
Tear Strength	D624	10 – 12 kN/m
24 Hours Pressure Persistence at 22°C	D395	1%
Shore A Hardness	D2240	43
Water Retention	D570-98	1,5%
Glass Transition Temperature	DSC Method	-5°C
Decomposition Temperature	Internal Method	>250°C ^[2]

[1] Final curing in glycerol or water for 5 minutes with LED curing at 20°C. These values may vary and depend on the individual machine process and subsequent hardening.

[2] Discoloration at 140°C, increased hardness at 220°C - Shore A 54. Partial cracking up to 250°C / 482°F.

Table 5.5 : Liquid properties of Elastomer-X [77].

Definition	Value
View	Clear liquid
Viscosity	25°C'de 2000 cps
Density	1.18 g/cm ³
Ec (405nm)	28.48 mJ/cm ²
Dp (405nm)	0.28 mm
Ec (385nm)	26.16 mJ/cm ²
Dp (385nm)	0.11 mm

5.3 Production Techniques

The performance of PHVs is undoubtedly influenced by the design, material selection and manufacturing technique. The ability to produce the planned geometry with the required precision varies with the change in production techniques. In the following sections, information about molding, film manufacturing, electrospinning, three-dimensional printing, and digital light processing techniques will be given.

5.3.1 Molding

Valves produced by dip molding are generally very strong. They have achieved several hundred million cycles in in vitro tests and have also shown good results in in vivo studies. This makes it a promising valve manufacturing method.

The mold (or mandrel) of the valve to be produced is immersed in the material, which is generally between 60 and 80°C. When it is removed, the polymer attached to the mold is pulled out of the mold. The remaining thin film can be thickened to the desired level by repeating this process.

One of the advantages of this process is that during the dipping process, the stent part of the prosthesis or the valve environment can be dipped with the prosthesis at any time (e.g. at the beginning or end) and a layer can be formed. This provides integrity in the prosthesis and a smooth transition between different parts. The repeatability of the manufacturing technique depends on several conditions. These are: including the shape of the model, making the mold clean and smooth, the way the mold is held according to the production stage, the concentration and viscosity of the selected material, the polymer, the dipping speed and environmental conditions (such as atmospheric pressure), and the mold direction during drying, dipping speed and atmospheric conditions. It requires precise control of many factors. If the necessary sensitivity is not shown under these conditions, the properties of the prosthesis may be immediately affected. Its thickness may change, the material may lose its homogeneous structure, etc. [78].

Another molding process is injection molding. In this method, the shape of the leaflet and the desired thickness are produced entirely by molding. This increases the repeatability of production. The molten material is transferred under pressure from the inlet to the mold. This transfer process has been used by some researchers to impart anisotropy to the blade. By pushing the polymer, it gives the polymer chains an orientation. Stasiak and his colleagues used this technique to achieve a two-way orientation in a material made from SIBS containing 30% styrene by weight (SIS30). This orientation is formed by the balance between flow and extensional flow. In the direction of the extensional flow, while there is a circumferential orientation in the centre of the thickness of the flaps, radial orientations occur on the surface of the flaps between the material and the mold.

In the compression molding technique, which is another molding method, the pre-heated material is poured into the open mold and the mold is closed. After the mold is closed, pressure is applied to the mold to ensure that all the parts are distributed in the molding box. The cooled material hardens and the model is produced. An example of this type of production is the work of Claiborne et al (Figure 5.5). The mold used to

produce the xSIBS aortic valve prosthesis was heated to 260°C and the mold was compressed to 1 ton [78].

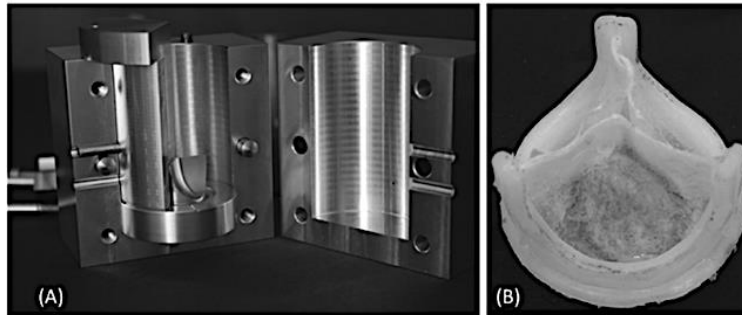


Figure 5.5 : Compression mold and prosthesis prototype for aortic valve prosthesis: A) compression mold, B) molded xSIBS prosthesis prototype [78].

Another advantage of using molds is that they allow layered production. With multi-stage injection, different components can be produced layer by layer. However, opening and closing the mold for the layers can cause problems in production. Various inconsistencies can occur. In addition, the layers in the lamellar structure are isotropic, whereas each phase in the tissue of the real aortic valve has anisotropic properties [79].

The multilayer injection method can be used not only to produce PHVs but also for cell transplantation in tissue engineering studies. Figure 5.6 shows the multilayer manufacturing process of the aortic valve.

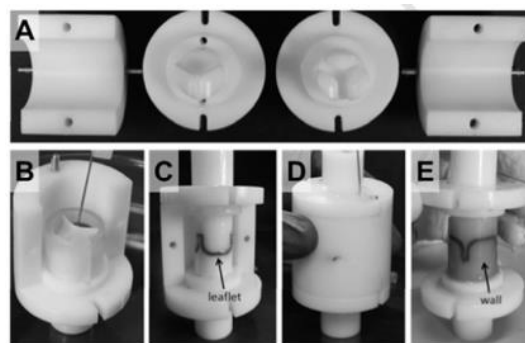


Figure 5.6 : Multi-injection construction process of the heart valve produced in different layers for tissue engineering studies. A) Valve geometry, B-E) injection stages.[79].

5.3.2 Film manufacturing

The aortic valve is also manufactured by film fabrication. In this technique, the parts of the prosthesis, the leaflets and the frame, are manufactured separately. The leaflets, produced as a polymer film, are cut and glued to the frame. In some cases, a heat

treatment is applied to ensure that the leaflets adhere to the frame. Whilst this production technique is superior in terms of leaflet design and rapid prototyping, there can be weaknesses in the strength of the frame and leaflets due to their attachment points. The reasons for the lack of strength can be explained as follows. During the process of attaching the leaflets with stitches, the stitches increase the tension. This reduces the tension in the leaflet. In addition, it requires manual sewing and is not scalable for high volume production [78].

5.3.3 Electrospinning

Electrospinning is a manufacturing technique that creates a 3D structure by applying a high voltage to the material, creating its micro/nanofiber structure through a needle. Although the material of choice is usually polymer, ceramics and composites can also be used. Electrospinning has been used in many fields of study, including cardiac tissue engineering. It contributes to the anisotropic structure of the produced product. Directional stiffness can be created at the microscale by controlling fiber orientation. In addition, electrospinning has been used in the manufacture of heart valve prostheses, such as the JetValve (Figure 5.7). In this type of production, the shape of the collectors, where the fiber exiting the needle is collected, is particularly important in creating the shape of the structure. Different collector geometries have been created for different covers (Figure 5.8).

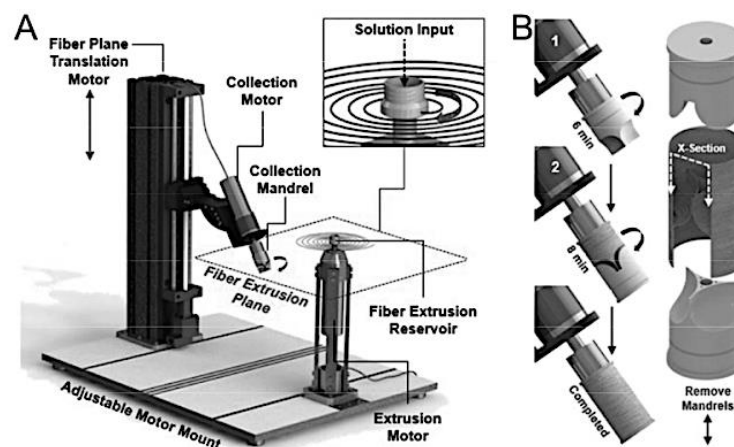


Figure 5.7 : JetValve is an example of electrospinning developed for heart valves.

A) A rotating fiber spinning chamber that has a significant effect on creating a physiology-like geometry B) collection of electrodes designed for the geometry of the valves [79].

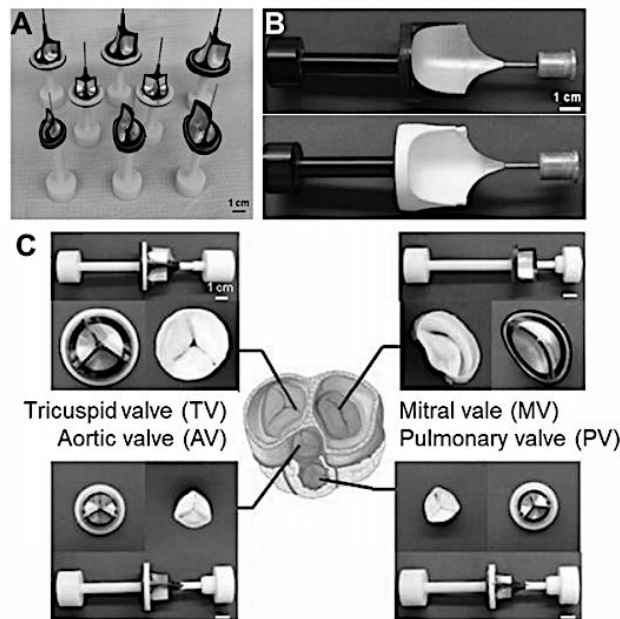


Figure 5.8 : Views of collector electrodes with different structures that contribute to the production of heart valves by electrospinning. A) Collecting electrode configurations, B) representation of the collector electrode after electrospinning, C) representation of the collector electrodes developed for different heart valves [79].

5.3.4 Three-dimensional printing

Everyone is different. Everyone also has a different medical history. There are also differences between people with heart valve disease. Patients may have different organ sizes, weights and ages. Because of this, the use of standard sizes of artificial heart valves in the body can cause problems in the future. Enlargement of the valve, backflow of blood, etc. In this context, a personalized treatment process will be beneficial in eliminating these problems. Receiving three-dimensional printouts of designs based on the person's computerized data contributes to the personalized treatment process. It enables more practical, faster, cheaper and more scalable printing of printable materials.

The geometries to be printed have been precisely designed as a result of *in silico* experiments in many studies. 3D printers can accurately print complex designs. In 2019, Coulter et al. used a 3D printer in their study of fiber-reinforced bio-inspired heart valves. Figure 5.9 and Figure 5.10 show images of the manufacturing process. From the extraction of anatomical images from patient data, to *in silico* analysis and production technology, the ideal treatment process prototype has been created.

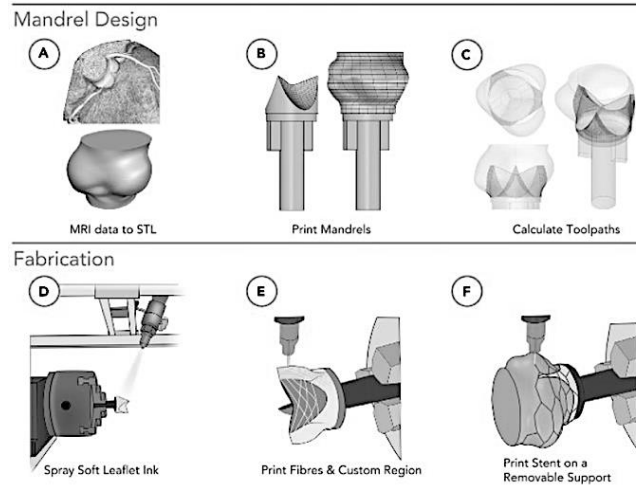


Figure 5.9 : Fabrication of bioinspired synthetic aortic valves. A) MRI image and digitalized model of the aortic root, B) Printed view of the mandrels of the leaflet and root, C) Virtual fitting of the valve to the anatomical image of the patient, D) Spraying soft silicone onto the leaflet mandrel to form the leaflets, E) 3D rendering of the fiber reinforcement and interleaflet triangles writing with a printer, F) printing the stent structure with a 3D printer [36].

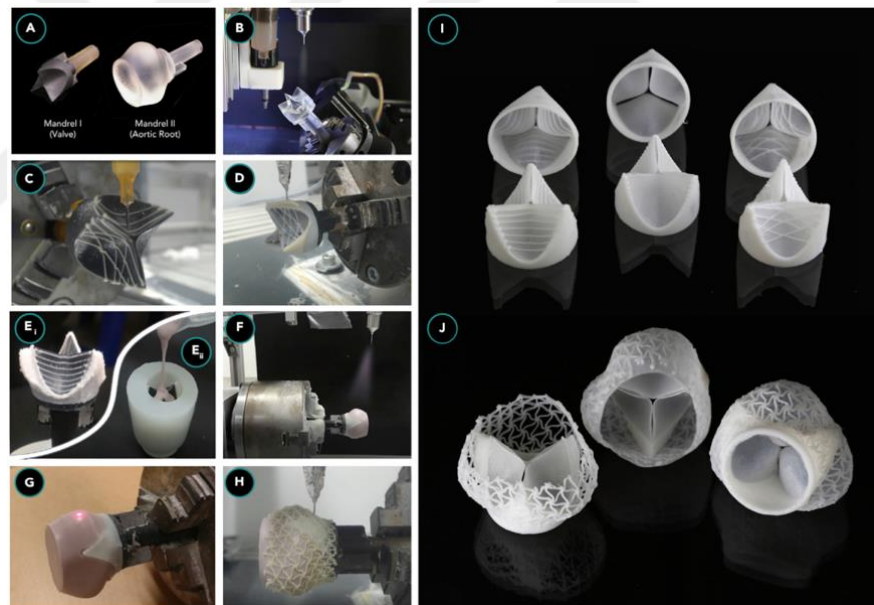


Figure 5.10 : Multi-material additive manufacturing process used in the production of customized silicone heart valves. A) View of the aorta and aortic root designed from MRI data and 3D printed with stereolithography, B) Production of leaflets by spraying thin soft silicone layers on the mandrel for the valve, C) Printing of hard fiber reinforcement patterns on the silicon sprayed mandrel using a 3D printer. D, E) Printing on the patient Printing specially designed interstitial triangles with a 3D printer Ei, Eii) An intermediate material is needed to print the stent structure together with the leaflets. After the molded pink structure stent is printed from the 3D printer, the fixed stent and leaflet structure will remain. F) Spraying a soft silicone membrane on the valve and the cast pink structure, H) 3D printing of the stent structure, I) Aortic valves in different fiber orientations, J) Aortic valves and stent structures in different fiber orientations [36].

5.3.5 DLP (Digital Light Processing)

DLP (Digital Light Processing) is a 3D printing technology developed by Texas Instruments in the 1980s. A DLP device consists of thousands of micro-mirrors that rotate independently and can change their open or closed position according to digital commands. Light is reflected through an optical system in a specific pattern onto the resin surface, causing the area exposed to the light to harden. The key functional component is the Digital Micro Mirror Device (DMD), which consists of small, individually controllable mirrors. These mirrors rotate during the printing process to direct and reflect light onto the photosensitive resin. Typical DMD arrays can be quite large, ranging from around one million to more than two million mirrors. However, the spacing between individual micromirrors is very small, only a few microns or sometimes only a few tens of microns. The resolution of DLP-based 3D printing depends on how the projection plane is adjusted by the DMD and optical lens. As a result, DLP printing technology is known for its relatively high precision, typically operating in the micron range. As a result, DLP-based 3D printing has high resolution. In addition, the fact that DLP does not require high temperature, pressure or shear stress offers potential for advanced applications such as cell-loaded 3D printing or bioprinting of human organs [82].

Configuration of DLP device

A Digital Light Processing (DLP) device consists of five main components. These components are the light source, pattern imaging system, control system, tank and build platform. The light source provides the energy required to cure the resins, usually using UV light or a laser. The pattern generation system is based on computer-aided design files and uses these files to create two-dimensional images. These images control the reflection of light onto the resin surface via optical paths and DMD. The control system consists of three basic sub-systems. The first is process control, which controls the sequence and timing of the process. The second includes position control, which operates according to computer instructions to raise and lower the build platform. Finally, there is environmental control, which regulates things like the temperature or humidity of the room. In addition, some DLP systems include a coating blade to smooth the resin surface when the liquid resin needs to be evenly distributed [83].

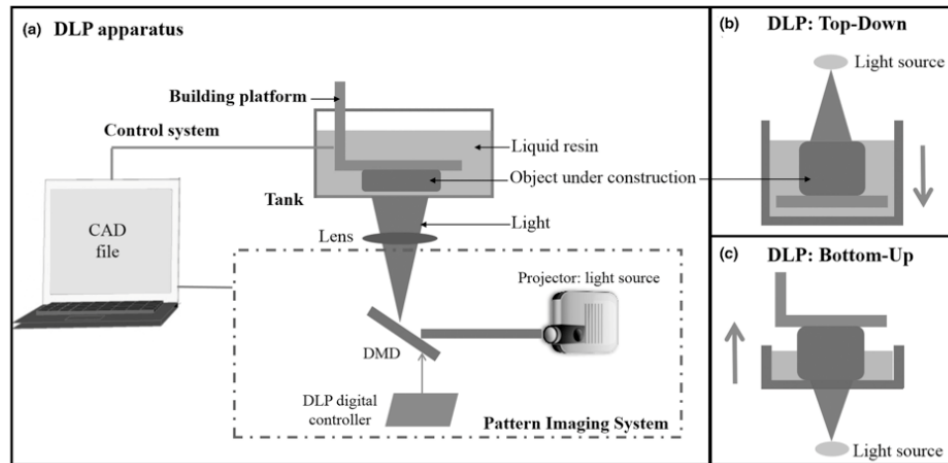


Figure 5.11 : Illustrating the working principle of Digital Light Processing (DLP) technology. A) the DLP apparatus, B) the top-down system, C) the bottom-up system [84].

DLP systems use two basic orientation approaches for 3D printing: top-down (i) and bottom-up (ii). In the top-down approach (i), the light source is positioned above the resin tank and the three-dimensional object is built from the bottom up (Figure 5.11b). The build platform is immersed in liquid resin and maintained at a layer thickness slightly above the resin surface. When the resin layer has cured, the platform is lowered one layer along the Z-axis to allow fresh resin to spread over the cured layer. The light curing process is then repeated. This process is repeated until a three-dimensional object is complete [84].

The top-down approach has a number of advantages and disadvantages. Firstly, precise control of the layer thickness can be challenging as the movement of the submerged platform can destabilise the resin. In addition, the new layer of liquid resin is constantly in contact with the oxygen in the air, which can inhibit the polymerisation of certain resins in the vessel, leading to insufficient curing or other 3D printing defects. Secondly, this method requires more resin to be used, as the height of the resin must be above the 3D printed part for each layer to be printed. Thirdly, when printing porous structures, there is a possibility of excessive curing, which can cause the pores to collapse. However, especially for materials such as ceramic suspensions, the top-down approach can provide high resolution in the X and Y directions and strengthen the bond between the layers by reducing light scatter.

