A combined experimental and computational framework to optimise processing and design of poly(L-lactic acid) bioresorbable stents

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A combined experimental and computational framework to optimise processing and design of poly(L-lactic acid) bioresorbable stents

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A thesis submitted to Queen’s University Belfast in fulfilment of the requirements for the degree of

Doctor of Philosophy

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November 2019
To my parents, Alan and Faith,
My brothers, Tom and Adam,
And my grandparents,
Sidney, Myrtle, William and Marcella
Declaration

I declare that I am the sole author of this thesis and that all the work presented in it, unless otherwise referenced, is my own. I also declare that this work has not been submitted, in whole or in part, to any other university or college for any degree or other qualification.

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Summary

Coronary heart disease, caused by inflammatory hardening and narrowing of arteries (atherosclerosis) is the largest cause of death in the world. Coronary stents, used to treat atherosclerosis, are typically manufactured from high strength metallic alloys; however such devices remain in the body permanently and can trigger undesirable immunological responses. Bioresorbable polymer stents offer an attractive solution, providing a temporary scaffold that resorbs once the artery heals. However, polymeric stents are mechanically inferior to their metallic counterparts, requiring thicker struts to provide equivalent radial support, which has been shown to cause elevated rates of thrombosis. This thesis aims to address the challenge of designing mechanically effective but sufficiently thin bioresorbable polymer stents through multi-objective optimisation of material parameters and stent geometry.

Initially, the processing history of a polymeric coronary stent was replicated using a custom-built biaxial tensile test machine in order to assess the improvement in short-term (pre-degradation) mechanical properties of extruded poly(L-lactic acid) (PLLA). Results of an extensive experimental programme to characterise the post-processing material properties of PLLA indicated that biaxial deformation has the potential to enhance the elastic modulus and yield strength of extruded PLLA sheet by approximately 80% and 70%, through selection of optimal processing conditions. Both elastic modulus and yield strength were highly dependent on the aspect ratio of the biaxial deformation. Response surface methodology was used to provide empirical correlations between aspect ratio and these mechanical properties. Using these empirical correlations, a rate-independent, transversely isotropic, temperature-dependent, elastic-plastic PLLA constitutive model was calibrated for finite element implementation.
Finally, an optimisation framework was developed that considered the combined
effect of the biaxial stretching processing history and the geometric configuration
when optimising the mechanical performance of a PLLA coronary stent. Forty
parametric stent designs were generated by varying the aspect ratio of the biaxial
deformation, along with the strut width, the strut thickness and the strut length.
Each stent design was evaluated computationally, using finite element analysis,
across a series of performance metrics: the cross-sectional area post-dilation,
foreshortening, stent-to-artery ratio and radial collapse pressure. Pareto fronts
highlighted that a change in one design parameter that improves one metric often
leads to a compromise in at least one of the other metrics. Based on the results of
these simulations, a set of statistical surrogate models were established that related
each performance metric to the design parameters. An objective function was
constructed that sought to minimise foreshortening and stent-to-artery ratio whilst
maximising cross-sectional area post-dilation and radial collapse pressure. Multi-
objective optimisation was conducted using the surrogate models to produce an
optimal poly(L-lactic acid) stent design that offered improved performance relative
to a baseline design for the same strut thickness.

In summary, this thesis addresses key limitations in polymeric stent design and the
results may be used to aid in the development of high stiffness, thin strut polymeric
stents.
Acknowledgements

Many people have assisted me over the course of this PhD. First of all, I would like to thank each of my supervisors, Dr Gary Menary, Dr Alexander Lennon and Prof. Nicholas Dunne for their advice, trust and guidance throughout the entirety of this PhD.

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I must also express my gratitude to the Bioengineering Research Group (BRG) and the Polymer Processing Research Group (PPRG) for making conferencing experience much easier, providing help when needed, promoting a friendly work environment and ensuring that my PhD experience was an enjoyable one. Within these groups, my thanks go to John, Jonathan, Hannah, Clare, Thomas, Katie, Ryan, Lucy, David, Shiyong, James, Josh, Huidong, Narendran and Surendra. Outside of these groups, I would also like to thank David, Alex, Stephen and Joanne who have contributed to the lively atmosphere in the third-floor office.

Finally, I would like to thank my friends and family, without whom this thesis would not have been possible. I am extremely grateful to my parents, Alan and Faith, and my brothers, Tom and Adam who have been incredibly supportive and encouraged me in every possible way on this journey.
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Nomenclature

Roman letters

$A_{\text{def}}$  Total area of deformation
$A_r$  Aspect ratio
$B$  Left Cauchy-Green deformation tensor
$C$  Compliance tensor
$C_{ij}, D_k$  Hyperelastic constitutive model coefficients
$D$  Stiffness tensor
$D_{\text{unload}}$  Unloaded diameter
$E$  Young’s modulus
$E'$  Storage modulus
$E^*$  Elastic modulus normal to the plane of isotropy
$\dot{\epsilon}_{pp}$  Post-processing extension rate
$F$  Deformation gradient tensor
$F^e$  Elastic deformation gradient tensor
$F^p$  Plastic deformation gradient tensor
$F^v$  Viscodastic deformation gradient tensor
$f$  Frequency
$G^*$  Shear modulus normal to the plane of isotropy
$H_{\text{c}}$  Enthalpy of cold-crystallisation
$H_m$  Enthalpy of melting
$H^f$  Enthalpy of fusion
$I$  Invariant
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>$K$</td>
<td>Hardening parameters</td>
</tr>
<tr>
<td>$L$</td>
<td>Stent length</td>
</tr>
<tr>
<td>$L_{\text{initial}}$</td>
<td>Initial stent length</td>
</tr>
<tr>
<td>$L_{\text{unload}}$</td>
<td>Unloaded stent length</td>
</tr>
<tr>
<td>$l$</td>
<td>Strut length</td>
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<tr>
<td>$M$</td>
<td>Moment</td>
</tr>
<tr>
<td>$n$</td>
<td>Sample number</td>
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<tr>
<td>$r$</td>
<td>Yield strength ratio</td>
</tr>
<tr>
<td>$R_{\text{load}}$</td>
<td>Stent radius following loading</td>
</tr>
<tr>
<td>$R_{\text{unload}}$</td>
<td>Stent radius following unloading</td>
</tr>
<tr>
<td>$R_{\text{central}}$</td>
<td>Central stent radius following loading</td>
</tr>
<tr>
<td>$R_{\text{distal}}$</td>
<td>Distal stent radius following loading</td>
</tr>
<tr>
<td>$SA_{\text{artery}}$</td>
<td>Surface area of a compatible cylindrical artery</td>
</tr>
<tr>
<td>$SA_{\text{stent}}$</td>
<td>Surface area of the stent</td>
</tr>
<tr>
<td>$T$</td>
<td>Processing temperature</td>
</tr>
<tr>
<td>$T_{cc}$</td>
<td>Cold-crystallisation temperature</td>
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<tr>
<td>$T_g$</td>
<td>Glass transition temperature</td>
</tr>
<tr>
<td>$T_m$</td>
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<tr>
<td>$T_{pp}$</td>
<td>Post-processing temperature</td>
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<tr>
<td>$t$</td>
<td>Strut thickness</td>
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<tr>
<td>$W$</td>
<td>Strain energy density</td>
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<tr>
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<tr>
<td>$X_c$</td>
<td>Crystallinity</td>
</tr>
<tr>
<td>$Y$</td>
<td>Predicted response</td>
</tr>
<tr>
<td>$\hat{Y}$</td>
<td>Normalised predicted response</td>
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<tr>
<td>$Y_{\text{max}}$</td>
<td>Predicted maximum response</td>
</tr>
<tr>
<td>$Y_{\text{min}}$</td>
<td>Predicted minimum response</td>
</tr>
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</table>
**Greek letters**

\( \alpha \)  
Hill plasticity coefficients

\( \gamma \)  
Shear strain

\( \varepsilon \)  
Strain tensor

\( \varepsilon \)  
Strain

\( \varepsilon^e \)  
Elastic strain

\( \varepsilon^p \)  
Plastic strain

\( \varepsilon_\rho \)  
Elongation to failure

\( \dot{\varepsilon} \)  
Strain rate

\( \dot{\varepsilon}_\rho \)  
Viscoelastic strain rate

\( \eta \)  
Viscosity

\( \theta \)  
Angle

\( \lambda \)  
Stretch ratio

\( \sigma \)  
Stress tensor

\( \sigma \)  
Stress

\( \sigma_0 \)  
Initial stress

\( \sigma_Y \)  
Yield strength

\( \sigma_{UTS} \)  
Ultimate tensile strength

\( \tau \)  
Shear stress

\( \tau_c \)  
Time constant

\( \tau_Y \)  
Shear strength

\( \nu \)  
Poisson’s ratio

\( \nu^* \)  
Poisson’s ratio normal to the plane of isotropy

\( \chi \)  
Curvature
Abbreviations

BRS  Biodegradable stents
FS   Foreshortening
SEQ  Sequential
SIM  Simultaneous

Acronyms

ANOVA Analysis of variance
BMS  Bare-metal stents
BVS  Biodegradable vascular scaffold
CE   Conformité Européenne
CHD  Coronary heart disease
CSA  Cross-sectional area
DES  Drug-eluting stents
DMA  Dynamic mechanical analysis
DoE  Design of experiments
DSC  Differential scanning calorimetry
ED   Extrusion direction
FDA  Food and Drug Administration
GPC  Gel permeation chromatography
ISAR-STEREO Intracoronary Stenting and Angiographic Results: Strut Thickness Effect on Restenosis Outcome
LHC  Latin hypercube
LST  Late stent thrombosis
MACE Major adverse cardiac events
MD   Machine direction
PBS  Phosphate-buffered saline
PCI  Percutaneous coronary intervention
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>PLA</td>
<td>Poly(lactic acid)</td>
</tr>
<tr>
<td>PLLA</td>
<td>Poly(L-lactic acid)</td>
</tr>
<tr>
<td>RF</td>
<td>Radial force</td>
</tr>
<tr>
<td>RCP</td>
<td>Radial collapse pressure</td>
</tr>
<tr>
<td>RSM</td>
<td>Response surface methodology</td>
</tr>
<tr>
<td>SA</td>
<td>Surface area</td>
</tr>
<tr>
<td>SAR</td>
<td>Stent-to-artery ratio</td>
</tr>
<tr>
<td>SBM</td>
<td>Stretch blow moulding</td>
</tr>
<tr>
<td>TD</td>
<td>Transverse direction</td>
</tr>
<tr>
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<td>z-direction</td>
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1. Introduction