In the bottom-up approach, the light source is positioned at the bottom of the vessel and three-dimensional objects are built upside down, as shown in Figure 1.1c. The

build platform is held only one layer thick at the bottom of the tank. After each layer is completed, the build platform moves up one layer thickness to print the next layer. In particular, a transparent tank bottom is required to allow light to pass through for each layer to cure. In addition, the adhesion of the layer to the build platform must be carefully controlled to ensure successful separation from the tank bottom and sufficient bond strength between the layers. The light dose must be high enough to facilitate successful separation from the platform and to achieve the necessary bond strength between the layers. Fresh resin has a faster polymerisation rate because it has less contact with ambient oxygen. The DLP positioning control system is managed by an elevator, allowing precise adjustment of the layer thickness. In addition, the bottom-up approach to DLP 3D printing requires less resin because the 3D object to be built does not need to be fully immersed in the resin in the tank. However, using the bottom-up approach to print long and heavy objects can be challenging and can result in preformed parts being completely separated from the build platform [83].

Basic parameters

The basic parameters of DLP include film thickness, energy density and exposure time, while other parameters are usually fixed in DLP printers. In DLP production, the film thickness generally varies between 10-100 μm . Thinner films are better for accuracy and film adhesion. However, thicker layers increase printing efficiency by offering benefits such as shorter print times.

The energy density of the light source used and the exposure time determine the total energy input required to cure each layer, and these factors have a significant impact on the quality of the 3D object produced. With sufficient energy input, DLP can form structures with high mechanical strength and good structural stability. Insufficient energy input can result in mechanically weak products and difficulties in finishing. More importantly, poor layer adhesion and insufficient curing depth can lead to layer separation and print defects.

On the other hand, too much energy can cause over curing, resulting in reduced accuracy. For this reason, the correct adjustment of energy dosage and curing depth is very important in DLP production. In fact, the cure depth can be calculated using Jacob's version of the Beer-Lambert law.

$$C_d = D_p \ln \left(\frac{E_{\text{resin surface}}}{E_c} \right) \quad (5.1)$$

Here, C_d represents the curing depth, D_p is the light penetration depth when the light intensity decreases to 37%, $E_{resin\ surface}$ is the energy value at the resin surface, and is the critical energy required to initiate polymerization.

In this context, D_p and E_c are inherent characteristics of the resin. By obtaining C_d values at different energy values at the resin surface values through experiments, a C_d - $\ln E$ curve can be plotted, allowing for the linear fitting of D_p and E_c values for the resin. Using equation 5.1, the curing depth can be mathematically calculated. This proves to be a useful tool for selecting appropriate printing parameters.

If ceramic suspensions are used in DLP 3D printing, adding ceramic powders to the suspension will alter the distribution of light intensity, thereby affecting the curing profile. Typically, when ceramic suspensions are used, the curing profile becomes shallower and wider because ceramic powders create high turbidity, reducing curing depth while light scattering expands the curing width and decreases dimensional accuracy. Detailed analyses and explanations can be found in the publication by Zakeri et al. [84]. Therefore, in the case of ceramic suspensions, curing depth has a different expression due to the presence of a high-volume ceramic powder fraction in the liquid. In this situation, C_d can be expressed by the following equation:

$$C_d = \frac{2}{3} \times \frac{d}{\phi \beta \Delta n^2} \left(\ln \left(\frac{E}{E_c} \right) \right) \quad (5.2)$$

In this context, ϕ represents the volume fraction of ceramic powder; β is a parameter related to the ceramic particle size and laser wavelength; and Δn represents the difference in refractive index between ceramic particles [84].

5.4 Production

Production of the aortic valve was first attempted using a 3D printer. However, this method failed to print the valve because the material collapsed under the force of gravity during the production phase. The required manufacturing precision could not be achieved in a 3D printer with a model the size of a valve.

The next step we conducted a collaboration with the Marmara University's Nanotechnology and Biomaterials Application and Research Centre. To print on a NovaFab DLP device, support structures must first be added to the model on the computer. The support structures prevent the model from sticking to the platform

during production and ensure that production takes place in a gravity-dependent manner. We used the CHITUBOX Pro® program to add the supports. Different support settings are available as shown in Figure 5.12. Support sizes are available in thin, medium and thick. The contact shape, diameter and depth of the support can be adjusted. In addition, the joint shape, diameter and length can be adjusted. The program can also automatically assign a support structure according to the shape of the model. Areas where more support is required are shown in red. Figure 5.13 shows the support settings we used for the models.

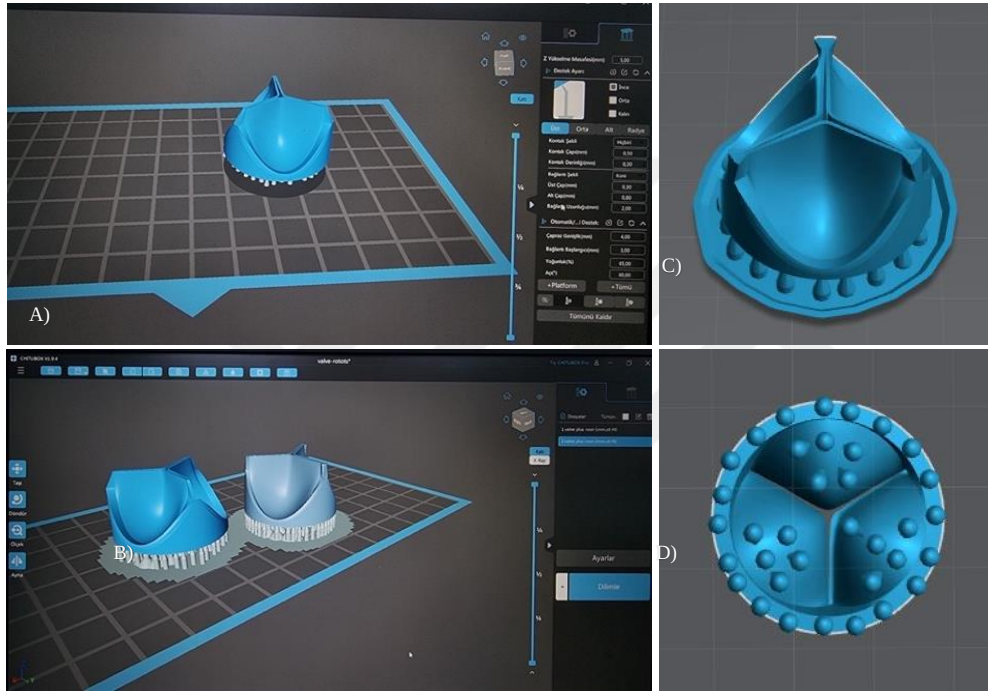


Figure 5.12 : Views after setting support structures we created and creating the support structure: A) setting the support structures B) view of the models after the support structures are discarded C) side view of the model with support structure, D) Ventricular view of the support structure model.

Once the support structures are created, the new supported model needs to be sliced. The DLP machine builds layer by layer. Each layer is formed as a result of slicing in a computer environment. The layer thickness is determined in the computer environment. We performed this slicing process (Figure 5.11) using the NovaFab® Soft Ver. 4.0.1 program of the DLP machine. The gridded area in Figure 5.12 represents the platform of the machine. The position of the model on the platform can be adjusted here.

We first loaded the supported model into the program in STL file format. Then we set the layer thickness to 50 μ as shown in Figure 5.13. After these steps, the G-code

created was transferred to flash memory and transferred to the DLP device via flash memory.

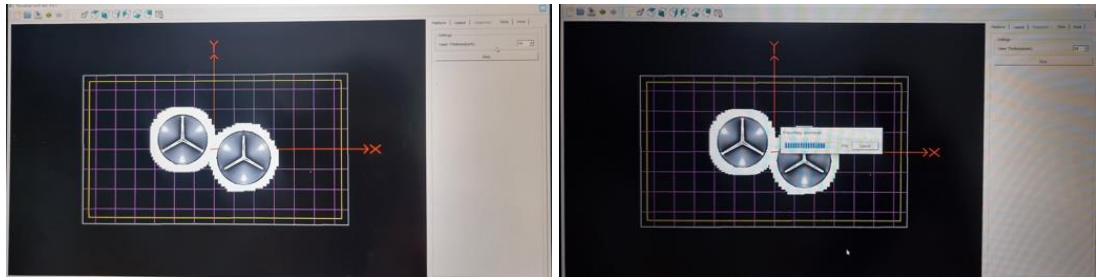


Figure 5.13 : Adjusting the layer thickness of the model for printing (left) and performing the slicing process (right).

The views of the different layers of the model during the production stages are shown in Figure 5.14. During production, the first layer starts and production continues. As can be seen from Figure 5.14, the support structures were printed first and then the model from base to tip.

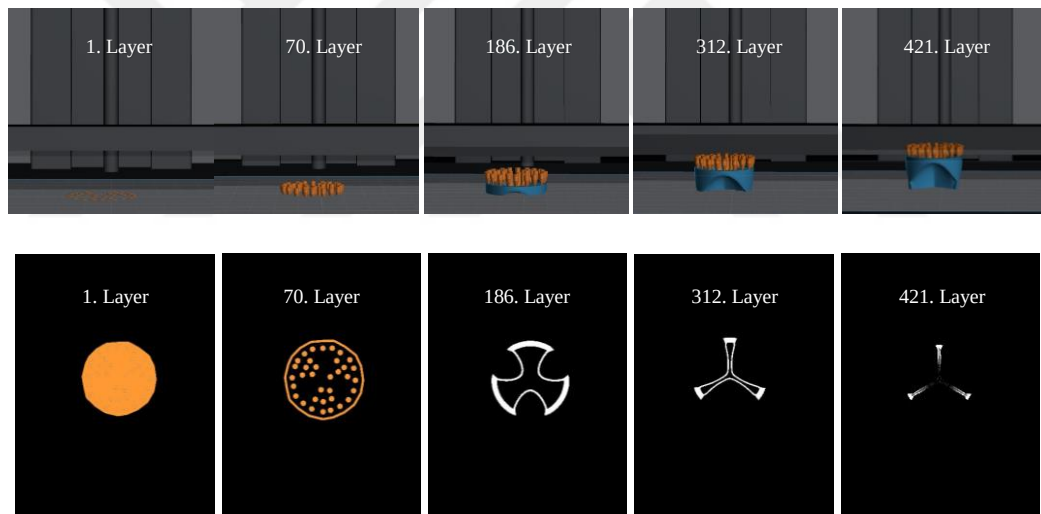


Figure 5.14 : Production simulations (top side) of the support structure model in different layer orders (1st, 70th, 186th, and 421st) and layer views printed at that production stage (bottom side) are seen.

For some DLP devices, such as the NovaFab DLP device (Figure 5.15), if a new material is to be used, the profile of the material must be loaded into the device by the authorized company for the device.



Figure 5.15 : View of the NovaFab DLP device we produce (left), the instrument tank and the build platform (right).

We tested the machine's ability to produce the model using DentaModel resin. We printed the aortic valve model properly and as desired according to the design details (Figure 5.16). However, we did not continue the experiments because this material was too hard to fit into the aortic valve.



Figure 5.16 : View of the model we produced with DentaModel on the platform of the DLP device (left) and top view of the model (right).

We experimented with Gingiva resin. The models were softer and more pliable than those made with DentaModel material. We checked both the smooth printability and softness of the model by varying the exposure time to different UVs. The exposure time can be adjusted on the screen of the DLP unit. For example, for an exposure time of 80%, the total number of layers is 446, the estimated material consumption is 21.1 grams and the print time is 24 minutes (Figure 5.17). All of this information can be

accessed from the machine's on-screen display after adjustments have been made. In this way, the amount of material to be placed in the machine's hopper is more obvious, and the estimated print time is useful for organising the trials.

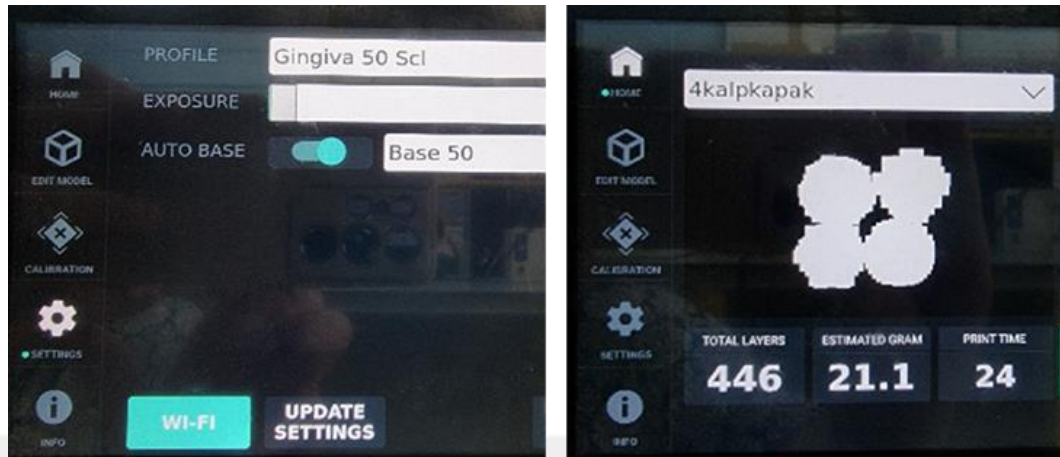


Figure 5.17 : The screen for setting the exposure time (left) and the screen for displaying information about the print.

The appearance of the valves on the platform after printing is shown in Figure 5.18. The first step is to remove the screws holding the platform in place and separate the platform from the machine. The models standing together with the support structures (Figure 5.19) should be separated from the platform using a spatula. This should be done very carefully to avoid damaging the model. The platform should also be cleaned so that no residue remains after the printing process. Any residue may cause the next model to be printed incorrectly.



Figure 5.18 : Post-printing view of the valve model we printed on the platform.

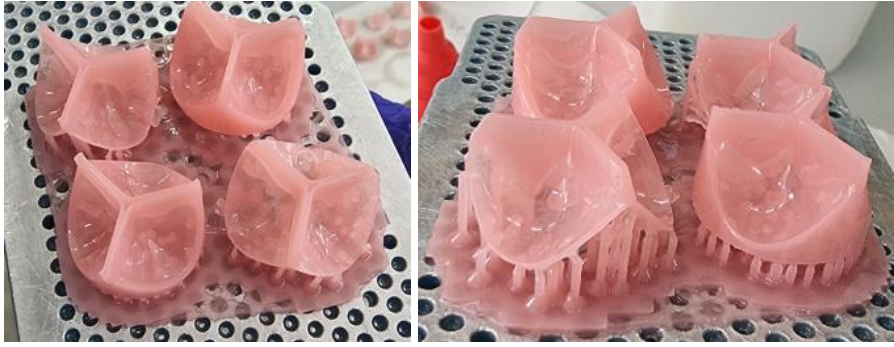


Figure 5.19 : View of the valve model we printed together with its support structure.

We carried out printing experiments using different percentages of exposure times (80%, 90%, 100% and 110%) (Figure 5.20). For example, if one layer of the model is not sufficiently exposed to UV, the layers may not fully adhere to each other. Unsuccessful printing of the model may be observed. Part of the model may remain in the tank. Layers may not continue to print and may be half printed. In addition, the softness of the model changes with different exposure time settings. Therefore, cracks may occur when the model is separated from the support structures. We had unsuccessful results during the printing phase of models without walls (Figure 5.21).

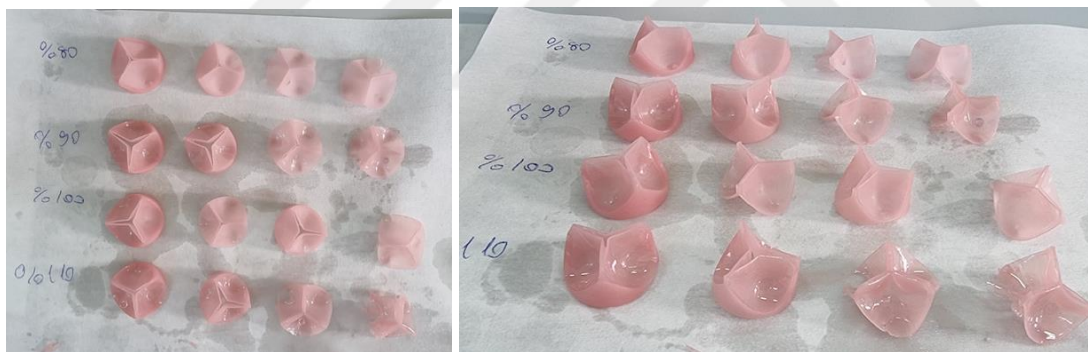


Figure 5.20 : Views of models we printed with different percentages of exposure time (80%, 90%, 100%, and 110%).

We experimented with 80% and 90% exposure time on different days. We obtained different printing defects from the results in Figure 5.21. Based on different results obtained on different days, we found that the printing results of this technique can vary depending on the ambient temperature, humidity and the amount of material in the chamber (even if it is more than the estimated amount indicated by the device). Not only the device parameters, but also the isolation of the environment in which the device is located, will improve the quality of the display and allow more consistent results to be obtained.

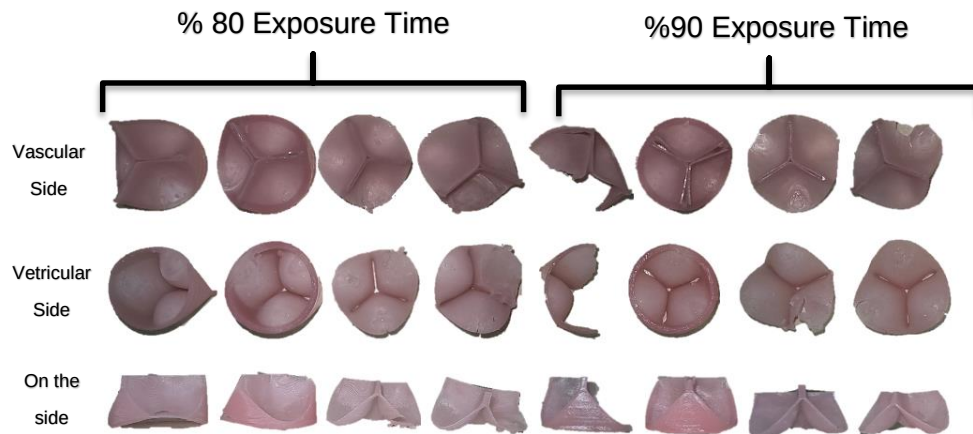


Figure 5.21 : Views of the models with 80% and 90% exposure time percentages

The structure of the model to be printed is very important. In addition to the support structures placed before printing, it is important to have structures in the design that make printing easier. For example, models with walls were more successful in production. However, as the leaflets are thin, choosing a much thicker wall will cause the model to break and deform with the movement of the leaflets, even if the model is successfully printed. It is also very important to adjust the amount of material placed in the print chamber of the DLP machine. The grams of material to be used, as specified by the machine, must be placed. However, in some cases it is not enough to put in the specified amount. More material should be added. The liquid material will harden and diminish in the areas where the UV comes in. Due to its high viscosity, it may not be distributed evenly in the chamber as it settles. This will cause curvature and incomplete printing. The percentage of exposure time also affects the print. If the layers are not sufficiently bonded and cured, they can both break off and disperse in the chamber during printing and quickly break off and disperse after printing.

The walled aortic valve model achieved better printing results than the other valve models. The images of the walled models printed from the model designed with 100% exposure time and 50 μ layer thickness are shown in Figure 5.22.

Although we were able to target the pressure, the material for the aortic valve remained stiff. The material was not flexible enough and there were cracks.

At the Nanotechnology and Biomaterials Application and Research Centre of Marmara University, pressure tests were carried out with Gingiva and Denta MODEL resins. Due to the inadequacies of the equipment and the fact that the parameters of

the prints produced there could not be adjusted and we could not produce products with the desired performance as shown in the figures (Figure 5.20), and because both models were not elastic enough. Therefore, the next printing process was planned in cooperation with Epoks Chemical Products Company, which has more advanced equipment and materials, and the printing process was planned and the details are given below.

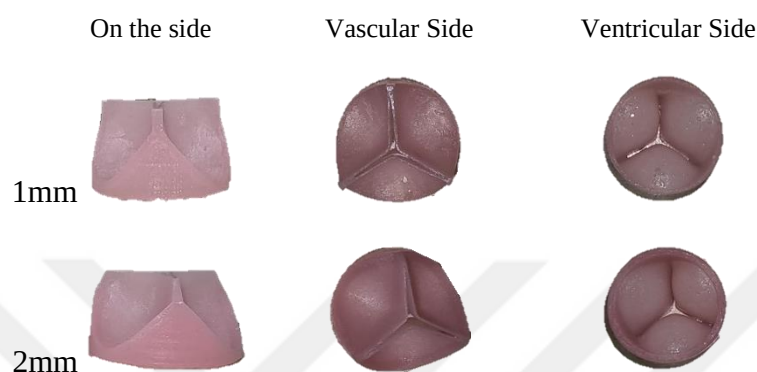


Figure 5.22 : Views of models with wall thicknesses of 1 mm and 2 mm, as a result of printing at 100% exposure time percentage

Printing trials were carried out at Epoks Chemical Products Company, with whom we collaborated, using the Anycubic® Photon Mono M5s DLP device (Figure 5.23). Printing trials were carried out using Flexible-X, a flexible resin, and Elastomer-X, a resin with mechanical properties similar to silicone. Pictures of these stages can be found in the section below.

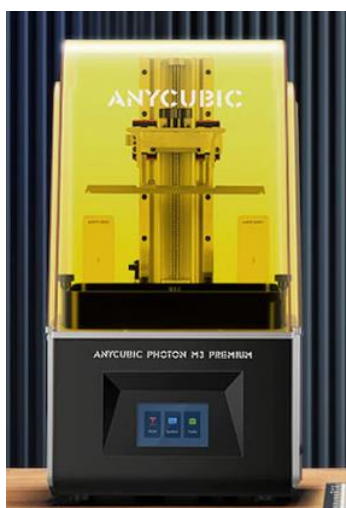


Figure 5.23 : Anycubic Photon Mono M5s DLP device.

A compression test with Flexible-X resin was performed to observe the elasticity of the material. However, as a result of the production (Figure 5.24), the material was not elastic enough for the aortic valve.



Figure 5.24 : Fabricated image of the aortic valve for Flexible-X resin.

Elastomer-X resin is a material with a lower hardness than the resins used in the DLP machine. This makes it more difficult to print than other materials. Especially in a thin and detailed design such as an aortic valve, this production process is even more challenging. At this stage, trial and error was used to try different parameters to get the right print for the design. Different combinations of layer thickness and exposure time were tried to see which would give the appropriate print for the design. Figure 5.25 shows the information on the parameters that gave incorrect results and the print results. Elastomer-X resin is a material with a lower level of hardness compared to the resins used in the DLP machine. This makes it more difficult to print than other materials. This makes the production process even more challenging, especially for a design that is both thin and detailed, such as the aortic valve. At this stage, a trial and error approach was used to test various parameters in order to achieve a suitable print for the design (Figure 5.25). It was attempted to determine which of the various combinations of layer thickness and exposure time would give the appropriate print for the design. Figure 5.25 shows the information for the parameters that gave incorrect results and the print results.

As the dimensions of the design are small and the design is curved and detailed, a trial and error method was used for successful production. Figure 5.26 shows the print parameters that ensure the print result is suitable for the design.

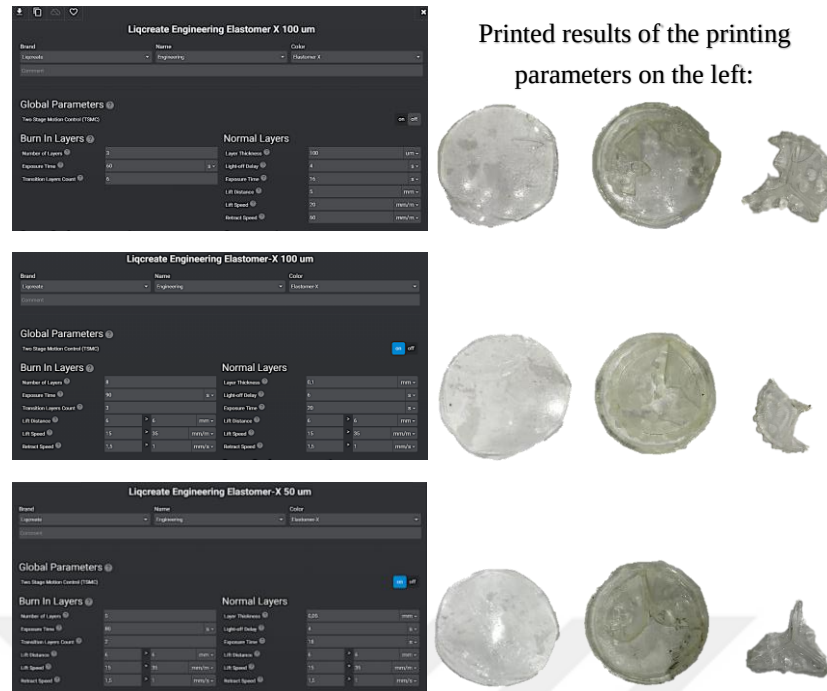


Figure 5.25 : Printing parameters and produced views of the trials that resulted in faulty printing.

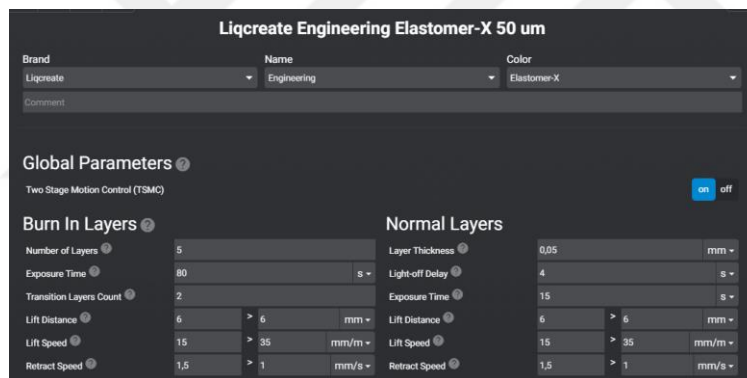


Figure 5.26 : Printing parameters result in printing following the design.

The production result that provides the desired material elasticity is shown in Figure 5.27 and Figure 5.28. Figure 5.27 shows the freshly printed version. Wetness and tackiness are observed in the model separated from the support structures prior to post production cleaning and final curing.

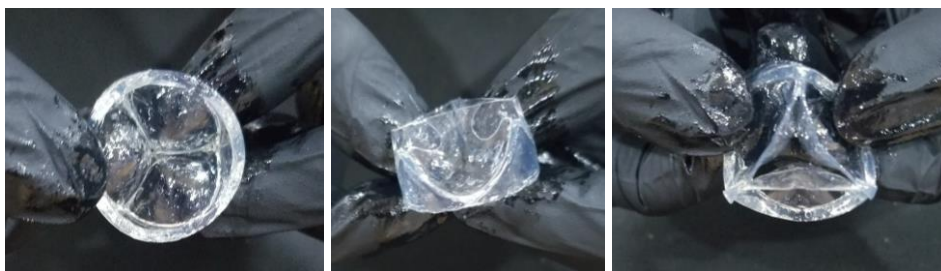


Figure 5.27 : The model is fresh off the press.

Figure 5.28 shows the state of the model after removing the wetness and stickiness from the support structures. Various cleaning and final curing procedures were carried out to achieve this. Information on the cleaning procedures is given in the following sections.



Figure 5.28 : Production results are printed by the design.

Figure 5.29 shows aortic valve models printed by the design in production trials.



Figure 5.29 : Views of the printed productions by the design as a result of printing trials

The DLP manufacturing process enables high-precision product manufacture with micron-scale layering. It was possible to print in sufficient detail to match the delicate structure of the aortic valve geometry. Printing trials were carried out with DentaModel, Flexible-X, GIngiva and Elastomer-X resins. The heart valve model using DentaModel and Gingiva resin was produced at the Nanotechnology and Biomaterials Application and Research Centre of Marmara University. Those made with Flexible-X and Elastomer-X resin were realized by Epoks Chemical Products Company. Among the materials, Elastomer-X has a hardness of 43 Shore A. Therefore, the product with the highest elasticity was the model made with Elastomer-X.



6. PROSTHETIC HEART VALVE CHARACTERIZATION METHODS

Heart valves open and close around 40 million times per year and approximately 3 billion times in an average lifetime. Prosthetic heart valves must be able to withstand the physiological and hemodynamic changes they will encounter. The ISO 5480 standards outline the conditions that heart valve prostheses must meet. This chapter will discuss hydrodynamic tests, structural tests, structural component fatigue tests, crushing tests, and accelerated fatigue tests.

6.1 Hydrodynamic Assessment

To assess the hydrodynamic efficiency of prosthetic heart valves in relation to blood, they should be tested under physiological conditions in non-patients and under various pathological conditions in patients. According to ISO-5480 standards, hydrodynamic testing should be conducted under both steady and pulsatile flow conditions.

6.1.1 Steady flow test

Performance measurements can be conducted by subjecting heart valve prostheses to constant flow cycles, following ISO 5840 standards. A straight tube with a diameter of 35 mm can be used to create a constant flow cycle. The properties of the saline solution to be used in the experiments are as follows: density of 1005 kg/m³ and viscosity of 1.0 cP. The pressure difference across the valve should be measured in 5 L/min increments over a flow rate range of 5-30 L/min. The pressure taps for the test rig must be positioned 35 mm (one pipe diameter) upstream and 10 mm (three pipe diameters) downstream of the valve. The static leakage should range from 40-200 mmHg at five backpressures. Figure 6.1 illustrates the setup for steady flow testing and the flow loop. Steady flow tests also aid in determining the accuracy of pulsatile flow tests [85].

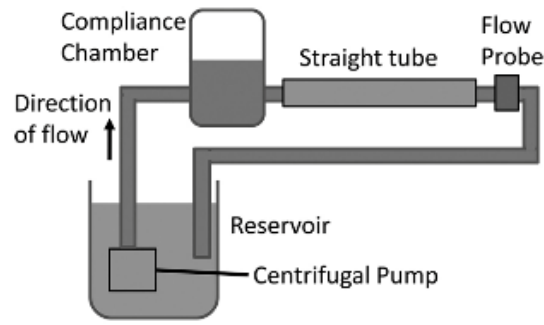


Figure 6.1 : Flow loop diagram for steady flow testing of heart valve prosthesis [85].

6.1.2 Pulsatile flow test

Heart valves experience pulsatile flow throughout their lifespan. The flow pattern in the cardiovascular system and testing of heart valve prostheses are crucial in assessing valve functionality. Flow systems are used to test pulsatile heart valve prostheses under conditions that simulate the cardiovascular flow system. A pulse multiplier can be used to simulate ventricular and arterial function and create a closed flow loop. A Pulse Replicator can achieve replication of the systemic circulation by incorporating a reservoir for the left atrium, a pump for the left ventricle, elements for aortic and peripheral compliance, and a resistance element for peripheral resistance (Figure 6.2) [10].



Figure 6.2 : Custom-made commercial pulse duplicator system [23].

Pulsed flow is created using a reciprocating diaphragm driven by hydraulic or pneumatic means. The transvalvular pressure gradient should be measured at a heart rate of 70 beats per minute and variable flow rates. Regurgitation volumes should be evaluated under three different pressure conditions to simulate hypotensive, normotensive and severe hypertensive conditions. The pressure and flow waveforms

obtained from a heart valve prosthesis should closely resemble the physiological conditions for the intended prosthetic valve application. To achieve this, it is necessary for pulsatile flow systems to mimic the physiological environment, which requires the geometry of the system to resemble the shape of the heart. In this study, geometrically similar structures made of different materials (acrylic, glass, silicone, etc.) and aortic roots taken from cadavers were used for the system. The working fluid properties should have a viscosity of 3-4 cP and a density of 1060 kg/m³.

6.2 Accelerated Wear Testing

Heart valve prostheses may experience wear and tear over time, which must be assessed before implantation. To simulate this wear and fatigue, accelerated wear testing is used. It is crucial that heart valve prostheses can withstand at least 200 million cycles in the human body, which is equivalent to approximately 5 years. For MHVs, the recommendation is 400 million cycles, equivalent to approximately 10 years. Figure 6.3 provides an example of an accelerated durability test.

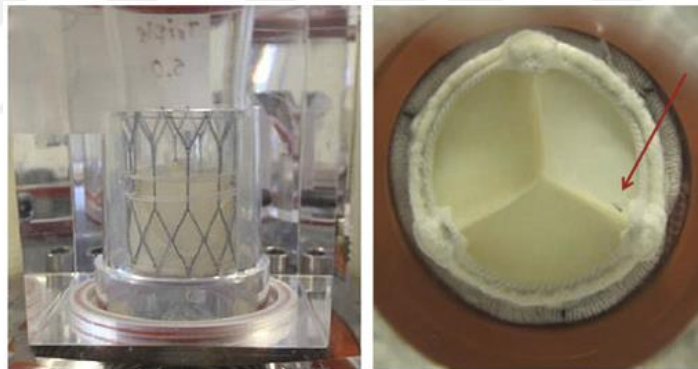


Figure 6.3 : View of the accelerated durability test (Left) and the heart valve prosthesis (Right) after 500 million cycles (approx. 12.5 years). Pinhole deformation is observed [86].

To conduct an accurate durability test, it is necessary to maintain the transvalvular pressure difference for 95% of the cycles and ensure that the peak differential closing pressure is greater than 95 mmHg. This will ensure that the valves perform the opening and closing phases in each cycle. The fluid used in the system should be at 37°C, which is the average body temperature. To monitor the system during this process, it is recommended to conduct periodic transvalvular pressure measurements on a daily basis, macroscopic examinations every 25 million cycles, microscopic examinations every 25 million cycles, and hydrodynamic evaluations.

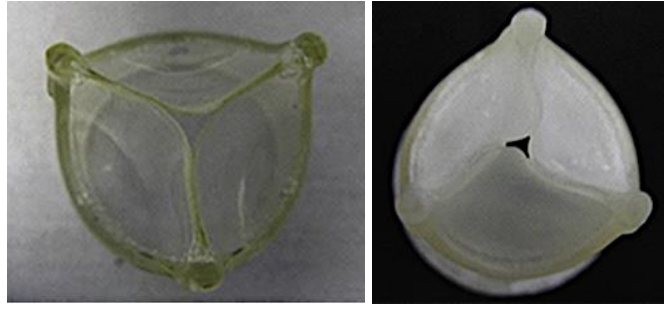


Figure 6.4 : Variation of the Angioflex PHV after more than 50 million cyclic loads with calcification solution. Before is shown on the left and after on the right [86].

Valves are subjected to accelerated endurance tests where they are overloaded beyond their physiological limits, resulting in damage such as excessive deformation, pinholes in the leaflets, fraying, and delamination. However, there is no consistent correlation between test results and clinical data, and variations in results have been observed across different institutions where the tests are performed. In this context, the ISO 5480 standards recommend abrasion testing at physiological heart rate in addition to the accelerated abrasion test. As heart valves degenerate mechanically and due to calcification, calcification-enhancing solutions are added to the fluid used in the system to assess calcium depletion and deposition in the valves. Figure 6.4 illustrates the change in the heart valve prosthesis with calcification solution.

6.3 Structural Assessment

To conduct in silico analysis of PHVs, it is necessary to model the behavior of the intended material in a computer environment. As previously mentioned, constitutive models predict the physical behavior of materials under specific conditions. The coefficients of these models must be defined in the analysis programs. The coefficient numbers for the material models of the produced material are obtained as a result of tensile tests, which analyze the deformation behavior of the material under stress.

6.3.1 Uniaxial testing

Tensile tests involve subjecting a specimen to controlled stress until it breaks. This test can determine properties such as tensile force, breaking force, Young's modulus, Poisson's ratio, yield strength, and strain hardening. Uniaxial tensile tests are typically performed on isotropic materials. Figure 6.5 shows the uniaxial tensile test rig.

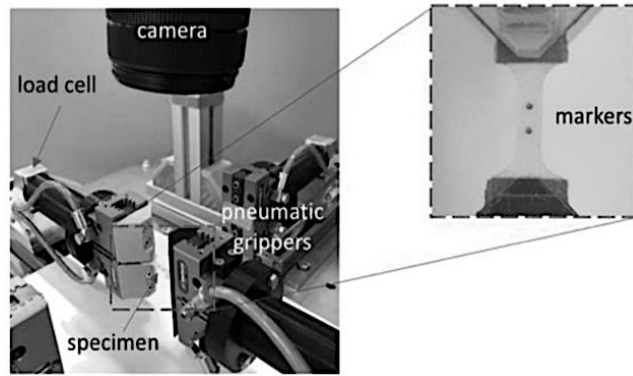


Figure 6.5 : Uniaxial tensile test rig [87].

Uniaxial and biaxial tensile tests were performed on biological tissues to better understand their mechanical properties for use in BHVs [87]. While uniaxial tests are limited to simulating only some physiological loading conditions, biaxial tests can more accurately simulate a wider range of conditions.

6.3.2 Planar testing

The planar test is distinct from the uniaxial tensile test in that it involves the presence of lateral stresses. Planar stresses are measured during this test. Specimens with a length considerably longer than the slope length are tested. The jaws are used to prevent the specimen from narrowing in width (refer to Figure 6.6). The specimen is clamped with four screws to ensure secure holding by the jaws. Perpendicular lines were drawn with a white marker along the two main axes to measure the axial extension and transverse contraction of the specimens.

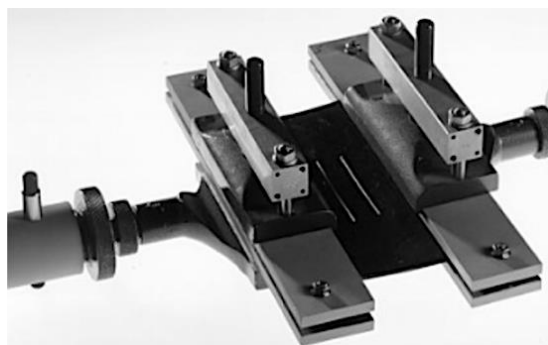


Figure 6.6 : Planar specimen and grips [88].

Planar test results are also used to find the coefficients of the material models.