1.1 Coronary angioplasty: a brief overview

Coronary heart disease (CHD) is the largest cause of death in the world, with an estimated 7.4 million people dying from this disease in 2015 (World Health Organization, 2017). It is commonly caused by atherosclerosis, in which fatty deposits (atheroma) develop on the arterial wall causing the artery to harden and narrow (Ludman et al., 2015). If left untreated, coronary atherosclerosis can lead to angina (discomfort in the chest), myocardial infarction and stroke.

The first documented human cardiac catheterisation was performed by Werner Forssmann, M.D. (1904–1979) in Eberswalde, Germany, 1929 (Forssmann, 1931), who inserted a uretic catheter into his right ventricular cavity via his antecubital vein under local anaesthetic (Packy et al., 2016). However, it wasn’t until 1977 that the first successful recorded percutaneous transluminal coronary balloon angioplasty was performed by Andreas Grüntzig, M.D. (1939–1985), who treated the left anterior descending artery of a conscious human (Murphy et al., 1978), initiating the modern era of percutaneous coronary intervention (PCI). However, balloon angioplasty suffers from a number of drawbacks, namely vessel occlusion and restenosis—the reclosure of the vessel following initial dilation—which propelled the development and first successful implantation of the metallic stent nearly a decade later, through Ulrich Sigwart, M.D. and Jaques Puel, M.D. (1949-2008) (Sigwart et al., 1987). The first U. S. Food and Drug Administration (FDA) approved stents, Gianturco-Roubin stent and the Palmaz-Schatz™ stent, came in 1994 (U. S. Food and Drug Administration, 1994), with clinical studies confirming that stenting led to
improved clinical outcome over balloon angioplasty alone (Fischman et al., 1994; Serruys et al., 1994).

Percutaneous coronary intervention is the most commonly employed revascularisation technique used in the treatment of narrowed arteries in which a small expandable scaffold (stent) is deployed at the site of an atherosclerotic lesion to dilate the artery and restore patency. An estimated 92,000 PCIs were performed in 2013, with approximately 90% of procedures requiring stent insertion and the majority of cases (4 in 5) treated by PCI. Percutaneous coronary intervention is considered as the most successful non-invasive surgical interventions for the treatment of CHD, with survival rates in excess of 95% at 10 years. The total number of annual PCIs has increased each year since 1991 (Ludman et al., 2015) and with the ageing of the world population (World Health Organization, 2011), the incidence and economic burden of heart disease is likely to continue increasing. A modern PCI procedure typically achieves arterial access through the femoral artery and is performed under local anaesthesia. Visualised using fluoroscopy and intracoronary injections of contrast medium, a soft tipped, guidewire is passed down the coronary artery, across the stenosis, and into a distal branch. A balloon or stent catheter is then passed over the guidewire and positioned at the stenosis (Figure 1.1). The stenosis may then be stented directly or dilated before stenting.

![Image of percutaneous coronary intervention procedure](image_url)

**Figure 1.1. Illustration of the percutaneous coronary intervention procedure on an occluded coronary artery. Adapted from Encyclopædia Britannica (2007).**
Whilst bare-metal stents (BMSs) reduced the incidence rate of restenosis when compared to balloon angioplasty, the introduction of a permanent metallic cage around the arterial wall provoked neointimal hyperplasia, an inflammatory response of the vessel wall (Windecker et al., 2001), and as a result, drug-eluting stents (DESs) succeeded BMSs. Drug-eluting stents contain a durable polymer coating which releases an antiproliferative drug (e.g. sirolimus or paclitaxel) which attenuates intrastent neointimal proliferation (Iqbal et al., 2014). The first FDA approved drug-eluting stent, Cypher™ stent (Cordis/Johnson & Johnson), (U. S. Food and Drug Administration, 2003) was developed to release antiproliferative agents at the site of arterial injury to attenuate neointimal formation. Modern DESs are subclassified as first generation or second generation, with second generation devices having decreased strut thickness, improved flexibility and enhanced drug-elution profiles (Simard et al., 2014).

Whilst current generation DESs somewhat mitigate the risk of restenosis when compared to previous generations and BMSs (Morice et al., 2002; Stettler et al., 2007), the higher cost of modern DESs is not compensated for by a reduction in follow-up procedural costs (Kaiser et al., 2005). Furthermore, they suffer from a number of inherent flaws based on the permanent nature of their design and issues have surfaced regarding the long-term (> 1 year) safety of these devices including delayed healing and late stent thrombosis (LST) (Bavry et al., 2006; Van Beusekom et al., 2007; Kang et al., 2016). This has prompted the development of bioresorbable stents (BRSs) with the hypothesis that a temporary scaffold may reduce LSR.

1.2 Bioresorbable stents: advantages and limitations

Bioresorbable stents offer an attractive solution, providing a temporary scaffold that resorbs once the artery has healed, a process that has been shown to take approximately 3 months (Serruys et al., 1988), beyond which the stent is no longer needed and may restrict lumen enlargement (Ormiston and Serruys, 2009).
Bioresorbable stents solve a number of the aforementioned problems associated with current generation DESs, and offer a number of key advantages over their permanent metal counterparts (Onuma and Serruys, 2011):

- bioresorption process permits late lumen enlargement and late expansive remodelling
- reduction in stent thrombosis upon completion of the resorption process, primarily due to the removal of foreign material from the artery
- fewer complications during repeat revascularisation procedures
- better suited to non-invasive imaging techniques (for follow-up) as they are less susceptible to the artefacts typically caused by the imaging of metallic stents
- more controllable and localised drug delivery through the stereochemical composition of the polymer

The Igaki-Tamai stent (Igaki Medical Planning Company, Kyoto, Japan) was the first BRS implanted in humans (Tamai et al., 2000). The first-in-man trial (n = 15) of the device showed promising results with no stent thrombosis or major adverse cardiac events (MACEs) after 30 days, with lumen loss after 3 months and 6 months comparable to BMSs (Bourantas et al., 2013). However, despite these favourable results, the device failed to progress for clinical application in coronary arteries over the concern that the heated dye used to inflate the balloon during the dilation process may cause vessel wall trauma, which has been associated with intima hyperplasia and increased thrombogenicity (Post et al., 1996). The device was therefore limited for use in peripheral applications.

Over the last 20 years, the bioresorbable coronary stent market has grown significantly, with the majority of major biomedical stent manufacturers developing their own variant of a BRS. To date, the Absorb bioresorbable vascular scaffold (BVS) (Abbott Vascular, Santa Clara, California) and the DESolve stent (Elixir Medical Corporation, Sunnyvale, California) hold the Conformité Européenne (CE) mark for use in coronary applications (Wiebe et al., 2014), both of which are
manufactured from poly(L-lactic acid) (PLLA). Poly(L-lactic acid) is a biodegradable, biocompatible semicrystalline polymer with relatively high tensile properties (Ang et al., 2017), and as a result, it has shown particular success as the platform material of a BRS. However, PLLA BRSs require significantly thicker struts in order to provide an equivalent level of arterial support when compared to their metallic counterparts due to PLLA’s inferior modulus. As a result, PLLA BRSs have higher stent-to-artery ratios (Kolandaivelu et al., 2011; Kawamoto et al., 2016) which has been shown to increase the risk of myocardial infarction, thrombosis and restenosis (Kastrati et al., 2001; Serruys et al., 2016).

1.3 Aim of this thesis

Poly(L-lactic acid) BRSs are still underperforming when compared to their metallic counterparts. Bulky strut geometry remains an issue for BRSs and is a barrier to clinical approval. In this thesis, the author aims to test the hypothesis that correct matching of material processing parameters to stent geometry may improve the performance of a PLLA coronary stent. Initially, it will be attempted to prove that the mechanical properties of PLLA may be enhanced as a result of biaxial deformation, and that these properties may be expressed as a function of the processing parameters. Secondly, it will be attempted to characterise the mechanical response of PLLA at physiologically realistic conditions in order to calibrate a representative constitutive model for finite element implementation. Finally, this research aims to address the challenge of designing mechanically effective but sufficiently thin bioresorbable polymer stents through multi-objective optimisation of processing parameters and stent geometry.
2. Literature review

2.1 Purpose of this chapter

The characteristics of PLLA and its application as a platform material for BRSs are reviewed first within this chapter. Secondly, an analysis of the stretch blow moulding (SBM) technique used to process PLLA is presented as background to the biaxial deformation experimental work conducted in the subsequent chapter. Next, the behaviour of PLLA under mechanical loading is assessed and a survey of constitutive models used to capture this behaviour is presented as a background to the work conducted in Chapter 4. Finally, an assessment of computational techniques reported in the literature for simulated testing and optimisation of coronary stents is presented as a background to the multi-objective optimisation in Chapter 5, and areas for further development are identified.

2.2 Poly(L-lactic acid)

2.2.1 Chemical composition and synthesis

Poly(lactic acid) (PLA) is an aliphatic polymer manufactured from renewable resources (Garlotta, 2002; Hamad et al., 2015) and is synthesised through direct condensation or ring-opening polymerisation of lactic acid monomers (Drumright et al., 2000) (Figure 2.1). Lactic acid exists in two optically active configurations and as result, PLA is one of the few polymers that possesses a stereochemical structure, existing as: poly(L-lactic acid) (PLLA), poly(D-lactic acid), or as the copolymer poly(DL-lactic acid) (Bergström and Hayman, 2015). The L-lactide of PLA is
commonly used as the platform material for BRSs, due to its excellent mechanical properties, processability and slow degradation profile (Hamad et al., 2015).

![Chemical structure of lactic acid and poly(lactic acid)](image)

**Figure 2.1.** Schematic illustrating the various synthesis routes that can be used to obtain poly(lactic acid) (PLA) from lactic acid (LA).

### 2.2.2 Processing and forming

Poly(L-lactic acid) resins can be tailor-made for different fabrication processes through the control of key molecular parameters, such as branching, D-isomer content, molecular weight distribution and the introduction of a plasticiser (Drumright et al., 2000). In general, PLLA is processed at temperatures in excess of 185–190 °C, at which chain scission occurs and has the potential for a loss of molecular weight (Spinnu et al., 1996). Extrusion, injection moulding and solution casting are amongst the most common processing techniques for the fabrication of PLLA (Lim et al., 2008). Table 2.1 shows a comparison of the mechanical and thermal properties of PLLA across these fabrication techniques. The elastic modulus, yield strength and elongation to failure are comparable across each of the processing techniques. Furthermore, by controlling the processing parameters for any one of these techniques, PLLA’s microstructure can be modified, which ultimately controls the mechanical response of the polymer.
Table 2.1. Comparison of room temperature (23 °C ± 3 °C) tensile properties, crystallinity and thermal transitions of virgin PLLA (<5% D-isomer) across various processing techniques. Approximate values taken from uniaxial tensile test results and differential scanning calorimetry (DSC) test results presented in the studies. $E =$ Young’s modulus, $\sigma_{\text{UTS}} =$ ultimate tensile strength, $\varepsilon_{\text{F}} =$ elongation to failure, $X_c =$ crystallinity, $T_g =$ glass transition temperature and $T_m =$ melting temperature. (Perego et al., 1996; Kim et al., 1998; Drumright et al., 2000; Garlotta, 2002; Baiardo et al., 2003; Ouchi et al., 2003; Harris and Lee, 2008; Stoclet et al., 2010; Wu et al., 2013; Bobel et al., 2016).

<table>
<thead>
<tr>
<th></th>
<th>Extruded</th>
<th>Injection moulded</th>
<th>Solution-cast</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E$ (MPa)</td>
<td>2500–3500</td>
<td>3500–4150</td>
<td>1210–3300</td>
</tr>
<tr>
<td>$\sigma_Y$ (MPa)</td>
<td>60.0</td>
<td>63.0–70.0</td>
<td>50.0</td>
</tr>
<tr>
<td>$\sigma_{\text{UTS}}$ (MPa)</td>
<td>60.0</td>
<td>47.0–70.0</td>
<td>33.1–66.0</td>
</tr>
<tr>
<td>$\varepsilon_{\text{F}}$ (%)</td>
<td>3.1–6.0</td>
<td>1.3–7.0</td>
<td>1.8–28.0</td>
</tr>
<tr>
<td>$X_c$ (%)†</td>
<td>1.0–40.0</td>
<td>3.8–42.0</td>
<td>41.1–44.3</td>
</tr>
<tr>
<td>$T_g$ (°C)</td>
<td>54.3–58.0</td>
<td>55.0–64.3</td>
<td>55.0–65.0</td>
</tr>
<tr>
<td>$T_m$ (°C)</td>
<td>143.1–150.0</td>
<td>172.4–181.0</td>
<td>173.6–176.0</td>
</tr>
</tbody>
</table>

† Large variation in crystallinity primarily due to whether the specimen was annealed following processing.

2.2.3 Microstructural and mechanical properties

Poly(L-lactic acid) is classified as a semicrystalline polymer. In general, polymers exhibit two different types of morphology in their solid state: amorphous and semicrystalline. In an amorphous polymer, the molecules are oriented randomly and entangled, which leaves the polymer with a glasslike (transparent) appearance. Semicrystalline polymers typically possess regions of tightly packed, ordered chains, referred to as spherulites, which can vary in shape and size, and scatter light leaving the polymer with an opaque appearance. These crystalline regions are separated by amorphous regions and their size and volume determines the crystalline fraction of the polymer (Figure 2.2).
Poly(L-lactic acid) possesses superior mechanical properties (Young’s modulus, tensile strength and flexural modulus) relative to traditional polymers, such as polypropylene, polystyrene and polyethylene (Hamad et al., 2015). Each of the aforementioned mechanical properties have been identified as key mechanical traits for the candidate material for a coronary stent (Onuma and Serruys, 2011). In addition to PLLA’s relatively good mechanical properties, its biocompatibility and slow degradation rate make it an ideal candidate for a stent (Wan et al., 2014).

2.2.4 Degradation and erosion

Poly(L-lactic acid) degrades by simple hydrolysis and is subsequently metabolised (through the Krebs cycle) into water and carbon dioxide. Initially, water is absorbed from the surrounding tissue (hydration) by the amorphous chains (Figure 2.3a). This triggers depolymerisation by hydrolysis, which splits the crystal lamellae into shorter segments resulting in a loss of molecular weight (Kenny and Hijazi, 2015) (Figure 2.3b). In the context of a coronary stents, depolymerisation typically occurs three to six months following implantation, after which the stent begins to lose its structural integrity (Serruys et al., 1988; Onuma and Serruys, 2011). Longer time frames may lead to inflammation with an increased risk of thrombosis and restenosis.

Figure 2.2. Schematic illustrating PLLA’s microstructure which includes crystalline (a) lamellae and (b) spherulites. Adapted from Bergstrom (2015).
(Brie et al., 2016). Following depolymerisation, fragments of low-molecular weight polymer are released resulting in a loss of mass and radial strength (Figure 2.3c), with full loss of support occurring after one year. In the final stage of degradation, chain-scission occurs across crystalline regions of the polymer causing shorter chains to diffuse out (Figure 2.3d). These short chain polymers are metabolised and broken down into carbon dioxide and water through the Krebs cycle (Onuma and Serruys, 2011; Gonzalo and Macaya, 2012). This process of bioresorption can take over two years (Wiebe et al., 2014).

![Figure 2.3](image)

**Figure 2.3.** The Absorb bioresorbable vascular scaffold (BVS) PLLA bioresorption process. The four stage process consists of (a) water molecules absorbed by the amorphous chains; (b) depolymerisation by hydrolysis; (c) fragmentation into low molecular weight polymer and (d) dissolution and diffusion. Adapted from Onuma and Serruys (2011).

### 2.2.5 Summary

In summary, PLLA’s superior mechanical properties relative to other semicrystalline polymers, combined with its processability and slow degradation rate, make it an ideal candidate for a bioresorbable coronary stent. As a result, many biomedical device companies have PLLA stents undergoing preclinical trials, clinical trials or have progressed their device to attain Conformité Européenne (CE) approval (Iqbal et al., 2014; Kenny and Hijazi, 2015).
2.3 Poly(L-lactic acid) bioresorbable stents

2.3.1 Clarification of terminology

The term ‘bioresorbable’ is often used interchangeably with ‘biodegradable’ when describing a polymer’s decomposition procedure, whilst the term ‘stent’ is often used interchangeably with ‘scaffold’, when describing a device that provides temporary arterial support. However, it is important to make clear distinctions between the different terminologies encountered within published literature. The term ‘biodegradable’ relates to those polymers that are decomposed in the body but whose degradation products remain in the tissues long-term, whilst the term ‘bioresorbable’ refers to those polymers that degrade upon implantation into non-toxic products which are then eliminated from the body or metabolized (da Silva Soares, 2008). The European Association of Percutaneous Coronary Interventions task force on the evaluation of coronary stents in Europe have adopted the term ‘bioresorbable stent’ (BRS), as opposed to ‘bioresorbable vascular scaffold’ (BVS) (Byrne et al., 2015), and hence the term BRS will be used hereafter, with the exception of any instances in which a company has named its product otherwise.