6.3.3 Biaxial testing

The tissues of heart valves have a layered structure, which adds anisotropic properties to the tissue. To test the specimen in a manner more similar to physiological loading, the biaxial tensile test is used. In this test, specimens are fixed in four linear arms, as shown in Figure 6.7. Strain measurements can be taken by sprinkling graphite on the surface, and a camera is used to observe the displacement of these markers over time. To simulate a physiological environment, the normal saline bath was heated to 37C.

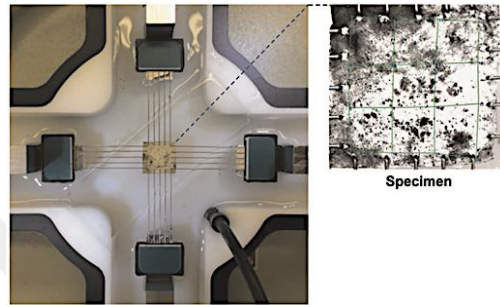


Figure 6.7 : Biaxial tensile test view of bovine pericardium [89].

If testing soft tissues, it is necessary to precondition them from an unloaded to a loaded state before beginning the measurement test. This is achieved by applying a load at a certain percentage of the maximum load in a specific cycle. The tissue is aligned with this loading, and the targeted test can then be performed using force or displacement-controlled cycles. Strain maps are generated to provide information about the mechanical properties of the specimen. Image tracking software is utilized. Various techniques are used to model the fiber structures of soft tissues. Two of these techniques are small angle light scattering and harmonic generation microscopy. Small angle light scattering is used to map rough collagen fiber orientation, while harmonic generation microscopy is used to characterize the organization of collagen fibers.

In 2023, A. Rassoli et al. conducted a study on human aortic valve leaflets obtained from healthy donors. The tissue samples underwent uniaxial and biaxial tensile testing within 8 hours of receipt, following storage in saline to preserve them. The thickness of the tissue varied continuously, so the average thickness was used to evaluate the samples that were cut into segments. The study comprized both uniaxial and biaxial tensile tests (refer to Figure 6.8).

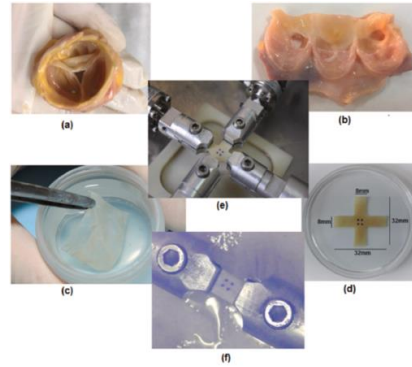


Figure 6.8 : Analysis of tissue from human aortic valve leaflets in uniaxial and biaxial tensile testing. a) Human aortic valve, (b) aortic valve leaflets, (c) specimen preservation in saline, (d) cross-shaped specimens, (e) a specimen under biaxial tension, (f) a specimen under uniaxial testing [90].

6.3.4 Triaxial testing

Triaxial mechanical testing is a method used to determine the mechanical movements of tissue outside the planes used in uniaxial or biaxial testing. Studies have been conducted on various cardiovascular tissues, but no testing devices have yet been developed to measure fine structures such as heart valves. However, this type of testing on heart valve tissues shows promise for more realistic studies.

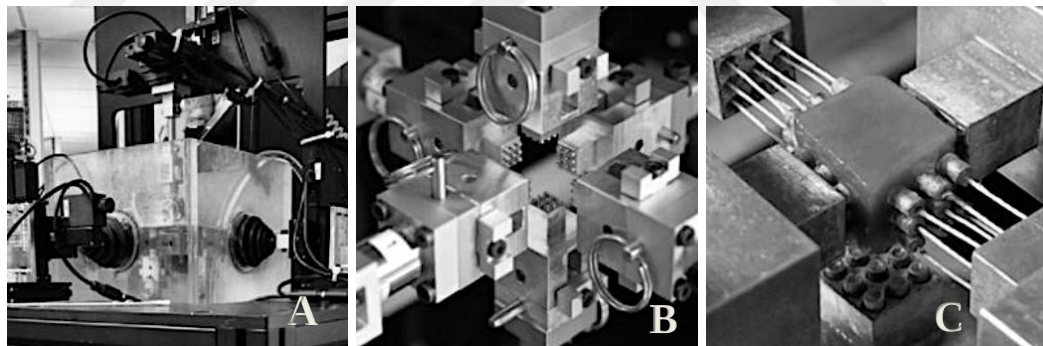


Figure 6.9 : Images of the TRIAX instrument, pad connections and pins connected to the sample. A) View of connection systems and liquid bath. B) View of the pad connection systems. C) View of the 9 pins on the pad attached to the sample [91].

6.3.5 Inverse finite element analysis

Inverse finite element analysis is a method used to analyse the mechanical properties of a heart valve prosthesis by studying the motion of the leaflets. Inverse finite element analysis can be performed using experimental optical measurements. The measurement system used in this technique is digital image correlation (DIC), which analyses deformation under physiological conditions (refer to Figure 6.10). DIC enables us to find the displacements and strains of the leaflets for deformation analysis

(refer to Figure 6.11). This facilitates the transfer of the anisotropic properties of the leaflets to the simulation.

There are two high-speed cameras in the DIC system. The cameras capture a stereometric image of the solid, which provides information about its volume and size. The data is generated with reference to random speckles that are added to the object (Figure 6.11).

The DIC system comprises of two high-speed cameras that capture a stereometric image of the solid, providing information about its volume and size. The data is generated with reference to random speckles that are added to the object (refer to Figure 6.11).

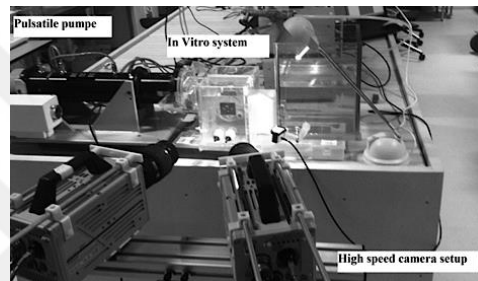


Figure 6.10 : View of the components of the DIC system. The movement of the heart valve prosthesis under physiological conditions is recorded [92].

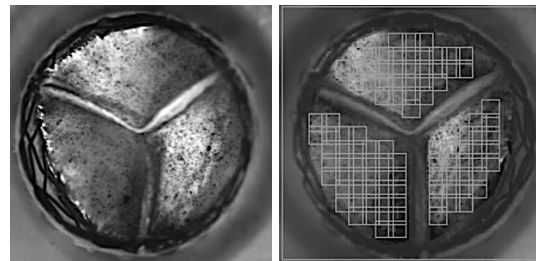


Figure 6.11 : DIC application of a heart valve prosthesis. Leaflets were speckled using ink with particles smaller than $1\text{ }\mu\text{m}$ (left). A post-processed version of the experimental data is shown (right). The pixels of the leaflets are marked with squares according to their gray level [92].

6.4 Fatigue Assessment of Structural Components

To assess the fatigue of structural components in heart valve prostheses, it is necessary to perform stress/strain analysis of the valve components through in silico loading with FEA. It is important to simulate the conditions at each stage, from the manufacturing stage to the application of the implant to the patient, to ensure that the loads are inclusive. Stress life characterization is then performed to verify the predictions

resulting from the stress-strain analysis, allowing for the evaluation of fatigue life. The fatigue safety factor is determined by comparing the results of the material's fatigue characterization tests.

6.5 Corrosion Assessment

Heart valve prostheses may contain metallic components to improve their durability. It is important to ensure that these components are corrosion-resistant to prevent valve failure. However, it is also important to consider the potential for immune responses and allergic reactions. Therefore, both pre- and post-fatigue tests should be conducted.

Additionally, corrosion resistance assessment is expected in transcatheter heart valve (THV) prostheses due to the presence of a metal stent. The evaluation of this study is challenging due to the difficulty in linking the analysis results with the in vivo response. Manufacturers must justify the acceptance criteria for the number of samples used in the analysis [85].

In this study, the material was produced with DLP and subjected to uniaxial and planar tensile tests. The aim is to revise the design using the strain-stress information obtained from the tests. Material model constants should be determined, and the design should be analyzed in silico again.



7. ASSESSMENT OF THE DESIGN PROCESS

The design process is evaluated by subjecting the Elastomer-X material, produced successfully, to mechanical tests. The test data is then adapted to the material model through a curve fitting process to obtain constants for different material models used in the literature. The following sections provide information about these stages.

7.1 Preparation of Specimens for Mechanical Testing

The DLP production technique is a novel method for producing polymeric aortic heart valves. It is commonly used in the biomedical field to print structures such as scaffolds for tissue engineering studies. Our study aims to use this technique to print the desired design with a material that meets the necessary flexibility requirements.

The resin is cured layer by layer using UV light, resulting in a three-dimensional structure formed by the layers that adhere to each other. The mechanical properties of Elastomer-X resin produced with this additive manufacturing technique were evaluated using uniaxial and planar tests in collaboration with the İTÜ Mechanical Faculty Biomechanics Laboratory. Figure 7.1 and Figure 7.2 provide the dimensions of the specimens to be used in these tests. The specimens were produced to adhere to these dimensions.

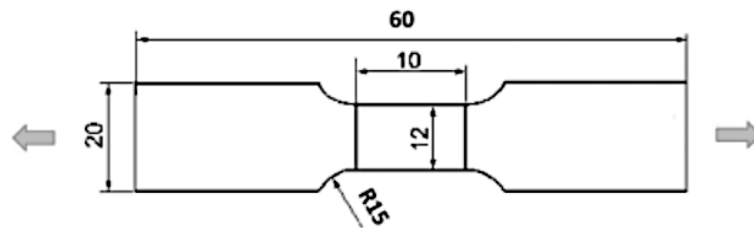


Figure 7.1 : The dimensions of the specimen to be prepared for the uniaxial test are written. Dimensions are planned in millimeters.

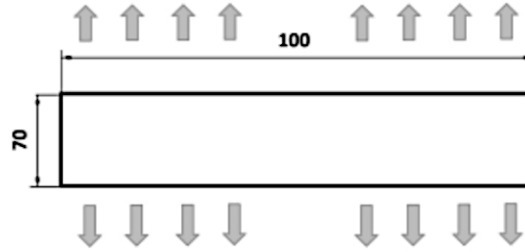


Figure 7.2 : The dimensions of the specimen to be prepared for the planar test are written. Dimensions are planned in millimeters.

The samples were printed in various ways on the DLP device's platform positioned along the x, y and z axes, in cooperation with Epoks Chemical Products Company. The mechanical tests conducted on these specimens aim to demonstrate the impact of the additive manufacturing technique on the alteration of mechanical properties.

Figure 7.3 provides the necessary parameters for printing Elastomer-X resin test specimens on the DLP device. Additionally, Figure 7.4 displays models of the intended print in the x, y, and z axes based on the DLP device platform. The samples' appearance during the printing stage and upon completion is depicted in Figure 7.5.

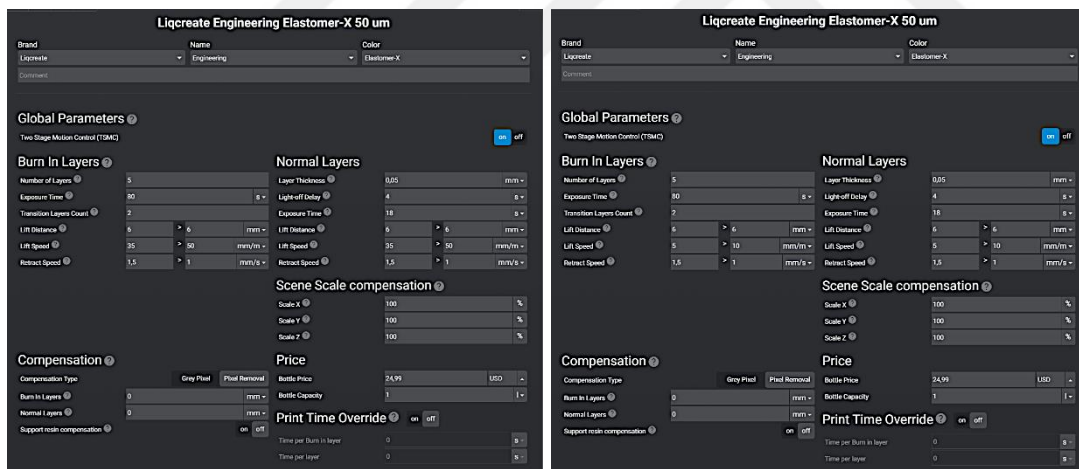


Figure 7.3 : Printing parameters. The printing parameters for the x and y axis are given on the left and the printing parameters for the z axis are given on the right.

Additionally, Figure 27 shows the models of the targeted pressure in the x, y and z axes according to the DLP device platform. The appearance of the samples during the printing phase and at the end of printing is shown in Figure 7.4.

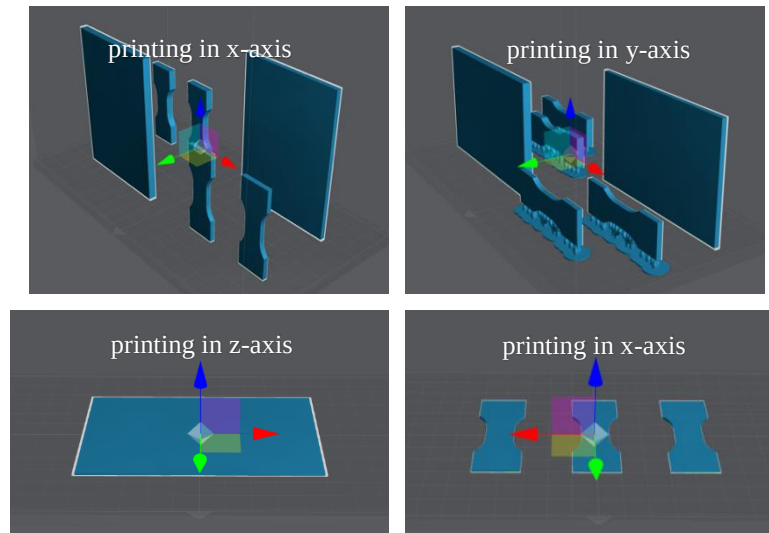


Figure 7.4 : Targeted print in x, y, and z axes relative to the DLP device platform.

Figure 7.5 shows the appearance of the samples during and after printing. Particularly, the deformed sample from the planar test samples shown in Figure 28-D has shown that 3 mm thickness does not allow production due to the elasticity of the material. The 5 mm thick sample enabled the printing of the planar test sample.

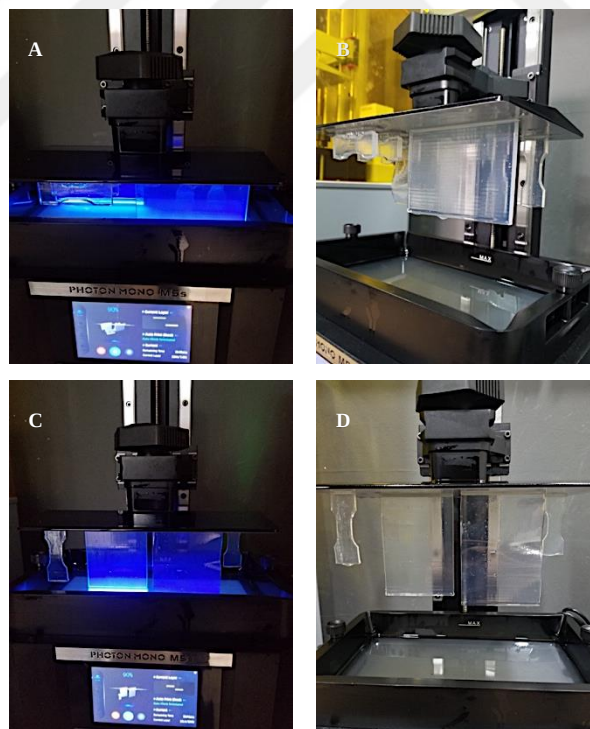


Figure 7.5 : Views of the specimens during and after printing. A) View of the sample during printing in x-axis. B) The view of the specimen printed on the x-axis on the device after the printing is finished C) The view of the specimen printed in the y-axis. D) View of the printed sample on the Y-axis in the device after printing.

After printing, the specimens should be separated from the platform with care. Figure 7.6 displays the process of separating the specimen from the platform using a spatula.

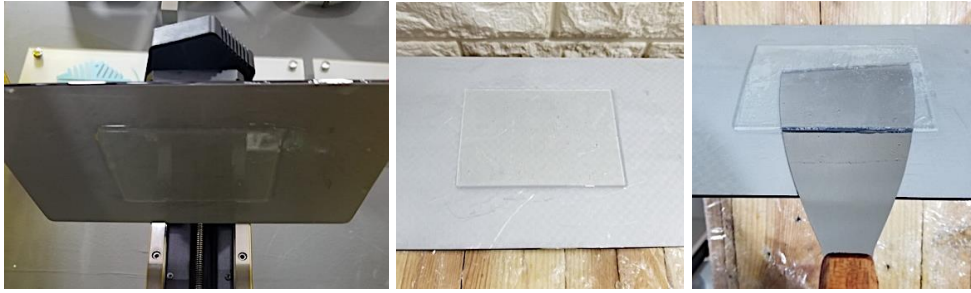


Figure 7.6 : Views of the sample printed in the z-axis on the platform. View on the device after printing (left). View of the sample adhered to the platform when the platform is detached from the device (center). Using a spatula to remove the sample from the platform (right).

The Elastomer-X resin is a soft material that resembles silicone. Sticky situations may arise on surfaces after the model is printed. To prevent this stickiness, cleaning steps are necessary after printing. Firstly, the samples are cleaned in water using an Anycubic wash&cure device for 5 minutes (refer to Figure 7.7).



Figure 7.7 : The test specimen is cleaned in water in the Anycubic wash&cure device for 5 minutes. The test sample is where the star symbol is.

The samples undergo a 25-minute cleaning process in the Crework ultrasonic cleaning device (Figure 7.8). Due to the high flexibility of the Elastomer-X material, it requires ultrasonic cleaning to ensure the adhesive structure is fully penetrated.



Figure 7.8 : The sample is cleaned in the Crework ultrasonic cleaning device for 25 minutes.

Finally, the sample is cured in Formlabs (Figure 7.9) to increase its stability. This step ensures that the samples become more stable.

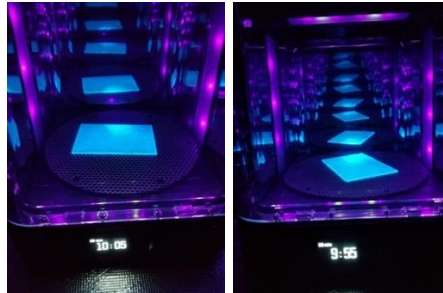


Figure 7.9 : View of the final curing process of the specimen in Formlabs device.

Figure 7.10 shows the final appearance of the samples used for uniaxial testing, while Figure 7.11 shows the final appearance of the samples used for planar testing. The images provide information on the thickness and compression axes of the samples.



Figure 7.10 : Specimens for the uniaxial test. The thickness and compression axes of the specimen are given in the images.