2.3.2 Survey of bioresorbable poly(L-lactic acid) coronary stents approved for commercial use

The Absorb BVS (Abbott Vascular, USA) and the DESolve stent (Elixir Medical Corporation, USA) are the current range of PLLA BRSs that hold the CE mark for use in coronary applications (Wiebe et al., 2014), with the Absorb BVS also having FDA approval (U. S. Food and Drug Administration, 2016a). The Absorb BVS and DESolve stents are currently undergoing clinical trials (ABSORB III and DESolve NX, respectively). Table 2.2 highlights key trial clinical outcomes at 12-month and 24-month intervals. In the ABSORB III trial, the XIENCE DES (Abbott Vascular, USA) was assessed for comparative purposes and has been included for reference.
Table 2.2. *Comparison of Conformité Européenne (CE) marked PLLA bioresorbable stents (BRSs) for use in coronary applications.* (Ellis et al., 2015; Abizaid et al., 2016; Kereiakes et al., 2017; Ellis et al., 2017a).

<table>
<thead>
<tr>
<th>Device</th>
<th>Absorb BVS</th>
<th>XIENCE</th>
<th>DESolve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Abbott Vascular</td>
<td>Abbott Vascular</td>
<td>Elixir Medical Corp.</td>
</tr>
<tr>
<td>Backbone</td>
<td>PLLA</td>
<td>Cobalt-chromium (CoCr)</td>
<td>PLLA</td>
</tr>
<tr>
<td>Classification</td>
<td>BRS</td>
<td>DES</td>
<td>BRS</td>
</tr>
<tr>
<td>Current clinical trial</td>
<td>ABSORB III (n = 1322)</td>
<td>ABSORB III (n = 686)</td>
<td>DESolve Nx (n = 126)</td>
</tr>
<tr>
<td>Trial outcomes (period)</td>
<td>12 months</td>
<td>24 months</td>
<td>12 months</td>
</tr>
<tr>
<td>MACE (%)</td>
<td>7.8 (102)</td>
<td>11.0 (143)</td>
<td>6.1 (41)</td>
</tr>
<tr>
<td>Thrombosis (%)</td>
<td>1.5 (20)</td>
<td>1.9 (24)</td>
<td>0.7 (5)</td>
</tr>
</tbody>
</table>

*BVS: Bioresorbable vascular scaffold, PLLA: Poly(L-lactic acid), and MACE: Major adverse cardiac event.*
The early-stage clinical outcomes (at one year) from the Absorb III trial, in which the Absorb BVS was compared against Abbott Vascular’s XIENCE DES (Abbott Vascular, USA), were promising. Results showed that MACEs, e.g., cardiac death, heart attack, or revascularisation procedure, occurred in 7.8% of patients in the Absorb group compared to 6.1% of patients in the XIENCE group. Furthermore, there was no significant difference between the Absorb group and the XIENCE group in rates of device thrombosis (1.5% and in 0.7%; \( p = 0.13 \)) (Ellis et al., 2015). In addition, Baron et al. (2017) conducted an evaluation into the economic impact of both stents and showed that whilst initial procedural costs were higher with the Absorb BVS, total one year health care costs were comparable. However, two-year results of the trial showed that the Absorb BVS group had an 11% rate of MACEs, compared to 7.9% in the XIENCE group \( (p = 0.03) \). Furthermore, a 1.9% rate of thrombosis was observed in the BVS group versus 0.8% within the XIENCE group (Ellis et al., 2017a). These findings were also supported by a meta-analysis across all ABSORB trials at two year follow-up (Ali et al., 2017). The FDA subsequently issued an urgent safety notice to health care providers treating patients with the Absorb BVS on 18 March 2017 (U. S. Food & Drug Administration, 2017) and Abbott Vascular recalled the stent in both Europe and Australia from all centres not studying the device.

Three year results of the ABSORB III trial continued to highlight issues with the ABSORB BVS, with significant differences between the Absorb group and the XIENCE group in rates of target-vessel myocardial infarction (8.6% and 5.9%, respectively; \( p = 0.18 \)) or device thrombosis (2.3% and in 0.7%; \( p = 0.01 \)) (Kereiakes et al., 2017). Following review of the data from the Absorb III trial, Abbott Vascular announced that all device sales would end on 14 September 2017 (U. S. Food and Drug Administration, 2017a). In an updated letter to healthcare providers, the FDA acknowledged that the thrombosis risk for Absorb BVS-treated patients was higher than for patients treated with the XIENCE stent. Furthermore, the majority of cases of thrombosis occurred within the first year after BVS
implantation, and beyond one year, the rate of new thrombosis events remained higher in BVS group compared to the XIENCE group (U. S. Food and Drug Administration, 2017c). These findings are supported by Lipinski et al. (2016), who conducted a meta-analysis which assessed the thrombosis risk of the ABSORB BVS against metallic DESs at six month follow up and concluded that patients undergoing PCI with the ABSORB BVS had an increased risk of thrombosis and myocardial infarction, compared to those treated with a DES.

A comparison of the early-stage clinical outcomes (at one year) from the DESolve Nx and ABSORB III trials showed that the DESolve stent was outperforming the Absorb BVS (Table 2.2). Major adverse cardiac events occurred in 5.7% of patients treated with a DESolve stent, whilst device thrombosis was recorded for 0.8% of patients. At two-year follow up, the device demonstrated sustained efficacy and safety, continuing to outperform the Absorb BVS and match the performance of the XIENCE DES. Whilst the two-year outcomes of the DESolve Nx trial are promising, care must be exerted in reviewing the study results given the relatively modest sample size for patients treated with a DESolve stent (n = 123), compared to patients treated with an Absorb BVS (n = 1322) or an XIENCE DES (n = 686). Furthermore, both studies were restricted to de novo lesions, i.e. arterial plaques that have not previously been treated with angioplasty or stenting.

It is of interest to note that different mechanisms for stent thromboses within and beyond one year have been proposed from prior clinical data analyses. It has been shown that short-term thrombotic events (< 1 year following implantation) are largely related to the thickness and the width of the struts, (Kolandaivelu et al., 2011; Kawamoto et al., 2015; Ellis et al., 2017b), whilst long-term thrombotic events (> 1 year following implantation) are primarily due to the stent becoming dismantled (Yamaji et al., 2017). This may explain the improved performance of the DESolve stent (relative to the Absorb BVS). The thickness of the Absorb BVS and the DESolve stent are identical (150 µm), however the Absorb BVS has much wider struts by comparison (215 µm vs. 165 µm). Furthermore, this also suggests that if
the short-term clinical outcomes for BRSs are not met, the theoretical long-term advantages for BRS cannot be guaranteed (Sakamoto et al., 2018).

### 2.3.3 Issues with current poly(L-lactic acid) stents

In general, polymeric BRSs require significantly thicker struts than metallic stents (Bergström and Hayman, 2015; Bobel et al., 2016) in order to improve radial strength, radial stiffness, reduce recoil to clinically acceptable levels (Kawamoto et al., 2016) and provide an adequate level of arterial support. A comparison of strut geometry and key performance metrics for PLLA BRSs and modern metallic DESs is presented in Table 2.3. It should be noted that PLLA BRSs are an emerging technology, with only two stents holding the CE mark for use in coronary applications (Ang et al., 2017). As a result, literature that evaluates the mechanical performance of BRSs is scarce, especially when compared to that of modern DESs, which have spent nearly 15 years in clinical practice (Chitkara and Gershlick, 2010).

**Table 2.3. Comparison of strut geometry and key performance metrics of modern PLLA bioresorbable stents (BRSs) and modern metallic (stainless steel 316L and cobalt-chromium alloy) stents for coronary application. Approximate values taken from experimental and simulated bench test results presented in the studies. (Mori and Saito, 2005; Schmidt et al., 2009, 2016; Menown et al., 2010; Grogan et al., 2012; Pauck and Reddy, 2015; Kawamoto et al., 2016; Ang et al., 2017).**

<table>
<thead>
<tr>
<th>Device</th>
<th>PLLA BRS</th>
<th>Metallic Stents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strut thickness (µm)</td>
<td>125–156</td>
<td>80–140</td>
</tr>
<tr>
<td>Strut width (µm)</td>
<td>140–216</td>
<td>80–132</td>
</tr>
<tr>
<td>Stent-to-artery ratio (%)</td>
<td>26.0–32.0</td>
<td>15.5–21.4</td>
</tr>
<tr>
<td>Recoil (%)</td>
<td>5.86–7.85</td>
<td>2.8–6.7</td>
</tr>
<tr>
<td>Radial strength (MPa)†</td>
<td>0.007–0.04</td>
<td>0.13–0.26</td>
</tr>
<tr>
<td>Flexibility (N/mm²)‡</td>
<td>0.13–0.24</td>
<td>0.0053–0.024</td>
</tr>
</tbody>
</table>

† Defined as the pressure required to cause a 10% reduction in stent diameter; ‡ Defined using the linear elastic portion of the stent’s moment-curvature behaviour.
The increased strut width, strut thickness and stent-to-artery ratio of PLLA BRSs increases the risk of arterial injury, hinders re-endothelialisation, and increases the risk of restenosis and thrombosis (Foin et al., 2014). Furthermore, an increased strut profile may contribute to increased flow disturbance (separation, stagnation and reattachment) (Bourantas et al., 2014). Whilst PLLA BRSs are typically more flexible than their metallic counterparts (Ang et al., 2017), their increased strut profile hinders deliverability when navigating tortuous anatomy (Ako et al., 2007) and restricts normal vasomotion (Iqbal et al., 2014). Furthermore, whilst PLLA BRS strut profiles are significantly increased compared to their metallic counterparts, the radial strength and radial stiffness of these devices are still lacking. Poly(L-lactic acid) BRSs have commonly been used for simple de novo lesions, i.e. arterial plaques that have not previously been treated with angioplasty or stenting, in a single coronary artery (Onuma et al., 2013; Serruys et al., 2015). Recent studies have shown that they are technically feasible for the treatment of complex lesions, such as coronary bifurcations (Džavik and Colombo, 2013; Kawamoto et al., 2015). However, given their reduced radial stiffness and poor deliverability, treatment of these more complex lesions often requires time-consuming pre-dilation and balloon inflation phases which may induce myocardial ischemia, i.e. reduced blood flow to the heart (Wiebe et al., 2014).