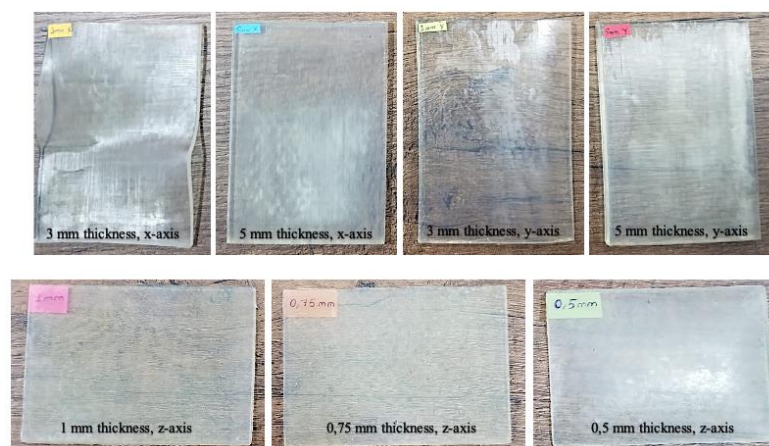


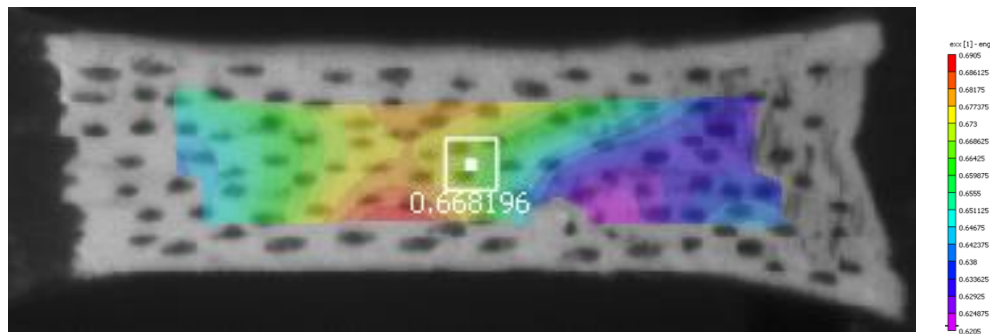
Figure 7.11 : Specimens for the planar test. The thickness and compression axes of the specimen are given in the images.

7.2 Testing

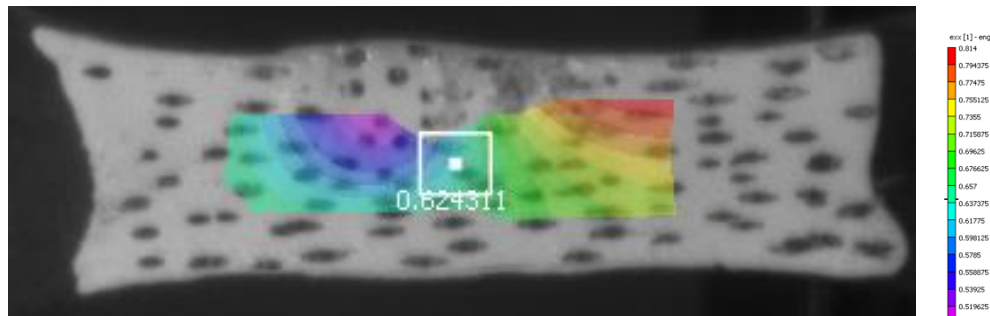
Uniaxial tensile and planar tests were conducted on the samples at the Biomechanics Laboratory of Istanbul Technical University, Faculty of Mechanical Engineering. Figure 7.12 shows images of samples with varying thicknesses during the uniaxial tensile test, while Figure 7.13 displays images of samples with varying thicknesses during the planar test. In the uniaxial tensile test, stress is expected to be lower in regions close to the support and higher in the middle regions for linear elastic materials. Figure 7.11 shows the stresses on the x-axis, with dots marking the midpoints of the samples. The middle area of the material experiences greater tension than the areas closer to the support, with tension increasing towards the ends of this region.



A) 0.5 mm thickness



B) 0.75 mm thickness



C) 1 mm thickness

Figure 7.12 : Views of samples of different thicknesses during the uniaxial tensile

Figure 7.13 shows the axial stresses. In planar testing, shear stresses are expected to be higher in the regions closer to the support and lower in the middle regions. Therefore, it is expected to see less tension in the central regions.

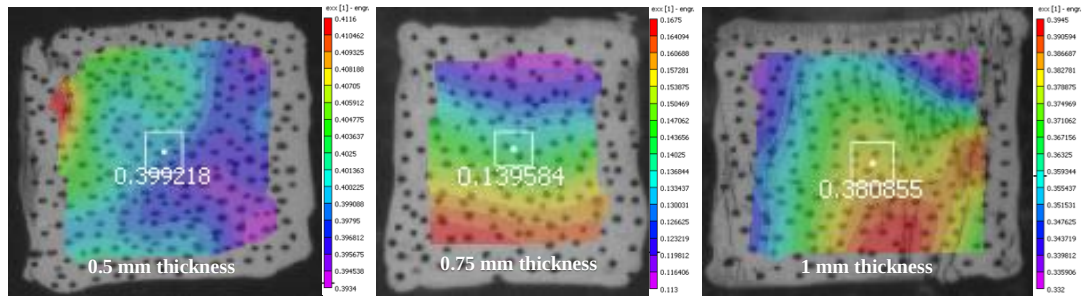


Figure 7.13 : Views of samples of different thicknesses during planar testing.

Figure 7.14 displays images of samples with varying thicknesses during planar testing, with transverse stresses highlighted in colour. As seen in both Figure 7.13 and Figure 7.14, stress levels are lower in the central regions.

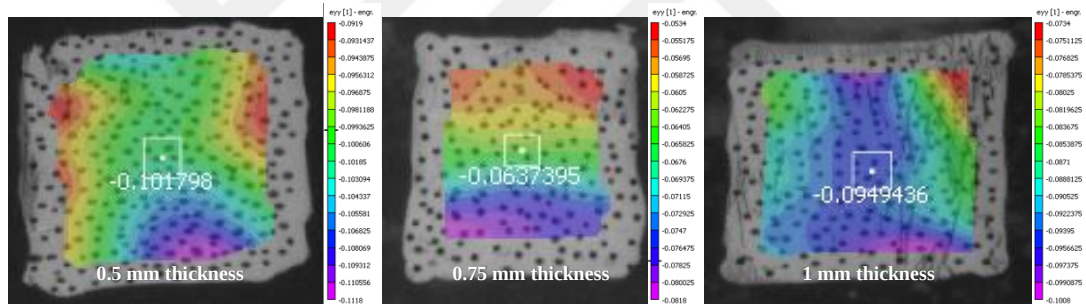


Figure 7.14 : Views of samples of different thicknesses during planar testing.

The following graphs present the mechanical test results of samples with different thicknesses. Figure 7.15 shows the force-axial strain for uniaxial tensile test, Figure 7.16 shows the force-axial strain for planar test, and Figure 7.17 shows the force-transverse strain for planar test. The strain increases as the force value increases.

According to the graph in Figure 7.15, the 0.5 mm thick sample has the highest axial tensile capacity for the uniaxial tensile test. All samples showed a linear increase, indicating linear material properties..

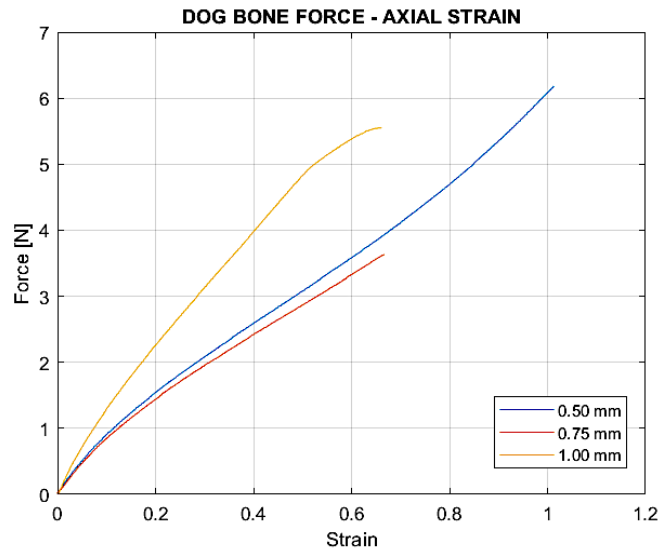


Figure 7.15 : Dog bone force axial strain graph for the uniaxial tensile test for specimens of different thicknesses

According to Figure 7.16, the 0.5 mm thick sample exhibited the highest axial tensile capacity for the planar test. Additionally, it showed a more linear increase than the other samples.

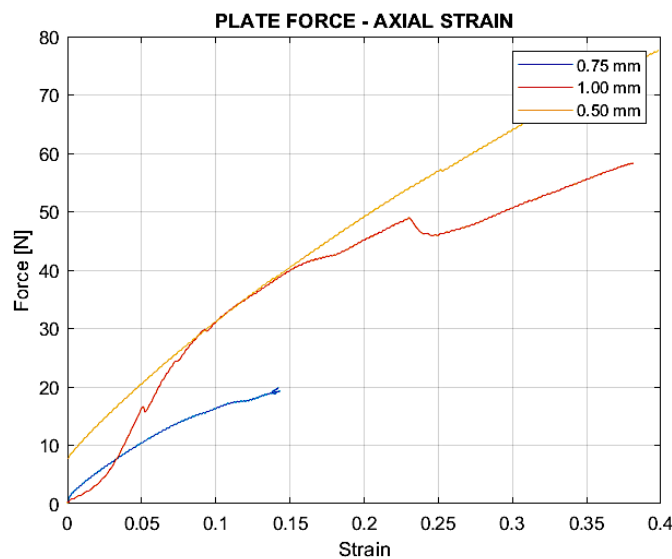


Figure 7.16 : Plate force axial strain graph for the planar test for specimens of different thicknesses

According to Figure 7.17, the 0.5 mm thick sample exhibited the highest transverse tensile capacity for the planar test. Additionally, the 0.5 mm and 0.75 mm thick samples demonstrated a more linear increase in comparison to the 1 mm thick sample.

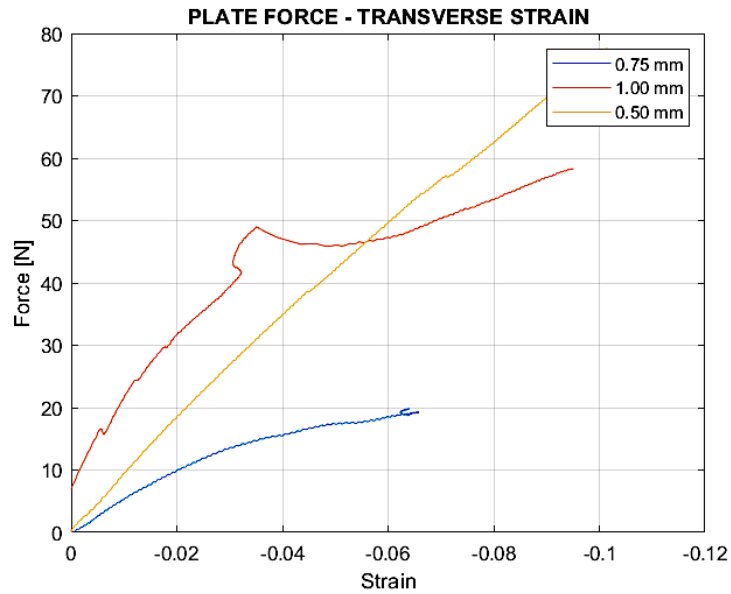


Figure 7.17 : Plate force transverse strain graph for the planar test for specimens of different thicknesses

The following comments can be made about the mechanical behavior of Elastomer-X material from the graphs obtained as a result of the test. In the tests carried out, it was observed that the 0.5mm thick sample had the highest tensile strength. It appears to have linear material properties.



8. OPTIMIZATION AND VALIDATION

The model of the heart valve prosthesis was successfully realized using the DLP production technique. As a result of production with Elastomer-X material, the model was found to have the desired softness. With the DLP production technique, the mechanical test results of this material are used to obtain the number of layers in the material model used in the computerized analysis of the design. While the design was being developed, analyzes were initially made with reference to the literature. Various optimization techniques were used to obtain the material coefficient from the data of the tests performed on the samples. FEM analysis was performed again using the coefficient number. In this section, these optimization and validation processes will be detailed. Standard tests can also be used to calibrate the parameters of material models. To obtain material model constants from mechanical tests, it is necessary to consider the stress equations of the material models under different loading conditions. Table 8.1 shows the stress equations for different loading conditions for different material models [93].

Table 8.1 : The stress equations for various loading conditions for different material models [93].

Model	Loading	Stress Equation	Referances
Neo-Hookean	Uniaxial Loading	$\sigma_{uniax} = \mu \left(\lambda^2 - \frac{1}{\lambda} \right)$	[93]
	Planar Loading	$\sigma_{planar} = \mu \left(\lambda^2 - \frac{1}{\lambda^2} \right)$	[93]
	Biaxial Loading	$\sigma_{biaxal} = \mu \left(\lambda^2 - \frac{1}{\lambda^4} \right)$	[93]
Mooney-Rivlin	Uniaxial Loading	$\sigma_{uniax} = 2 \left(\lambda^2 - \frac{1}{\lambda} \right) [C_{10} + \frac{C_{01}}{\lambda}]$	[93]
	Planar Loading	$\sigma_{planar} = 2 \left(\lambda^2 - \frac{1}{\lambda^2} \right) [C_{10} + C_{01}]$	[93]
	Biaxial Loading	$\sigma_{biaxal} = 2C_{10} \left(\lambda^2 - \frac{1}{\lambda^4} \right) + 2C_{01} \left(\lambda^4 - \frac{1}{\lambda^2} \right)$	[93]

Table 8.1 (continued): The stress equations for various loading conditions for different material models [93].

Model	Loading	Stress Equation	References
Ogden	Uniaxial Loading	$\sigma_{uniax} = \sum_{k=1}^N \frac{2\mu_k}{\alpha_k} [\lambda^{\alpha_k} - \left(\frac{1}{\sqrt{\lambda}}\right)^{\alpha_k}]$	[93]
	Planar Loading	$\sigma_{planar} = \sum_{k=1}^N \frac{2\mu_k}{\alpha_k} [\lambda^{\alpha_k} - \left(\frac{1}{\lambda}\right)^{\alpha_k}]$	[93]
	Biaxial Loading	$\sigma_{biaxal} = \sum_{k=1}^N \frac{2\mu_k}{\alpha_k} [\lambda^{\alpha_k} - \left(\frac{1}{\lambda^2}\right)^{\alpha_k}]$	[93]
Prony Series	Stress-relaxation Loading	$\sigma(t) = \varepsilon_0(E_0 + \sum_{i=1}^I E_i e^{-\frac{t}{\tau_i}})$	[94]

Curve fitting and material constant calculations of the test data according to different material models were performed using the ANSYS® Engineering Data module. Uniaxial tensile tests and planar tensile tests of the specimens printed on the x-axis were loaded into the program. After selecting the material model, there is an Error Norm for Fit option under the Curve Fitting tab as shown in Figure 8.1. There are Normalized Error and Absolute Error options.

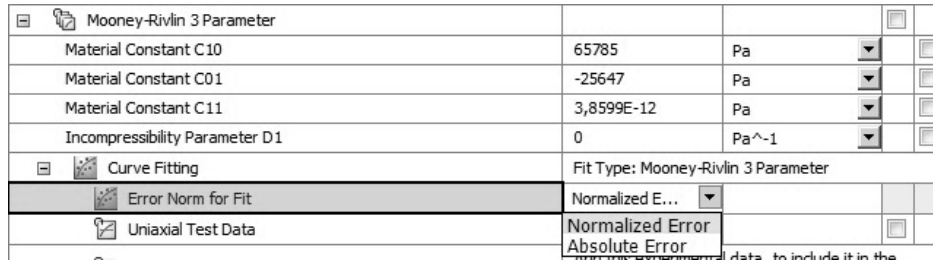


Figure 8.1 : View of Error Norm for Fit options

The Absolute Error formula is as follows.

$$E_{absolute} = \sqrt{\sum_{i=1}^N (\sigma_i^{trial} - \sigma_i^{experiment})^2} \quad (8.1)$$

The Normalized Error formula is as follows.

$$E_{normalized} = \sqrt{\sum_{i=1}^N \frac{(\sigma_i^{trial} - \sigma_i^{experiment})^2}{(\sigma_i^{experiment})^2}} \quad (8.2)$$

As shown in Figure 8.2, when Solve Curve Fit is selected, curve fitting is performed according to the selected model with the test data. The test data is best fitted with the Absolute Error option. When the Copy Calculated Values to Property option shown in Figure 8.2 is selected, the constant information of different material models is obtained according to the test data.

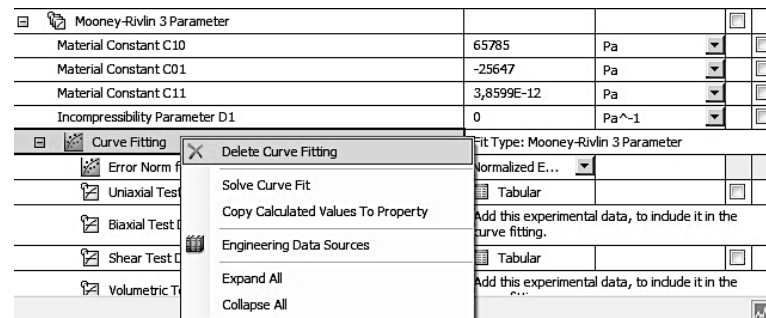


Figure 8.2 : View of Solve Curve Fit and Copy Calculated Values to Property

The material constants for specimens of different thicknesses printed on the x-axis are given in Table 8.2.

Table 8.2 : Material constants for specimens of different thicknesses printed on the x-axis

Model	Constants
Material constants for 0,5 mm thick specimen printed in x-axis	
Neo-Hookean	$\mu=1,6737\text{E}+05$ Pa; $d=0$
Mooney-Rivlin 2. Orders	$C_{10}=83333$ Pa; $C_{01}=352,69$ Pa; $d=0$
Mooney-Rivlin 3. Order	$C_{10}=83333$ Pa; $C_{01}=9408,2$ Pa; $C_{11}=-1,1557\text{E}-12$ Pa; $d=0$
Ogden 1. Order	$\mu=5,9134\text{E}+05$ Pa; $\alpha=1,9294$; $d=0$
Ogden 2. Order	$\mu_1=6,2531$ Pa; $\alpha_1=2,5296$; $\mu_2=6,2531$ Pa $\alpha_2=2,5288$; $d_1= d_2=0$
Ogden 3. Order	$\mu_1=5,5849$ Pa; $\alpha_1=2,5129$; $\mu_2=5,5849$ Pa $\alpha_2=2,5129$; $\mu_3=5,585$ Pa $\alpha_3=2,5129$; $d_1= d_2= d_3=0$
Material constants for 0.75 mm thick specimen printed in x-axis	
Neo-Hookean	$\mu=1,463\text{E}+05$ Pa; $d=0$
Mooney-Rivlin 2. Order	$C_{10}=55556$ Pa; $C_{01}=17656$ Pa; $d=0$

Table 8.2 (continued): Material constants for specimens of different thicknesses printed on the x-axis

Model	Constants
Mooney-Rivlin 3. Order	$C_{10}=65785 \text{ Pa}$; $C_{01}=-25547 \text{ Pa}$; $C_{11}=3,8599\text{E-}12 \text{ Pa}$; $d=0$
Ogden 1. Order	$\mu=9,1919 \text{ Pa}$; $\alpha=2,5446$; $d=0$
Ogden 2. Order	$\mu_1=4,0276 \text{ Pa}$; $\alpha_1=2,5511$; $\mu_2=4,0276\text{Pa}$ $\alpha_2=5,5528$; $d_1= d_2=0$
Ogden 3. Order	$\mu_1=2,9589 \text{ Pa}$; $\alpha_1=2,5469$; $\mu_2=2,9589 \text{ Pa}$ $\alpha_2=2,5462$; $\mu_3=2,9589 \text{ Pa}$ $\alpha_3=2,5465$; $d_1= d_2= d_3=0$
Material constants for 1 mm thick specimen printed in x-axis	
Neo-Hookean	$\mu=1,3523\text{E}+05 \text{ Pa}$; $d=0$
Mooney-Rivlin 2. Order	$C_{10}=67462 \text{ Pa}$; $C_{01}=153,01 \text{ Pa}$; $d=0$
Mooney-Rivlin 3. Order	$C_{10}=67462 \text{ Pa}$; $C_{01}=-17819 \text{ Pa}$; $C_{11}=2,6887\text{E-}12 \text{ Pa}$; $d=0$
Ogden 1. Order	$\mu=661,57 \text{ Pa}$; $\alpha=2,2987$; $d=0$
Ogden 2. Order	$\mu_1=3,5166 \text{ Pa}$; $\alpha_1=2,5518$; $\mu_2=3,5166 \text{ Pa}$ $\alpha_2=2,5542$; $d_1= d_2=0$
Ogden 3. Order	$\mu_1=3,8721 \text{ Pa}$; $\alpha_1=2,5512$; $\mu_2=3,8728 \text{ Pa}$ $\alpha_2=2,5568$; $\mu_3=3,8728 \text{ Pa}$ $\alpha_3=2,5264$; $d_1= d_2= d_3=0$

The process of evaluating the design process is the process of evaluating the successful pressure achieved as a result of production. Specimens of Elastomer-X material were fabricated for uniaxial tensile and planar testing. Mechanical tests were performed. The data from the mechanical tests were loaded into the ANSYS® program. These test data were used to generate constants for various material models used in the literature. In this way, constants were obtained for different material models used in the literature. Appendix A shows the plots generated from the test data for the specified material models.

The model obtained with Neo-Hookean material constants calculated for the 0.5mm thick sample was used. This model, which has an initial shear modulus of 167370 Pa, tends to change shape more than the Neo-Hookean model generated from the literature results shown previously. Figure 8.3 shows the equivalent stress values in the second period for the Neo-Hookean material obtained from the test data and the deformation of the aortic valve over time.

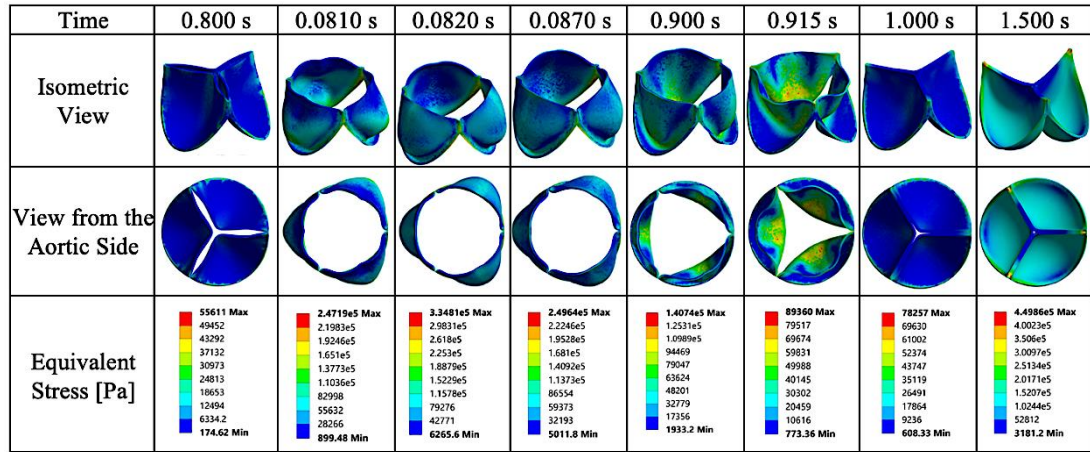


Figure 8.3 : Equivalent stress values taken in the second period for the Neo-Hookean material obtained with test data and deformation of the aortic valve over time. Image taken with special permission from Emirhan Yiğit, member of İTÜ Informatics Institute Computational Biomechanics Group and Mechanical Engineering Department

The highest equivalent stress values observed are broadly similar to the Neo-Hookean model modelled in the previous analysis. However, the aortic valve remains open for longer.

Data from uniaxial, planar and biaxial tests on Elastomer-x, the material of the manufactured model, are of great importance for the accurate modeling of material models. The tests carried out within the available resources are described in detail in the previous sections.

In this context, to support the reality of the models, the coefficients of the material models were obtained using data from biaxial tests performed on ascending aortic tissue in the literature. The test data were processed in the MCalibration® program. These test data were derived from the test results applied to the ascending aorta of a 54 year old individual in the study conducted by Labrosse et al. in 2013. The test data loaded into the program must be introduced in detail [97]. The loading modes are shown in Figure 8.4. For the biaxial test, the loading direction was determined as follows.

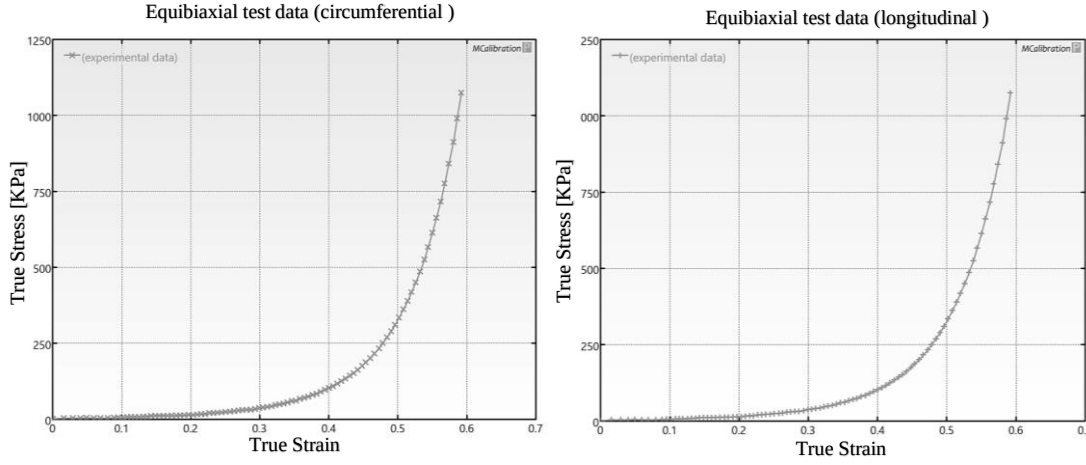


Figure 8.4 : Simulated stress–strain curves for planar equibiaxial test data of 54-year-old human ascending aorta under maximum tension of 2000 N/m.

The reference section contains critical information that forms the basis of the calibration. In this section, data units can be set in the Units section. Solver Type and Error Type are among the features that can be selected here. Error Type options include critical evaluation methods such as Normalized Median Absolute Difference, Mean Square Difference, Coefficient of Determination, Relative Error. General information on these error types is given below:

The Normalized Mean Absolute Difference (NMAD) is a statistical measure used to quantify the mean absolute difference between the corresponding values of two sets, normalized by a scaling factor. It is similar to the Mean Absolute Difference, but includes normalisation for better interpretability and comparability. The formula for calculating the NMAD is as follows

$$NMAD = \frac{1}{n} \sum_{i=1}^n \frac{|X_i - Y_i|}{MAD} \quad (8.3)$$

X_i and Y_i are corresponding values in two sets or distributions being compared. n is the number of data points. MAD is the Mean Absolute Difference, calculated as $MAD = \frac{1}{n} \sum_{i=1}^n |X_i - Y_i|$.

The NMAD is obtained by dividing the sum of the absolute differences by the Mean Absolute Difference, providing a normalized measure of the average discrepancy between the two sets. This normalisation is often useful when comparing differences between data sets with different scales. NMAD is widely used in various fields, including statistics and data analysis, as a robust measure of discrepancy that is less sensitive to outliers than other metrics [97].

The Mean Square Difference (MSD) is a statistical measure that quantifies the average squared difference between the corresponding values of two sets. It provides a way of assessing the overall discrepancy or variability between the values in two data sets. The formula for calculating the Mean Square Difference is given by:

$$MSD = \frac{1}{n} \sum_{i=1}^n (X_i - Y_i)^2 \quad (8.4)$$

X_i and Y_i are corresponding values in two sets or distributions being compared. n is the number of data points. The MSD involves squaring the differences between the corresponding values, summing these squared differences and then dividing by the number of data points. It provides a measure of the average squared deviation or error between the two data sets [98].

The Coefficient of Determination (R^2) is a statistical measure that assesses the proportion of the variance in the dependent variable in a regression model. It is used to evaluate the goodness of fit of the regression model. The formula for calculating the R^2 is given by:

$$R^2 = 1 - \frac{\text{Sum of Squared Residuals}}{\text{Total Sum of Squares}} \quad (8.5)$$

Sum of Squared Residuals is the sum of the squared differences between the observed values and the values predicted by the regression model. *Total Sum of Squares* is the sum of the squared differences between the observed values and the mean of the dependent variable.

The R^2 value ranges from 0 to 1, where:

$R^2 = 0$ indicates that the model does not explain any variability in the dependent variable. $R^2 = 1$ indicates that the model perfectly explains the variability in the dependent variable.

In general, higher R^2 values suggest a better fit of the regression model to the data. However, it is important to consider other factors, and R^2 should be interpreted in the context of the specific dataset and the goals of the analysis [99].

Relative error is a measure of the accuracy of an approximation compared to the true value of a quantity. It is often expressed as a percentage and provides insight into the magnitude of the error relative to the actual value. The formula for calculating the relative error is given by:

$$\text{Relative Error} = \left| \frac{\text{Approximate Value} - \text{True Value}}{\text{True Value}} \right| \times 100\% \quad (8.6)$$

Approximate Value is the estimated or calculated value. *True Value* is the actual or known value. A relative error of 0% indicates a perfect match between the approximation and the true value, while a higher percentage indicates a greater deviation or error from the true value. Relative error is a useful metric for assessing the accuracy of measurements or the accuracy of mathematical approximations.

In addition, the MCalibration® program offers various optimization methods. These methods include detailed options such as fast scanning and user-specified iteration numbers. The program is a powerful tool for producing more accurate models from experimental data.

In terms of optimization methodology, MCalibration® uses algorithms based on well-known optimization techniques such as random search, genetic algorithms, Levenberg-Marquardt, quasi-Newton (L-BFGS), global optimum search, automatic (using library models), NEWUOA. MCalibration® also recommends some methods. One of these methods is "Slow careful optimization from the current material parameter set (Simplex)". The other recommended methods are "Fast automatic method", "Extensive automatic method" and "Global search when initial parameters are poor (CMA-ES)" (Figure 8.5).

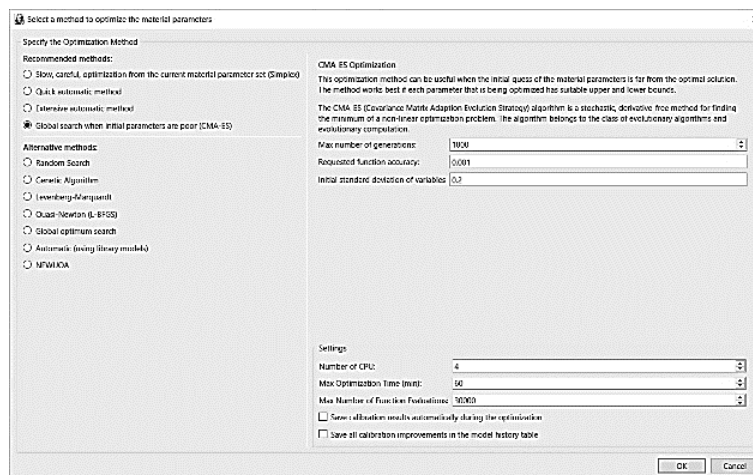


Figure 8.5 : View of the "Select a method to optimize the material parameters" page, showing the optimization techniques that must be selected to start the calibration in the MCalibration program.

If the option "Slow, careful, optimization from the current material parameter set (Simplex)" is selected, the Nelder-Mead Simplex algorithm is used. This algorithm is

very stable and robust. It is a useful method in cases where material parameters have correct relative values and are off. A minimum and maximum number of iterations can be specified. In addition, there is a calibration option to cycle until there is no improvement. In this way greater convergence can be achieved. The Nelder-Mead algorithm is an iterative optimization technique used for non-linear optimization problems. The typical steps of the Nelder-Mead algorithm are as follows.

Initialisation begins by selecting an initial set of $n+1$ points in the solution space, and the objective function is evaluated at each of these points. The points are then ordered by their function values, with the best point having the lowest function value and the worst point having the highest. Next, the centroid of the n best points (excluding the worst point) is calculated. A reflection operation is performed where the worst point is reflected through the centroid to obtain a new trial point, known as the reflection point. The objective function is then evaluated at this point. The function value of the reflection point is compared with the best, second worst and worst points in the simplex.

Depending on the results of the comparison, the set of points is updated. For example, if the reflection point is better than the best point, an expansion may be attempted. If the reflection point is worse than the second worst point, a contraction is considered. If the reflection point is better than the worst point but worse than the second worst point, the worst point is replaced by the reflection point. If no improvement is observed by reflection, contraction or expansion, the simplex is contracted or shrunk towards the best point. The algorithm checks for convergence based on specified criteria, such as a small change in the function values or the size of the simplex. If the convergence criteria are met, the algorithm stops and reports the best solution found. Otherwise, the process is iterated, repeating the above steps until convergence or a predefined number of iterations is reached [100].

Automatic optimization options include fast and extensive options. The quick automatic method is an optimization technique that is set to time out quickly, making it useful for performing quick calibrations. It finds the optimum material parameters by quickly switching between optimization techniques according to the data. This method does not use adjustable parameters. The comprehensive automatic method switches between different optimization methods to find the optimal set of material parameters. There are options to include random search at the beginning, Levenberg-

Marquardt search and NEWUOA search later. The “Repeat optimization until no further improvements” option is also available for the most accurate calibration possible.

The Covariance Matrix Adaptation Evolution Strategy (CMA-ES) is a versatile and powerful evolutionary algorithm that has been widely used for global optimization, uncertainty handling and minimisation of complex equations. Its ability to adapt the covariance matrix and efficiently navigate the search space makes it a valuable tool for a wide range of optimization problems. This optimization method can be useful when the initial guess of the material parameters is far from the optimal solution. The CMA-ES algorithm uses two main principles to adjust the parameters of the search distribution. The first principle is Maximum Likelihood. The mean of the distribution is maximized based on the successful solutions in the previous steps. Similarly, the covariance matrix of the distribution is adjusted accordingly, increasing the probability of previous successful search steps [101].

Random search is an optimization technique in which random samples are taken from a predetermined search space. It is a simple, effective and efficient way to explore the solution space. It does not get stuck in local optima. Random search has been shown to be effective in scenarios where the search space is high dimensional or non-convex, making it a valuable tool in optimization problems with complex and diverse solutions.

Random search is used to sample hyperparameters from a pre-defined range and provides a cost-effective approach. Random search has been shown to be as competitive as more advanced optimization methods such as grid search and Bayesian optimization, especially in high-dimensional spaces [102].

Genetic algorithms (GAs) perform optimization inspired by the process of natural selection and genetics. They are widely used in various fields due to their ability to effectively search large and complex solution spaces. Gas use genetic operators such as selection, crossover and mutation. Solution populations consist of candidate solutions over successive generations.

Each individual in the population is evaluated in terms of its fitness, which indicates how the optimization problem can be solved for each individual in the population based on the objective function. Individuals with high fitness for the next generation are selected from the population to serve as parents. New individuals (offspring) are

created by combining the genetic material (chromosomes) of the selected parents and through crossover (recombination) processes. Small random changes in the genetic material of the offspring help to maintain diversity in the population and prevent premature convergence to suboptimal solutions. Replacement by new offspring forms the next generation [103].

The Levenberg-Marquardt algorithm (LMA) is an iterative optimization method used to minimise the residuals of the nonlinear least squares problem. Curve fitting is widely used in numerical optimization for parameter estimation and solving nonlinear optimization problems.

Residuals are computed with updated parameter estimates. The balance between Gauss-Newton and gradient descent steps should be checked. This is done by adjusting the damping parameter (usually denoted λ or μ). The damping parameter should decrease as the fit improves. If the fit is not achieved, the parameter is increased and the process is continued in small steps [104].

The limited-memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) algorithm is an optimization algorithm belonging to the family of quasi-Newtonian methods. For large unconstrained optimization problems, the computation of the full Hessian matrix is impractical. The L-BFGS method is efficient for such problems with many variables. To guide the search in variable space, L-BFGS uses an approximation of the inverse Hessian matrix.

In the L-BFGS algorithm, an initial guess is made for the optimal solution. The memory size is determined by the number of iterations. Since the vector is limited to the specified memory, the limited memory approximation of the inverse Hessian matrix is preserved. Iterations and gradients are followed and continued by evaluating the objective function and the gradient in the iteration. At each iteration, it updates the limited memory approximation, determines a search direction based on this approximation, performs a row search to find the optimal step size, and updates the iteration. Convergence is checked against certain criteria, such as a change in the objective function or a decrease in the slope norm below a threshold. The algorithm terminates when the convergence criteria are met [105].

In Global Optimum Search, the following steps occur in one cycle. i) Execution of the automatic (comprehensive) optimization algorithm (with maximum number of

function evaluations) ii) Saving of the parameters if the last one specified is better than the best one. In this optimization technique, convergence is achieved by switching between the optimization techniques registered in the programme. In addition, this optimization option obtains information from the user on the rate at which the selected material parameters randomly deteriorate.

The automatic (using library models) optimization algorithm first quickly examines all material models of the same type in the material model library. It runs the automatic optimization algorithm on the most promising material model. It also obtains from the user the maximum number of function evaluations for each initial model optimization. This provides a more appropriate optimization design opportunity.