Poly(L-lactic acid) has an elastic modulus between 3–7 GPa (Bergström and Hayman, 2015), which is significantly lower than that of stainless steel (190 GPa; Murphy et al., 2003) or cobalt chromium (243 GPa; Poncin and Proft, 2003). In order to address these issues and reduce the strut profile of PLLA BRSs, the designer may focus on improving the mechanical properties of the platform polymer. Figure 2.4 highlights the improvements that must be made to PLLA’s key mechanical properties such as strength, stiffness and elongation to failure in order to address current issues with PLLA BRSs such as excessive strut profiles (with respect to strut width and strut thickness) and fracture risk (McMahon et al., 2018). Key material properties such as yield strength, elastic modulus and elongation to
failure must be increased to address the issues surrounding strut geometry, radial stiffness, radial strength, fracture and the suitability of these devices for complex lesions (McMahon et al., 2018). In order to improve these mechanical properties, an additional stretch blow moulding (SBM) step may be implemented in the manufacturing process (Wu et al., 2013).

![Graph showing stress-strain relationship](image)

**Figure 2.4.** Comparison of the mechanical response between PLLA and a typical metal used in coronary stents. Adapted from McMahon et al. (2018).

### 2.4 Biaxial stretching of poly(L-lactic acid)

#### 2.4.1 Stretch blow moulding

Stretch blow moulding is a processing technique commonly employed in the commercial production of carbonated drinks bottles to improve their tensile modulus, strength-to-weight ratio, fracture strain and shelf-life (Brandau, 2016), and was adopted for use in the production of the Absorb BVS. In an SBM procedure for
PLLA stents, the polymer is initially melted and extruded to form a thick walled tube, commonly referred to as a parison (or preform) (Figure 2.5a). The parison is heated above its glass transition temperature, at which its behaviour switches from a glass-like (brittle) state to a rubber-like (ductile) state (Bergström, 2015), and is stretched at high speed circumferentially using pressurised air, and axially using a mechanical device such as an actuator (Figure 2.5b). The process creates a thin-walled large diameter tube (Figure 2.5c), typically 3 to 5 times the initial parison outer diameter (Alexy and Levi, 2013; Bergström and Hayman, 2015). The SBM process imposes a state of biaxial strain on the parison and this process of biaxial deformation has been shown to improve the mechanical properties of PLLA (Alexy and Levi, 2013).

Figure 2.5. *Schematic illustrating the stretch blow moulding process for a stent in which the polymer is (a) heated and stretched in the axial and circumferential direction to produce (b) an expanded tube with improved mechanical properties.*
The biaxial deformation induced in the PLLA tube during the SBM process (Figure 2.6a) may be replicated using a biaxial tensile test machine that stretches polymer sheet in a planar configuration (Menary et al., 2012) (Figure 2.6b). Following biaxial deformation, the mechanical and thermal properties of PLLA may be evaluated using specimens punched from the stretched sheet. In general, the post-processing mechanical behaviour of biaxially stretched polymers exhibits a dependence on temperature, deformation mode, strain rate and stretch ratio during processing (Ou and Cakmak, 2008; Menary et al., 2012; Løvdal et al., 2016, 2017). Understanding the degree to which each of these processing parameters affects PLLA’s mechanical properties (such as elastic modulus, yield strength and elongation to failure) is of particular use to the engineer when designing a new BRS.

Figure 2.6. Schematic illustrating how the state of biaxial strain in the axial direction ($\varepsilon_1$) and the circumferential direction ($\varepsilon_2$) during (a) the stretch blow moulding process for a stent is replicated using (b) planar biaxial deformation.

2.4.2 Effect of biaxial stretching processing parameters on poly(L-lactic acid)’s mechanical properties

The temperature window for biaxial processing of PLLA is limited by the glass transition temperature and the cold-crystallisation temperature of the polymer, both
of which vary depending on the chemical composition and processing history (Ou and Cakmak, 2008). However, for PLLA, in general, the glass transition temperature is within the range of 50-65 °C (Ou and Cakmak, 2008; Wu et al., 2013; Bergström and Hayman, 2015; Lövdal et al., 2016), whilst the cold-crystallisation temperature is within the range 110–145 °C (Stoclet et al., 2010). Lövdal et al., (2017) suggested that PLLA should be processed above the glass transition temperature but below 85 °C in order to suppress thermally-induced crystallisation and facilitate strain-induced crystallisation, which subsequently improves both the strength and stiffness of the polymeric sheet.

The deformation mode during biaxial stretching may be defined as simultaneous or sequential, the latter consisting of an initial constant width stretch, followed by a secondary constant width stretch in the transverse direction. The deformation mode has been shown to affect the structural evolution of the polymer (Lövdal et al., 2016; Ou & Cakmak, 2008, 2010). Lövdal et al., (2016) found that the sequence in which the strain occurs during biaxial processing influences crystal orientation and interplanar spacing, but not the degree of crystallinity. Simultaneous stretching leads to in-plane isotropy with relatively poorly ordered crystalline regions (Ou and Cakmak, 2008). In a stepwise sequential deformation process, the high degree of orientation induced during the initial strain (in the machine direction) reduces the ability to form highly orientated crystals during the subsequent strain (in the transverse direction). The morphology developed in the second (transverse) stretching is highly dependent on the crystalline structure developed as a result of the first stretch, with the crystals formed during the initial stretching phase serving as physical crosslinks during transverse stretching (Ou and Cakmak, 2008).

The elastic modulus and yield strength of PLLA post biaxial deformation have been shown to be a function of both the strain rate and stretch ratio during biaxial processing. Low strain rates (0.1 s\(^{-1}\)) permit chain relaxation during biaxial processing, which subsequently result in reduced mechanical properties of the stretched polymer, however increasing strain rate (2.1 s\(^{-1}\)) has been shown to
increase crystallinity and molecular orientation, subsequently improving the mechanical properties of the stretched polymer (Løvdal et al., 2017). An increase in modulus and yield strength of biaxially stretched PLLA may also be achieved through an increase in area expansion during processing, defined as the product of the stretch ratios in the machine and transverse directions (Løvdal et al., 2016; Wu et al., 2013). The slow crystallisation rate of PLLA is enhanced by deformation, which facilitates strain-induced molecular ordering (Stoclet et al., 2010; Tsai et al., 2010; Zhang et al., 2011), with Løvdal et al. (2016) hypothesising that the mechanical properties of PLLA are related to strain-induced amorphous orientation rather than strain-induced crystallinity.

In summary, temperature, stretch ratio, strain rate, and deformation mode during biaxial stretching affect key mechanical properties of PLLA such as elastic modulus, yield strength and elongation to failure. From the reviewed literature, it is not clear which of these processing parameters have the strongest effect on the mechanical response of PLLA, suggesting an area for investigation. Furthermore, by evaluating the interdependencies between these processing parameters, a set of constitutive equations may be developed which relate PLLA’s mechanical properties to its processing history.

2.5 Characterisation and constitutive modelling of poly(L-lactic acid)

Computational modelling is commonly used as a preclinical testing tool in order to refine and optimise stent geometry, in order to improve the safety and efficacy of these devices (Lally et al., 2005). The FDA recommends that computational modelling studies should be presented to support medical device submissions (U. S. Food and Drug Administration, 2016b) and specifically recommends that mechanical properties of the platform material be presented, along with the corresponding constitutive model, that describes how the material responds to
various loadings through the use of equations that link the states of stress and strain (Ottosen and Ristinmaa, 2005; U. S. Food and Drug Administration, 2010).

Constitutive modelling is a corollary of continuum mechanics, which focuses on the mechanical behaviour of materials modelled as a continuous mass as opposed to discrete particles (Helena, 2017). Whilst the microscopic (or atomic) structure of materials is inconsistent with the concept of continuum, this idealisation provides a useful tool to model physical reality through constitutive equations. Constitutive models, in the context of engineering materials, can be categorised under two discrete headings: phenomenological (or statistical) and micromechanical (or mechanistic) (Bergstrom, 2015). The former refers to a model in which the relationship serves only to best describe the data, whilst the latter refers to a model in which the relationship is specified in terms of the material’s microstructure that is thought to have given rise to the data. Whilst micromechanical models are amongst the most physically accurate models available, they often require extensive characterisation due to the complexity of the deformation characteristics. Phenomenological models suffer from the limitation that they are only applicable for the exact loading conditions they were validated against (Bergstrom, 2015), however require significantly fewer tests to characterise.

Constitutive models that accurately represent the complex mechanical response of PLLA (prior to degradation) are relatively scarce in the literature, with many studies focusing on modelling the long-term response (> 1 year) of the polymer as it degrades (Soares et al., 2008; Muliana and Rajagopal, 2012; Khan and El-Sayed, 2013; Hayman et al., 2014). Whilst modelling the long-term response of the polymer is essential, one of the primary issues with the current generation of BRSs lies with stent fracture during deployment and the stent having insufficient radial stiffness to resist the compressive force of the artery immediately following deployment, both of which may be considered to be short-term (pre-degradation) phenomena (Bourantas et al., 2013; Brie et al., 2016). In addition, the majority of commonly constitutive models employed to capture the mechanical behaviour of PLLA in literature are
classified as phenomenological, in that they accurately capture material behaviour within a specific range of conditions. Hence, in this section, focus is placed on studies that characterise and model the mechanical response of PLLA prior to degradation using a phenomenological approach.

2.5.1 Introduction to constitutive modelling principles

Phenomenological models range in complexity and the majority may be categorised into one of the models outlined in Figure 2.7. Springs, dashpots and sliders have been used to represent the elastic, viscous and plastic components, respectively. A brief overview of each model and relevant theory is presented herein, however the theory behind each of these models is extensive. Hence, the reader is directed towards the work of Bergstrom (2015) and Holzapfel (2002) for further reading on fundamental principles, governing equations and criteria for implementation.

![Diagram of constitutive models](image)

**Figure 2.7.** Schematic illustrating common constitutive modelling approaches including (a) elastic; (b) viscoelastic, which combines an elastic component with a time-dependent component; (c) elastic-plastic, which combines an elastic component with a plastic component; and (d) viscoplastic, in which the left hand network captures the time independent elastic-plastic response of the polymer whilst the right hand network captures the time-dependent response.

At this point, it is also necessary to introduce the concept of true stress and strain. True stress refers to the stress determined by the instantaneous load acting on the instantaneous cross-sectional area whilst true strain relates to the rate of
instantaneous increase in the instantaneous gauge length of the specimen (Bergstrom, 2015). Stresses and strains of this nature will be explicitly referred to as ‘true stress’ and ‘true strain’ hereafter.

2.5.1.1 Elasticity

Elastic models (Figure 2.7a) can be categorised as linear elastic or hyperelastic, both of which can be further categorised as isotropic or anisotropic. Linear elastic models are capable of predicting those materials that obey Hooke’s law, i.e. the strain in the material is proportional to the applied stress within the elastic limit, and are therefore often only valid when the strains in the material are small (< 5%) (Bergstrom, 2015). Hooke’s law may be written in tensor notation and expressed as a function of the stress state, using the stiffness tensor \( \mathbf{D} \) (2.1), or as a function of the strain state, using the compliance tensor \( \mathbf{C} \) (2.2) (Hibbitt et al., 2016b).

\[
\mathbf{\sigma} = \mathbf{D}\varepsilon \\
\mathbf{\varepsilon} = \mathbf{C}\mathbf{\sigma}
\]

(2.1) \hspace{1cm} (2.2)

where \( \mathbf{\sigma} \) represents the total stress tensor, \( \mathbf{\varepsilon} \) represents the total (elastic) strain tensor, \( \mathbf{D} \) represents the stiffness tensor, \( \mathbf{C} \) represents the compliance tensor (which is the inverse of \( \mathbf{D} \)), \( \gamma \) represents shear strain and \( \tau \) represents shear stress.

Depending on the number of symmetry planes for its elastic properties, a material can be classified as either isotropic (infinite number of symmetry planes) or anisotropic (no symmetry planes). Anisotropic materials can have up to 21 independent elastic constants within the compliance tensor, as a result of directional dependent elastic moduli, shear moduli and Poisson’s ratios. However, by utilising symmetry properties, the number of independent constants can be reduced. An isotropic linear elastic material can be fully defined by two constants; the elastic modulus and the Poisson’s ratio. In the case of orthotropic elasticity (in which the material has two orthogonal symmetry planes) and transversely isotropic elasticity (which has a plane of isotropy at every point in the material), the number of
independent elastic constants can be reduced to nine and five, respectively (Hibbitt et al., 2016b).

Hyperelastic models are used when the strains in the material are large (> 5%) and when the stress cannot be represented by a linear function of the strain. For these models, the stress-strain relations are typically derived from a strain energy density function (W), which represents the true stress per unit undeformed volume (Bower, 2009; Bergstrom, 2015). For an isotropic hyperelastic material, the strain energy density can be written as a function of the deformation gradient (F), which is used in continuum mechanics to express the deformation state relative to its initial (undeformed) configuration, or the three invariants (I₁, I₂ and I₃) of the Left Cauchy-Green deformation tensor (\( \mathbf{B} = \mathbf{F} \mathbf{F}^T \)), each of which remain unchanged under coordinate transformations (2.3). For modelling hyperelastic behaviour, phenomenological polynomial models are commonly used which take the general form of (2.4) (Bower, 2009). The stress-strain law is constructed by computing the derivative of this strain-energy density function (2.5). This theory can be extended to anisotropic hyperelastic materials by modification of the strain energy density function or the strain invariants (Bergstrom, 2015).

\[
W = W \mathbf{F} = W I_1, I_2, I_3 \quad (2.3)
\]

\[
W = \sum_{i+j=1}^{n} C_{ij} I_1 - 3^i I_2 - 3^j + \sum_{k=1}^{n} \frac{1}{D_k} J - 1^{2k} \quad (2.4)
\]

\[
\mathbf{\sigma} = 2\text{dev}\left[ \left( \frac{\partial W}{\partial I_1} I_1 + \frac{\partial W}{\partial I_2} I_2 \right) \mathbf{B} - \frac{\partial W}{\partial I_2} \mathbf{B} \cdot \mathbf{B} \right] + J \frac{\partial W}{\partial J} \mathbf{I} \quad (2.5)
\]

where \( C_{ij} \) and \( D_k \) are material constants and \( J \) is the Jacobian, i.e. the total change in volume at a point, calculated as the determinant of the deformation gradient.

2.5.1.2 Viscoelasticity

Linear viscoelastic models (Figure 2.7b) are capable of predicting the material response when there is a dependence on the rate of loading. They can also be used to model hysteresis, i.e. when the loading and unloading curves do not coincide.
(Lakes, 2009). The general principle for linear viscoelastic models relies on the fact that the total strain ($\varepsilon$) can divided into an elastic part ($\varepsilon^\varepsilon$) and a viscoelastic part ($\varepsilon^\eta$), represented by the spring and dashpot (Figure 2.7b), respectively. For a 1-dimensional model, (2.6)–(2.8) hold true (Roylance, 2001).

\[
\varepsilon^\varepsilon = \frac{1}{E}\sigma \quad (2.6)
\]
\[
\varepsilon^\eta = \frac{1}{\eta}\sigma \quad (2.7)
\]
\[
\varepsilon = \varepsilon^\varepsilon + \varepsilon^\eta \quad (2.8)
\]

where $E$ represents the elastic modulus of the spring, $\varepsilon^\eta$ represents the viscoelastic strain rate and $\eta$ represents the viscosity of the dashpot.

Substituting (2.6) and (2.7) into (2.8) and introducing the term $\tau_\sigma$, which represents the ratio of viscosity to stiffness ($\eta/E$), gives (2.9). For the case of stress relaxation, in which there is a decay in stress whilst the strain is held constant (i.e. $\varepsilon = 0$), (2.9) can be integrated to give an exponentially decaying stress relaxation as a function of time ($t$), based on an initial stress ($\sigma_0$) (2.10). This 1-dimensional model can be extended to the 3-dimensional case and may also be manipulated to capture creep behaviour, i.e. the increase in strain as stress is held constant, using Laplace transformations (Roylance, 2001; Bergstrom, 2015).

\[
E\varepsilon = \sigma + \frac{1}{\tau}\sigma \quad (2.9)
\]
\[
\sigma(t) = \sigma_0 e^{-t/\tau} \quad (2.10)
\]

### 2.5.1.3 Plasticity

Elastic-plastic models (Figure 2.7c) are capable of capturing the permanent deformation which remains after the removal of load. The general principle for elastic-plastic models relies on the fact that the total strain can divided into an elastic part and a plastic part ($\varepsilon^p$) (2.11), in which only the elastic strain contributes to the stress response (2.12) (Bergstrom, 2015; Hibbitt et al., 2016a).
\[ \varepsilon = \varepsilon^e + \varepsilon^p \]  
\[ \sigma = E(\varepsilon - \varepsilon^p) \]

A yield criterion must be prescribed in order to control when plastic flow is active. Additionally, a flow rule must be prescribed to define how the material’s stress response changes (during yielding) as strain is increased and is defined using a set of hardening parameters (K). Taking the Von Mises yield criterion as an example, in which the initial yield surface is written in the form \( f_0(\sigma) \) (2.13), if \( f(\sigma, K) < 0 \), the stress magnitude is not large enough to initiate yield and hence, plastic flow is not active. If \( f(\sigma, K) = 0 \), the stress magnitude is equal to the current yield stress (\( \sigma_y \)) and plastic flow occurs if the loading continues (Hibbitt et al., 2016a). If the yield surface expands proportionally in all directions, it is termed as isotropic hardening. Conversely, if the yield surface gets shifted but its shape and size remain constant, it is termed as kinematic hardening (Lee and Barkey, 2012).

\[ f_0(\sigma) = \frac{1}{\sqrt{2}} \sqrt{\sigma_1 - \sigma_2}^2 + \sigma_2 - \sigma_3}^2 + \sigma_3 - \sigma_1}^2 - \sigma_y \]  
\[ (2.13) \]

where \( \sigma_1, \sigma_2, \) and \( \sigma_3 \) represent principal stresses.