NEW Unconstrained Optimization Algorithm (NEWUOA) is a derivative-free optimization algorithm. It is suitable for optimising smooth functions without gradient information. The algorithm belongs to the family of confidence region methods, which iteratively build a model of the objective function and update the solution within a confidence region. NEWUOA uses a confidence region mechanism and a quadratic interpolation scheme. It builds and maximises quadratic models of the objective function within the confidence region. It efficiently optimises problems with a large number of variables. The quadratic model is given by:

$$m_k(p) = f_k + g_k^T p + \frac{1}{2} p^T B_k p \quad (8.7)$$

The objective function value at x_k is represented as f_k , the gradient of the objective function at x_k as g_k , a symmetric positive definite matrix approximating the Hessian at x_k as B_k . Solve the trust-region subproblem to find the optimal step p_k that minimizes the quadratic model within the trust region:

$$\min_p m_k(p) \quad (8.8)$$

subject to $\|p\| \leq \Delta_k$. Update solution:

$$x_{k+1} = x_k + p_k \quad (8.9)$$

The radius of the confidence zone should be adjusted according to the agreement between the actual reduction in the objective function and the reduction predicted by the quadratic model. Convergence can be checked by looking at certain criteria, such as changes in the objective function or the norm of the step [106].

Calibration experiments were performed with both fitness function and optimization options to ensure that the prediction plots generated in different material models approximated the experimental data. Even when using the same data, different choices for different models can ensure convergence. The material constants for planar equibiaxial test data from a 54-year-old human ascending aorta are shown in Table 8.3.

Table 8.3 : Material constants for planar equibiaxial test data of 54-year-old human ascending aorta.

Model	Constants
Anisotropic Hyperelastic Model: Exp	A1=0.0684701; C1=12.0621; dirA1=4.35243; dirB1=0.236705; E1=24.211; A2=0.844562; C2=1.5381; dirA2=2.10631; dirB2=2.47833; E2=0.473776; A3=0.0753277; dirA3=0.649299; dirB3=3.32137; D=9.61123e-05
Polynomial(3)-Prony Series(5) Model	C10=5592.44; C20=97.8357; C30=-35.6766; C01=1142.24; C02=15186.8; C03=21.5302; C11=77.8597; C12=-15.7524; C21=52.3923; d1=229.14; d2=0.485592; d3=77.682; rel_g1=54.5885; rel_k1=12.0442; tau1=10.7585; rel_g2=241.895; rel_k2=451.019; tau2=29.2687; rel_g3=53.357; rel_k3=0.257914; tau3=0.494253; rel_g4=0.103184; rel_k4=202.238; tau4=89.185; rel_g5=107.531; rel_k5=31.8006; tau5=48.4697; sum_g=0.0781631; sum_k=0.00319812;
Bergström-Boyce Model	muA=64.5642; muB=0.0495453; NA=1.60676; NB=1.60676; fac=0.168771; C=-0.00158655; m=9.03163; D=0.00290392;

Constants for the anisotropic hyperelastic material model (Anisotropic Hyperelastic Model: Exp), hyperelastic-linear viscoelastic material model (Polynomial-Prony Series) and hyperelastic-nonlinear viscoelastic material model (Bergström Boyce) were obtained. Appendix A shows plots generated from the test data for the specified material models. Appendix B contains USERMAT code files generated to analyse the specified material models in ANSYS.



9. CONCLUSIONS AND FUTURE WORK

PHV technology is being developed to overcome the limitations of current heart valve prostheses. Material selection, valve geometry design, structural mechanical analysis, hemodynamic analysis and manufacturing techniques are investigated to achieve a high-performance PHV. The material must have high elasticity. Ideally the material should be biocompatible. In this study, printing experiments were carried out with DentaModel, Flexible-X, Gingiva, Elastomer-X resins during the material selection process.

Since it is possible to work with biocompatible materials in the production of three-dimensional printers, printing tests were first tried with this technique. However, during the first test to see if the design shape could be printed, the model crashed. A successful production was not achieved. Since the model is fragile, it must be supported by a mold from below in order to print the model.

We continued production trials using a DLP device. With micron-scale layering capability, it was possible to print valves in detail enough to fit the precise structure of the aortic heart valve geometry. Printing trials were carried out with DentaModel, Flex-X, Gingiva and Elastomer-X resins. Among the materials, Shore hardness of Elastomer-X is 43A, Flexible-X is 55A and Gingiva is 81A. Therefore, the product with the highest flexibility was the model made with Elastomer-X.

One of the advantages of this production technique is that the model does not need to be printed on a mold. The use of molds in production both creates material costs for mold making and limits the ability to produce different sizes required for personalized processing. In this context, production with DLP is more advantageous. However, photopolymers are used in DLP production. New engineering resins are being researched and developed in this field. With the development of more materials that will be both biocompatible and highly flexible, DLP will be more widely used in PHV production. However, the production of a material with Shore hardness of 43A with such detailed printing without the need for additional molds is a pioneer.

Uniaxial tensile and planar tests were performed to characterize the mechanical properties of the Elastomer-X material under DLP production conditions. Mechanical characterization of material produced in layers with DLP paves the way for the derivation of new coefficients for material models. Elastomer-X material samples were prepared for uniaxial tensile and planar tests. Mechanical tests were performed. Data obtained from mechanical tests were loaded into the ANSYS® program. Constants were obtained for the Neo-Hookean, Mooney-Rivlin (2nd and 3rd order), and Ogden (1st, 2nd and 3rd order) models. FEM analysis was performed again using the Neo-Hookean model coefficients from the obtained coefficients. The observed peak equivalent stress values were found to be generally similar to the Neo-Hookean pattern modeled in the previous analysis.

In this context, in order to support the realism of the models, the coefficients of the material models were obtained using data obtained from biaxial tests on ascending aortic tissue reported in the literature. Test data was processed using the MCalibration® program. MCalibration® is a powerful program for modeling from test data with comprehensive optimization techniques. Test data were used to obtain coefficients for the anisotropic hyperelastic material model (Anisotropic Hyperelastic Model: Exp), the hyperelastic linear viscoelastic material model (Polynomial-Prony Series) and the hyperelastic nonlinear viscoelastic material model (Bergström Boyce). This stage was carried out using the MCalibration program. Obtaining these coefficients is useful in modeling both the viscoelastic properties and hyperelastic properties of the heart valve.

The use of realistic computer simulations in the PHV development process will reduce production costs. Adapting the prosthesis according to the patient's physiological information will contribute to the advancement of personalized medicine. As a manufacturing technique, valve prosthetics are a challenge to precisely and accurately fabricate the thin-layered leaflet structure and curved geometry of the valve. This study shows that DLP can be used to produce a heart valve model. We also explained the process of mechanically testing the prostheses produced with this technique and obtaining the coefficients of different material models from the test data. With the connection between production and computational analysis, the prosthetic development process will accelerate.

In future studies, with this production technique, it may be possible not only to print the geometry correctly, but also to print fiber-oriented structures in a more realistic way. Fiber orientations may help the valve better resist the tensile forces it encounters during opening and closing. Additionally, the alignment of fibers can affect the shape and stability of the valve, which may increase the long-term durability and functionality of the valve. In addition, in future studies, it is necessary to use highly flexible materials that are biocompatible with heart tissue for heart valves. Thus, it will reduce the risk of thrombosis and calcification of the prosthesis and enable the prosthesis to be used in the clinic. Performing biaxial tensile tests and stress-relaxation tests on samples taken from the model produced with DLP can provide more accurate coefficient numbers for the material models used in the analyses. Analyses made with more realistic material layer numbers will enable the model to exhibit more realistic behavior. Finally, the model must be produced with its stent and the analyses to be performed must be applied to the entire structure, since it is common to use the prosthesis with the stent structure in the clinic. During this process, various tests must be performed to evaluate the biocompatibility, durability and performance of the prosthesis. These tests include biocompatibility tests, mechanical tests (e.g. tensile tests, compression tests), durability tests (e.g. cyclic fatigue tests), fluid dynamics tests (e.g. blood flow simulations) and clinical studies to evaluate the long-term stability of the prosthesis. Completion and successful passing of these tests will ensure that heart valve prostheses can be used safely and effectively in clinical practice.



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<https://doi.org/10.3390/app132412983>

APPENDICES

APPENDIX A: Graphs with test data in different material models

APPENDIX B: USERMAT Model Folders for ASYS



APPENDIX A: Graphs with test data in different material models

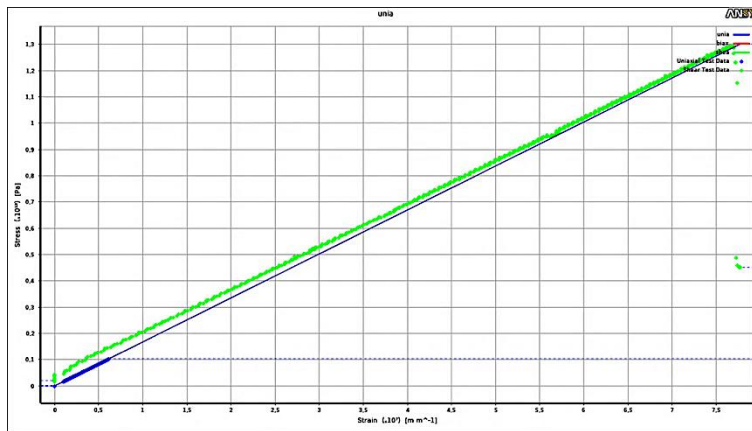


Figure A.1 : The curve of the Neo-Hookean model was obtained from test data of the 0.5 mm thick specimen printed on the x-axis.

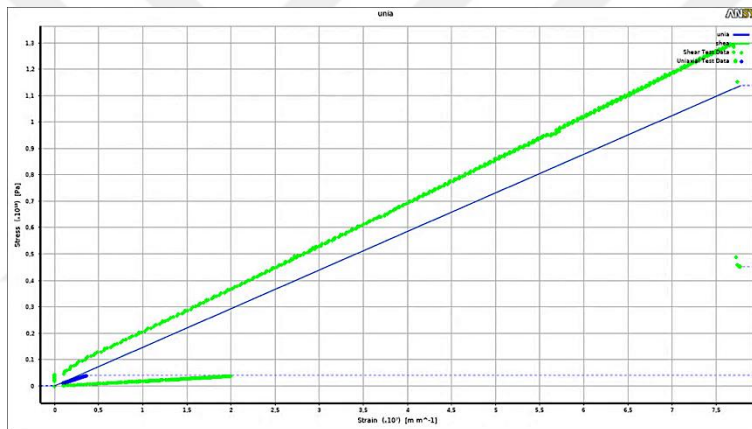


Figure A.2 : The curve of the Neo-Hookean model was obtained from test data of the 0.75 mm thick specimen printed on the x-axis.

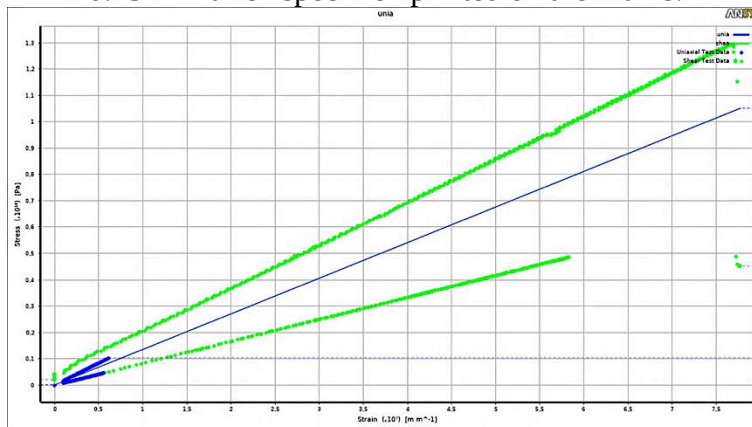


Figure A.3 : The curve of the Neo-Hookean model was obtained from test data of the 1 mm thick specimen printed on the x-axis.

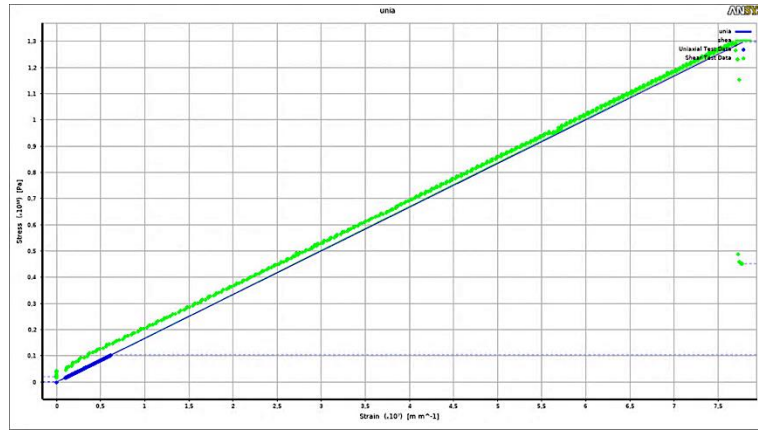


Figure A.4 : The curve of the Mooney-Rivlin 2. order model was obtained from test data of the 0,5 mm thick specimen printed on the x-axis.

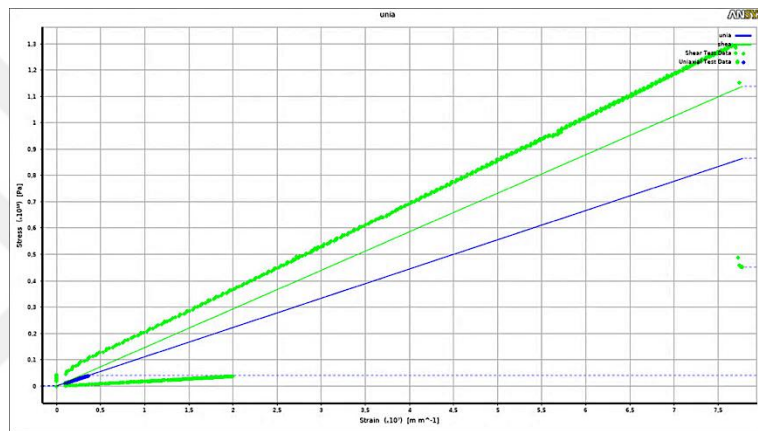


Figure A.5 : The curve of the Mooney-Rivlin 2. order model was obtained from test data of the 0,75 mm thick specimen printed on the x-axis.

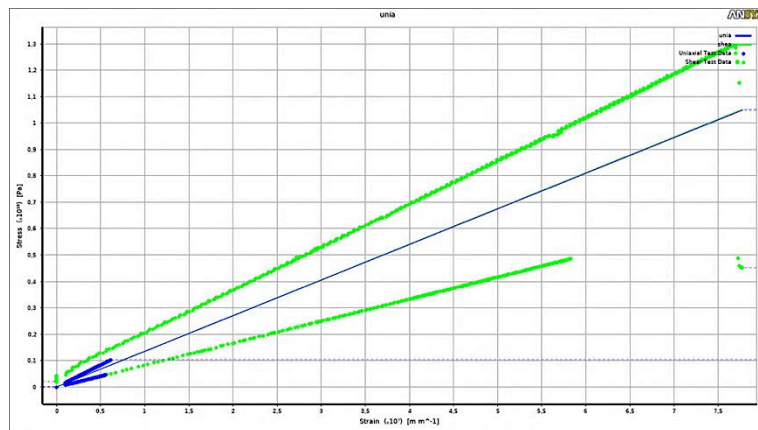


Figure A.6 : The curve of the Mooney-Rivlin 2. order model was obtained from test data of the 1 mm thick specimen printed on the x-axis.

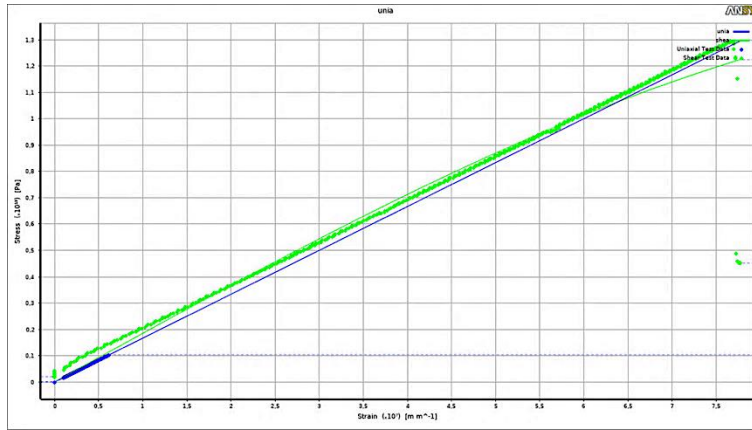


Figure A.7 : The curve of the Mooney-Rivlin 3. order model was obtained from test data of the 0,5 mm thick specimen printed on the x-axis.

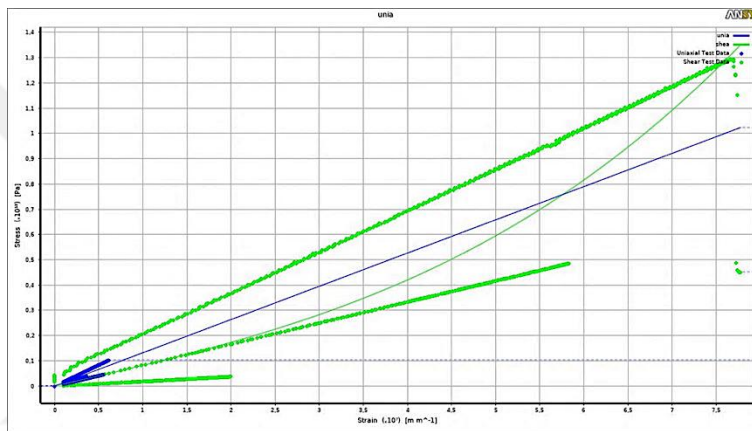


Figure A.8 : The curve of the Mooney-Rivlin 3. order model was obtained from test data of the 0,75 mm thick specimen printed on the x-axis.

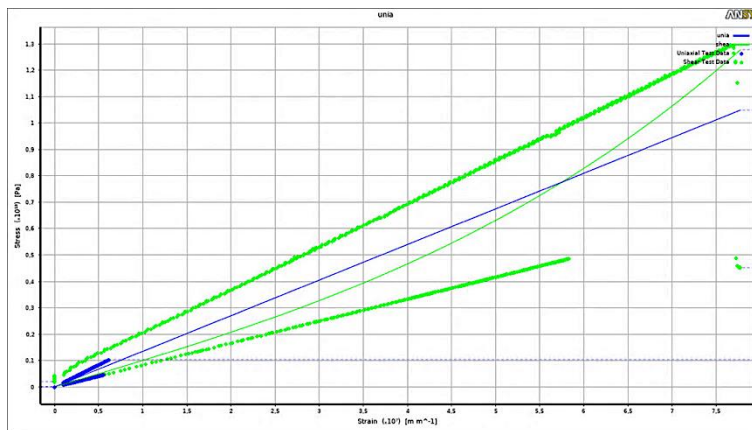


Figure A.9 : The curve of the Mooney-Rivlin 3. order model was obtained from test data of the 1 mm thick specimen printed on the x-axis.