### 2.5.1.4 Viscoplasticity

Viscoplastic models (Figure 2.7d) are amongst the most sophisticated constitutive models and are capable of modelling plasticity and nonlinear viscoelasticity, i.e. when there is a dependence on the rate of loading and the level of strain. This is often achieved by combining a number of the previously mentioned elements in a parallel network. The deformation gradient is acting on parallel networks and hence, (2.14) holds true. The deformation gradient acting on the left hand network (\( F_L \)) can be further decomposed into elastic (\( F^e_L \)) and plastic (\( F^p_L \)) components using a multiplicative split (2.15), whilst the deformation gradient acting on the right hand network (\( F_R \)) can be further decomposed into elastic (\( F^e_R \)) and viscous components (\( F^v_R \)) (2.16). The total true stress in the network (\( \sigma \)) is calculated as the sum of the
true stresses in the left hand network \((\sigma_L)\) and the right hand network \((\sigma_R)\) (Bergstrom, 2015).

\[
\mathbf{F} = \mathbf{F}_L = \mathbf{F}_R
\]  
(2.14)

\[
\mathbf{F} = \mathbf{F}_L^o \mathbf{F}_L^p
\]  
(2.15)

\[
\mathbf{F} = \mathbf{F}_R^o \mathbf{F}_R^p
\]  
(2.16)

\[
\sigma = \sigma_L + \sigma_R
\]  
(2.17)

The concept of a parallel network is not restricted to two networks and hence, an extensive number of permutations of the model can be developed using elastic, viscous and plastic components. As a result, viscoelastic models are capable of capturing highly complex material behaviour. However, as constitutive model complexity increases, the number of experimental tests required to calibrate the model increases, as does the required computational power to solve the model.

2.5.2 Mechanical response of poly(L-lactic acid)

A PLLA BRS is exposed to a variety of processing techniques, temperatures and environmental conditions during its lifecycle, from the manufacturing process, to crimping through to deployment within the body. Given the complex loading scenarios that a stent experiences and the demanding environment of the artery, it is essential that the mechanical response of PLLA is understood, in order to accurately calibrate constitutive models and guide stent design (Bergström and Hayman, 2015). A number of studies have investigated the (post-processing) mechanical response of PLLA during uniaxial tensile testing and evaluated the effect of processing history, temperature and strain rate on key mechanical properties, such as elastic modulus, yield strength, ultimate tensile strength and elongation to failure. (Eswaran et al., 2011; Wu et al., 2013; Bobel et al., 2015; Debusschere et al., 2015; Wang et al., 2017).
Biaxial stretching has been shown to improve the mechanical properties of PLLA (Alexy and Levi, 2013). Wu et al. (2013) showed that biaxially stretched specimens exhibited up to a twofold increase in yield strength when compared to unstretched sheet. Furthermore, elongation to break increased from approximately 10% to 100% depending on the biaxial stretching processing conditions. Given that a stent can experience strains of up to 50% during deployment (Bobel et al., 2015), the biaxial deformation procedure may be a necessary addition to the stent’s manufacturing process as opposed to a desirable addition, given the increased risk of failure should it be omitted. During biaxial stretching, directional dependent mechanical properties may be imparted to the stent that vary the in the circumferential and axial directions. This anisotropy has been observed by Eswaran et al. (2011) who evaluated specimens punched from stretch blow moulded PLLA tubing in the circumferential and axial directions, noting that specimens punched from the circumferential direction exhibited higher yield strength and strain-hardened post-yield. Pauck and Reddy (2015) observed an increase in elastic modulus and yield strength of 40% and 15%, respectively, when comparing the circumferential direction to axial direction at room temperature (20 °C) and an increase of 20% and 3%, respectively, at body temperature (37 °C).

The temperature-dependent mechanical response of PLLA has been evaluated by (Bobel et al., 2015), who observed a reduction in yield strength, coupled with a shift from (brittle) glass-like to (ductile) rubber-like behaviour as the temperature was increased from 20 °C to 42 °C. Wang et al. (2017) performed tensile testing on PLLA tubes at 37 °C, representative of body temperature, and 48 °C, representative of the temperature at which a stent is crimped at, and observed a similar reduction in yield strength of 14%. At this temperature, the shape of the stress-strain curve for PLLA resembles that of a typical semi-crystalline polymer with a pronounced yield followed by softening behaviour, after which the material behaves perfectly plastic, i.e. a change in strain causes no observable change in stress. As the temperature is increased, this yield point becomes less pronounced and as the
temperature approaches the glass transition temperature (approximately 65 °C),
ductile behaviour is observed with hardening behaviour post-yielding (Bergström
and Hayman, 2015). This brittle-to-ductile shift at temperatures approaching the
glass transition temperature is particularly useful during the crimping process where
the stent is exposed to high strains and the risk of fracture is high.

Poly(L-lactic acid) has also been shown to exhibit a rate-dependent response, with
yield strength increasing with strain rate in uniaxial tensile tests (Bobel et al., 2015;
Debusschere et al., 2015). Debusschere et al. (2015) performed uniaxial tensile
testing on dumbbell specimens punched from extruded PLLA tubing at 0.1, 1 and
10 mm/min (at 37 °C). The authors showed that as the strain rate was increased,
the yield strength increased, as did the amount of softening post-yield, whilst the
general shape of the curve remained consistent. However, the effect on the elastic
modulus was negligible and the elongation to failure decreased as the strain rate was
increased. Bobel et al. (2015) reported similar findings in which uniaxial tensile
testing was conducted on dumbbell specimens punched from solvent cast PLLA at
extension rates of 1, 10 and 100 mm/min at 20, 37 and 42 °C. The authors noted
that the yield strength exhibited a strain rate dependency for all temperatures
tested, however similar to the findings of Debusschere et al. (2015), the elastic
modulus was not affected by the strain rate. In general, increasing the strain rate of
the tensile test increases the yield strength for each specimen; however this has
minimal effect on the elastic modulus and ultimate tensile strength.

Figure 2.8a-d presents a relative comparison of the mechanical response of PLLA
(during uniaxial tensile testing) across specimens subjected to various processing
histories and temperatures, based on the reviewed literature within this section.
Figure 2.8a and Figure 2.8b represent specimens that have been punched from
biaxially stretched tubing in the circumferential direction and axial direction,
respectively, and are tested below the glass transition temperature. Figure 2.8c and
Figure 2.8d represent specimens punched from tubing that has not been biaxially
stretched, and are tested below the glass transition temperature and above the glass
transition temperature, respectively. In general, Figure 2.8a and Figure 2.8b have superior mechanical properties to Figure 2.8c as a direct result of biaxial stretching. Furthermore, Figure 2.8a has improved mechanical properties relative to Figure 2.8b, and tends to strain harden, with the stress response increasing until it reaches its ultimate tensile strength, occurring at the point of failure. Figure 2.8b and Figure 2.8c both tend to exhibit perfect plasticity post-yielding. Figure 2.8d highlights the brittle-to-ductile behavioural shift that Figure 2.8c experiences at temperatures approaching the glass transition temperature. Figure 2.8d has no pronounced yield and generally possesses inferior mechanical properties to Figure 2.8c, with the exception of elongation to failure which tends to increase. In general, increasing temperature tends to reduce yield strength but increase elongation to failure for Figure 2.8a-d, whilst increasing the strain rate has the converse effect.

Figure 2.8. Comparison of the mechanical response of PLLA across specimens during uniaxial tensile testing, in terms of elastic modulus (E), yield strength (σ_Y), ultimate tensile strength (σ_{UTS}) and elongation to failure (ε_F). Specimens have been punched from (a) biaxially stretched tubing in the circumferential direction, tested below the glass transition temperature (T_g); (b) biaxially stretched tubing in the axial direction, tested below the T_g; (c) tubing that has not been biaxially stretched, tested below the T_g and (d) tubing that has not been biaxially stretched, tested near the T_g.
2.5.3 Comparison of constitutive models for poly(L-lactic acid)

Poly(L-lactic acid)’s mechanical response depends on temperature, strain rate and processing and each must be accounted for in a constitutive model. As a result, simplistic constitutive models that neglect the anisotropic, rate-dependent and temperature-dependent nature of the polymer are often insufficient. For example, linear elastic models are unable to capture the permanent set due to plastic deformation, which is necessary for a stent to prevent recoil and ensure adequate radial stiffness (Debusschere et al., 2015). Schultze et al. (2008) also found that an elastic-plastic constitutive model significantly over-predicted the radial strength of three polymeric BRSs by approximately 30-100%, when compared against experimental collapse test results. These examples of oversimplifications have prompted a number of studies to develop and calibrate constitutive models capable of capturing one or more of the rate-dependent, temperature dependent and anisotropic properties of PLLA (Table 2.4).