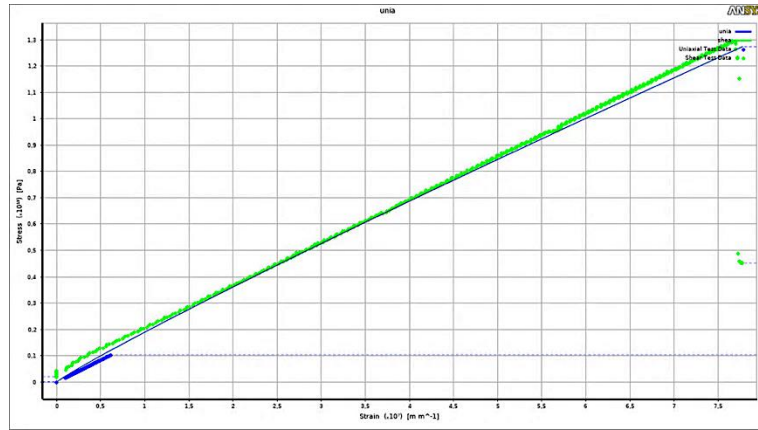


Figure A.10 : The curve of the Ogden 1. order model was obtained from test data of the 0,5 mm thick specimen printed on the x-axis.

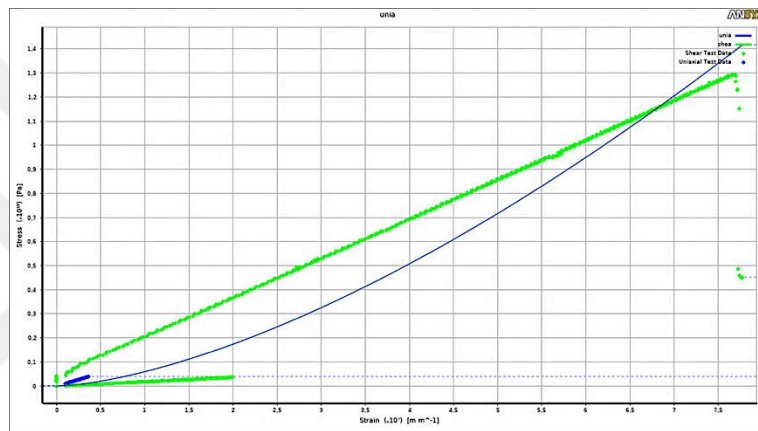


Figure A.11 : The curve of the Ogden 1. order model was obtained from test data of the 0,75 mm thick specimen printed on the x-axis.

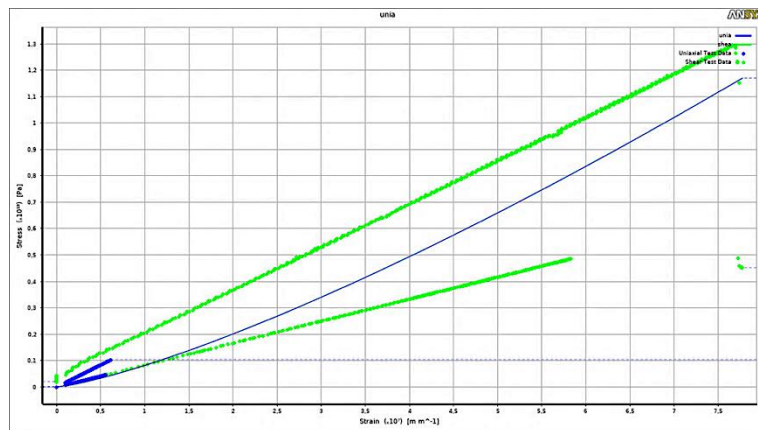


Figure A.12 : The curve of the Ogden 1. order model was obtained from test data of the 1 mm thick specimen printed on the x-axis.

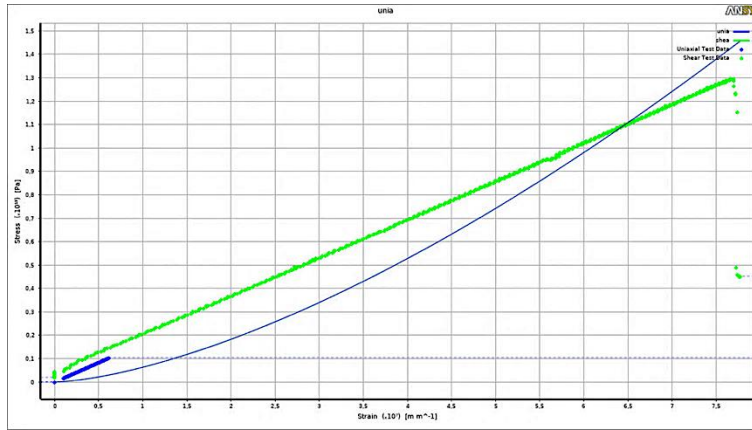


Figure A.13 : The curve of the Ogden 2. order model was obtained from test data of the 0,5 mm thick specimen printed on the x-axis.

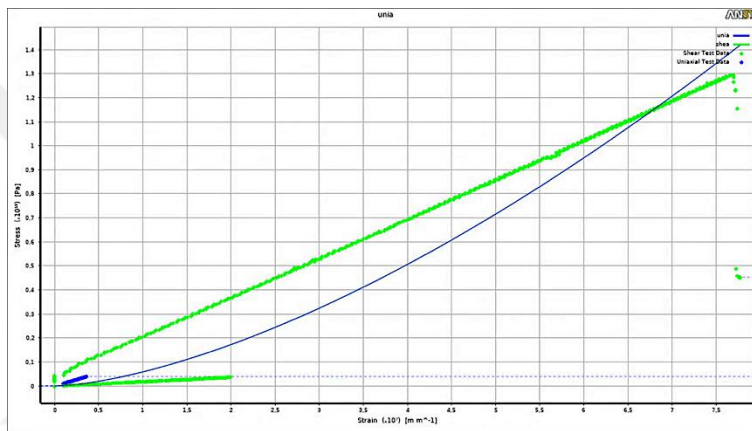


Figure A.14 : The curve of Ogden 2. order model was obtained from test data of the 0,75 mm thick specimen printed on the x-axis.

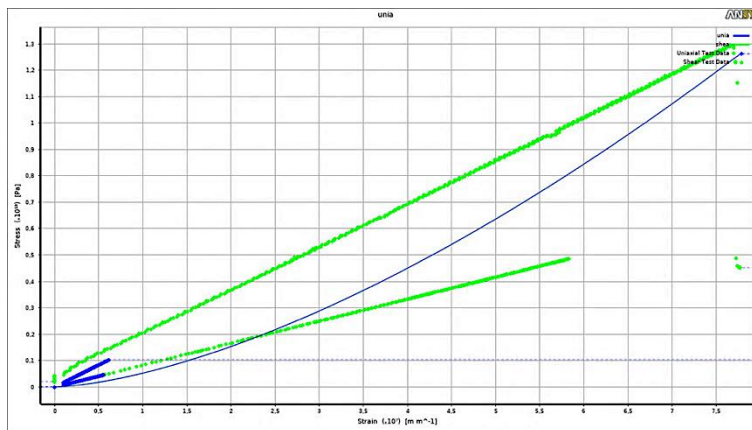


Figure A.15 : The curve of the Ogden 2. order r model was obtained from test data of the 1 mm thick specimen printed on the x-axis.

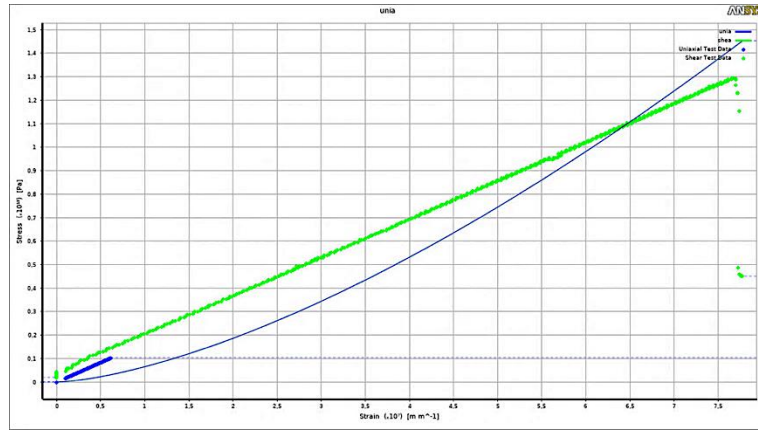


Figure A.16 : The curve of the Ogden 3. order model was obtained from test data of the 0,5 mm thick specimen printed on the x-axis.

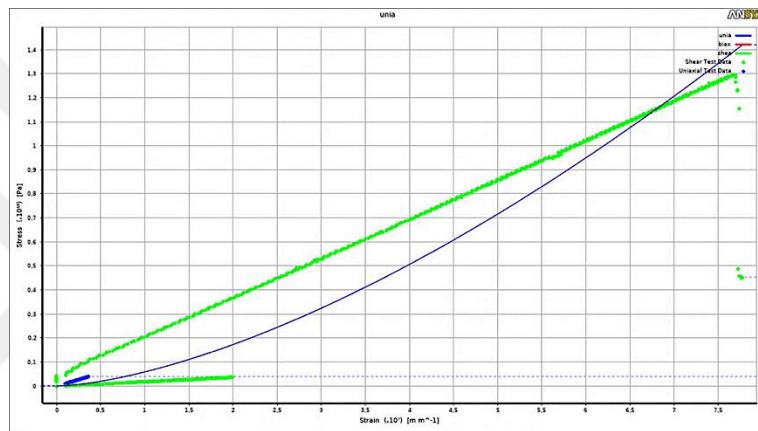


Figure A.17 : The curve of Ogden 3. order model was obtained from test data of the 0,75 mm thick specimen printed on the x-axis.

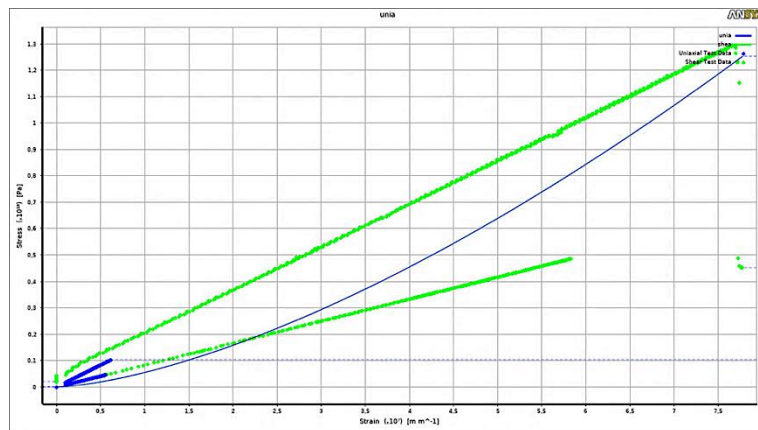


Figure A.18 : The curve of the Ogden 3. order model was obtained from test data of the 1 mm thick specimen printed on the x-axis.

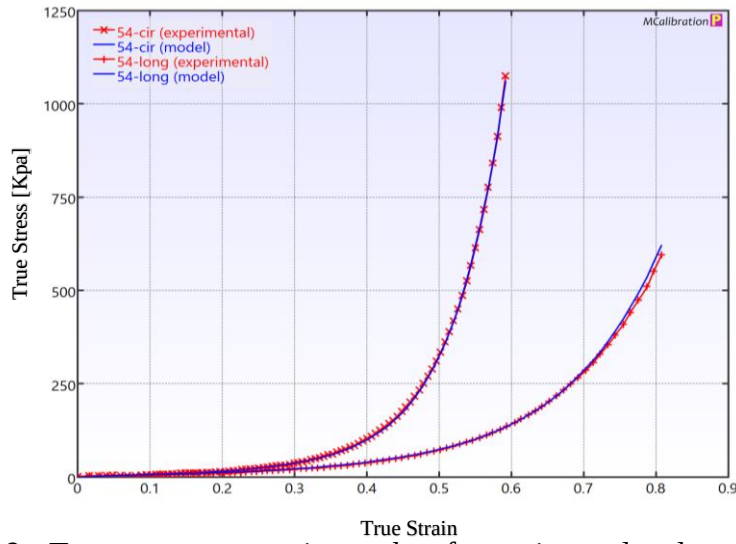


Figure A.19 : True stress-true strain graphs of experimental and model data for the anisotropic hyperelastic (exp) model

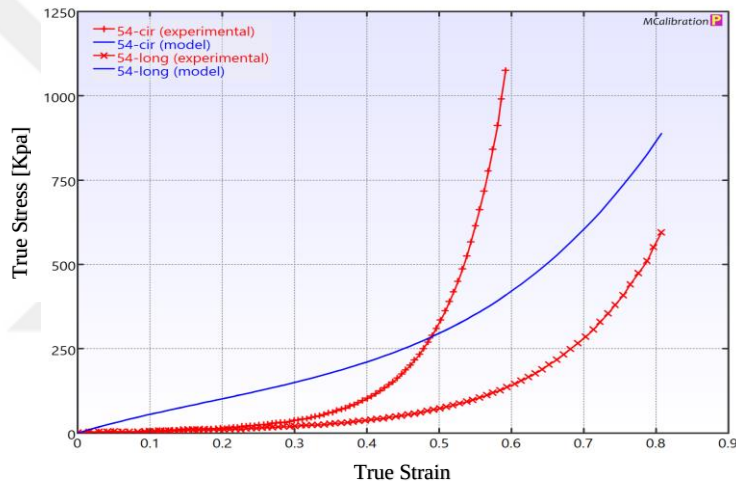


Figure A.20 : True stress-true strain graphs of experimental and model data for the Bergström-Boyce model

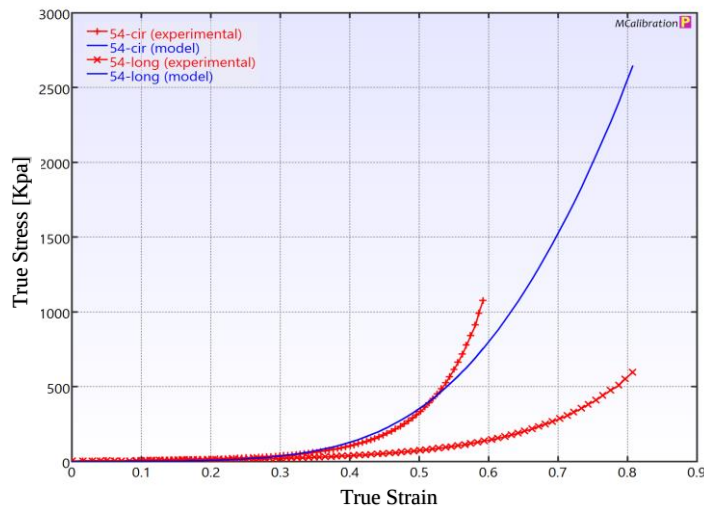


Figure A.21 : True stress-true strain graphs of experimental and model data for the Polynomial(3)-Prony Series(5) Model.

APPENDIX B: USERMAT Model Folders for ASYS

ANSYS USERMAT Dictionary File 1: Anisotropic Hyperelastic: Exponential Model file.

```
! MCalibration defined material model -- start

! Units: [length]=meter, [force]=Newton, [time]=seconds,
[temperature]=Centigrade

! Material Model: Ansys-AHyperExp

! Calibration file name: Untitled

TB, AHYPER, matid, 1, 10, EXP
TBDATA, 1, 68.4700529838 ! A1
TBDATA, 2, 844.561816349 ! A2
TBDATA, 3, 75.3277476746 ! A3
TBDATA, 4, 0.0 ! B1
TBDATA, 5, 0.0 ! B2
TBDATA, 6, 0.0 ! B3
TBDATA, 7, 12062.1381057 ! C1
TBDATA, 8, 1.53810048335 ! C2
TBDATA, 9, 24211.0345434 ! E1
TBDATA, 10, 0.47377555978 ! E2
```

```

TB, AHYPER, matid, 1, 1, PVOL
TBDATA, 1, 9.61123036858e-08 ! D

TB, AHYPER, matid, 1, 3, AVEC
TBDATA, 1, 0.892128077703
TBDATA, 2, 0.431734788475
TBDATA, 3, 0.133088562221

TB, AHYPER, matid, 1, 3, BVEC
TBDATA, 1, 0.0570256215908
TBDATA, 2, 0.59706479161
TBDATA, 3, 0.80016355397
MP, DENS, matid, 1e-06

! MCalibration defined material model -- end

```

ANSYS USERMAT Dictionary File 2: Bergstrom-Boyce Model file.

```

! MCalibration defined material model -- start

! Units: [length]=meter, [force]=Newton, [time]=seconds,
[temperature]=Centigrade

! Material Model: Ansys-Bergstrom-Boyce

! Calibration file name: Untitled


! Material Parameters for the Bergstrom-Boyce model
TB, BB, matid, 1, 7, ISO
TBDATA, 1, 64.5642013378 ! mu for network A
TBDATA, 2, 1.60675642974 ! N=lamLock^2 for network A
TBDATA, 3, 0.0495453414537 ! mu for network B

```

```

TBDATA, 4, 1.60675642974 ! N=lamLock^2 for network B
TBDATA, 5, 0.168771042641 ! 1/tauBase^m
TBDATA, 6, -0.00158654851392 ! C
TBDATA, 7, 9.03163037744 ! m
TB, BB, matid, 1, 1, PVOL
TBDATA, 1, 0.00290392430

```

ANSYS USERMAT Dictionary File 3: Polynomial-Prony Model file

```

! MCalibration defined material model -- start
! Units: [length]=meter, [force]=Newton, [time]=seconds,
[temperature]=Centigrade
! Material Model: Ansys-Polynomial3-Prony05
! Calibration file name: Untitled
TB, HYPER, matid, 1, 3, POLY
TBDATA, 1, 5.59244e+06
TBDATA, 2, 1.14224e+06
TBDATA, 3, 97835.7
TBDATA, 4, 77859.7
TBDATA, 5, 1.51868e+07
TBDATA, 6, 35676.6
TBDATA, 7, 52392.3
TBDATA, 8, -15752.4
TBDATA, 9, 21530.2
TBDATA, 10, 0.22914
TBDATA, 11, 0.000485592
TBDATA, 12, 0.077682

```

```

TB, PRONY, matid, 1, 5, SHEAR
TBDATA, 1, 0.00932684995169 ! alphaG1
TBDATA, 2, 10.7585087829256 ! tau1
TBDATA, 3, 0.04132964832745 ! alphaG2
TBDATA, 4, 29.2687124370923 ! tau2
TBDATA, 5, 0.00911643945488 ! alphaG3
TBDATA, 6, 0.49425256703871 ! tau3
TBDATA, 7, 1.7629828485e-05 ! alphaG4
TBDATA, 8, 89.184999895111 ! tau4
TBDATA, 9, 0.01837249020528 ! alphaG5
TBDATA, 10, 48.4696502718848 ! tau5

TB, PRONY, matid, 1, 5, BULK
TBDATA, 1, 5.5235134898e-05 ! alphaK1
TBDATA, 2, 10.7585087829256 ! tau1
TBDATA, 3, 0.00206839130995 ! alphaK2
TBDATA, 4, 29.2687124370923 ! tau2
TBDATA, 5, 1.1828017121e-06 ! alphaK3
TBDATA, 6, 0.49425256703871 ! tau3
TBDATA, 7, 0.00092747225116 ! alphaK4
TBDATA, 8, 89.184999895111 ! tau4
TBDATA, 9, 0.00014583865548 ! alphaK5
TBDATA, 10, 48.4696502718848 ! tau5

MP, DENS, matid, 1e-06

! MCalibration defined material model --

```

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