**Table 2.4. Summary of the capabilities of published constitutive models developed to capture the short-term (pre-degradation) mechanical response of PLLA.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Strain rate</th>
<th>Temperature</th>
<th>Anisotropy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debusschere et al. (2015)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Wang et al. (2017)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pauck and Reddy (2015)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bobel and McHugh (2017)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Eswaran et al. (2011)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Numerous studies have calibrated constitutive models that capture only one of the rate-dependent, temperature dependent and anisotropic properties of PLLA (Debusschere et al., 2015; Pauck and Reddy, 2015; Wang et al., 2017). Debusschere et al. (2015) calibrated a viscoplastic model of PLLA to uniaxial tensile test data at 0.1, 1 and 10 mm/min at 37 °C, representative of body temperature. The authors showed that expanding a stent gradually reduces the build-up of internal stresses
and consequently reduces the likelihood of fracture during deployment. Wang et al. (2017) calibrated a temperature-dependent constitutive model against experimental data from tensile testing of PLLA tubes at 37 °C and 48 °C, representative of the temperature at which a stent is crimped at. The authors used this constitutive model in conjunction with finite element analysis to compare the radial strength of a stent against an *in vitro* test, predicting the radial strength to within 6%; a significant improvement to Schultze et al. (2008). Pauck and Reddy (2015) performed uniaxial tensile testing on PLLA tubing in the axial and circumferential direction at an extension rate of approximately 5 mm/min and calibrated an anisotropic elastic-plastic constitutive model. A yield strength ratio which related the circumferential and axial strengths was prescribed within the plastic region. The authors noted that this model was adequate for large deformations up to 40%, stating that strains beyond this threshold are not commonly experienced by stents.

The most advanced constitutive models to date combine the rate-dependent, temperature dependent or anisotropic properties of PLLA (Eswaran et al., 2011; Bobel and McHugh, 2017). Bobel and McHugh (2017) calibrated a model using the parallel rheological framework model within Abaqus (Dassault Systèmes, France). The first network consisted of an isotropic neo-Hookean hyperelastic model in series with a plastic isotropic hardening component, whilst the second network consisted of a viscoelastic Bergstrom-Boyce component. Eswaran et al. (2011) adopted a similar approach and modelled PLLA as a rate-dependent, anisotropic, viscoplastic material. The first network consisted of an isotropic neo-Hookean hyperelastic model in series with a viscoplastic flow component, whilst the second network consisted of an anisotropic, hyperelastic component. Both studies showed good correlation with experimental tests results, with Eswaran et al. (2011) also performing a validation study through monotonic and cyclic loading to failure on a single ring of a stent.

In summary, constitutive models have been developed that capture the (i) temperature-dependent behaviour (Wang et al., 2017); (ii) rate-dependent behaviour (Debusschere et al., 2015) and (iii) anisotropy as a result of the
processing history (Pauck and Reddy, 2015). In general, the majority of constitutive models are phenomenological and range in their complexity, however they should be made as simple as possible, such that they capture only the behaviour observed from mechanical testing. Once a constitutive model has been established, it may be implemented in finite element simulations to capture the mechanical behaviour of a stent during crimping, deployment or bench tests, i.e. tests in which the mechanical performance of a stent is assessed. These finite element simulations ultimately aid in the design and optimisation of a stent, reducing trial and error and time-to-market.

2.6 Optimisation of poly(L-lactic acid) bioresorbable stents

Optimisation problems are typically comprised of three fundamental elements: (i) an objective function (or response variable) to be maximized or minimized; (ii) a collection of input variables (or parameters), whose values can be manipulated in order to optimise the objective and (iii) a set of constraints, which are restrictions on the values that the input variables can take. The concept of parameterising input variables with the intention of improving (or optimising) an output function has been in use for centuries (Hernandez, 2006). However, it was not until the development of the first computer aided design system by Sutherland in 1963 that this technique would begin to utilise computational power (Sutherland, 1964; Woodbury, 2010) and pave the way for the adoption of the technique within the fields of architecture, automotive engineering, aerospace engineering, turbomachinery and stretch blow moulding (Gao et al., 1997; Yang et al., 2004; Cheung and Zhang, 2008; Athanasopoulos et al., 2009; Koini et al., 2009; Jabi, 2013).

More recently, the technique of parametric design and optimisation has seen use in the field of computational biomechanics where in vivo testing is exceptionally challenging, and may be used as a preclinical testing tool to improve stent geometry
prior to any form of physical testing (Lally et al., 2005; Bedoya et al., 2006). In order to evaluate the performance and efficacy of a stent design, simulated bench tests are typically conducted in which one (or more) performance metrics are assessed (using finite element analysis) across a variety of parametric stent geometries. For a stent to be approved for commercial application, it must fulfil a broad range of technical requirements which ensure that the device is both deliverable and deployable (Watson et al., 2017). Consequently, there is an ongoing quest to identify and design the ideal stent (De Feyter, 2001).

2.6.1 The ideal stent

It is difficult to define what constitutes an optimal stent design, given that the definition of ‘optimal’ depends on the parameters investigated and the performance metrics assessed. The ideal stent is typically considered as one that is highly deliverable, with thin-struts (to aid delivery through tortuous vascular paths) but with high radial strength and radial stiffness in order to minimise elastic recoil and to resist restenosis (Ota et al., 2014). However, this statement in itself presents a number of conflicting requirements and as a result, an optimised design will always be a trade-off. Comparative iterative refinement and parametric optimisation studies are amongst the main methods used to attain an optimum material and geometric configuration, with clinical trials employed to evaluate the efficacy of such a design. Often, a stent is required to fulfil a specific criterion based on a number of carefully selected performance metrics which ensure the safety and efficacy of the design.
2.6.2 Performance metrics

The performance metrics through which the efficacy of a stent design may be assessed fall under three main headings, dilation metrics, mechanical metrics and arterial metrics. It should be noted that the metrics discussed in this section are generally concerned with the short-term (pre-degradation) performance of the stent and are evaluated during or immediately following deployment.

2.6.2.1 Dilation metrics

Dilation metrics are concerned with the behaviour of the stent both during and immediately following deployment, and include radial recoil, foreshortening and dog-boning (Barragan et al., 2000; Migliavacca et al., 2002, 2005; Kiousis et al., 2009; Zahedmanesh et al., 2010; Pant et al., 2012; Li et al., 2017). Dog-boning refers to the faster expansion of the stent’s peripheral (or distal) edges, relative to its central region during dilation (Figure 2.9a). It is calculated as the percentage reduction between the stent’s distal radius ($R_{\text{distal}}$) and the stent’s central radius ($R_{\text{central}}$).

Dilation of the angioplasty balloon causes both elastic and plastic deformation in the stent, the elastic portion of which is recovered following deflation (unloading) of the balloon. Foreshortening of a stent refers to the axial contraction of the stent following unloading (Figure 2.9b) and is calculated as the percentage reduction between the stent length in its crimped state ($L_{\text{initial}}$) and the stent length following unloading ($L_{\text{unload}}$). The radial recoil of a stent is defined as the reduction in diameter following unloading (Figure 2.9c) and is calculated as the percentage reduction between the stent’s radius in its expanded (loaded) state ($R_{\text{load}}$) and the stent’s radius in its unloaded state ($R_{\text{unload}}$).
High values of dog-boning, foreshortening and radial recoil all negatively impact the performance of the stent. A high value of dog-boning is undesirable as the stent’s edges can lacerate the arterial wall causing neointimal proliferation, which has the potential to cause clotting and thrombosis (Lim et al., 2008). A high value of foreshortening is undesirable as excessive axial contraction of the stent affects the device positioning and may injure the endothelial layer of the artery (Kiousis et al., 2009). A high value of radial recoil is undesirable as a reduction in diameter reduces the efficacy of the stent (by reducing blood flow) and also increases the potential for restenosis (Ota et al., 2014; Wang et al., 2018).

2.6.2.2 Mechanical metrics

Mechanical metrics are concerned with the performance of the stent prior-to or immediately following inflation, with flexibility, radial stiffness and longitudinal resistance amongst the most commonly selected metrics (Grogan et al., 2012; Pant et al., 2012; Pauck and Reddy, 2015; Bobel et al., 2016; Li et al., 2017). The flexibility of a stent is commonly evaluated through the application of linearly increasing opposite moments, M, at each end rotating the stent about an angle, θ, which is normalised with respect to the length and defined as curvature, χ. The initial linear portion of the M-χ curve represents the stent’s bending stiffness, the reciprocal of which is flexibility (Petrini et al., 2004; Wu et al., 2007) (Figure 2.10a).
The radial stiffness of a stent is a measure of the change in stent diameter as a function of uniformly applied external radial force (Figure 2.10b). Alternatively, radial stiffness can be inferred from the pressure required to promote a given percentage reduction (e.g. 10%) in the stent’s outer diameter, (Grogan et al., 2012), with a minimum allowable collapse pressure of 40 kPa suggested by Agrawal et al. (1992). The longitudinal resistance of a stent is commonly evaluated through the application of a compressive load at one end and is calculated as the force required to cause a given amount of compression (Ormiston et al., 2011) (Figure 2.10c).

![Figure 2.10](image)

**Figure 2.10.** Mechanical metrics used to evaluate the performance of coronary stents including (a) flexibility; (b) radial stiffness and (c) longitudinal resistance.

High values of flexibility, radial stiffness and longitudinal resistance are ideal for stent performance. A highly flexible stent enables the surgeon to navigate tortuous anatomy when delivering the stent to the lesion and ensures that the stent conforms with the vessel after the stent is deployed (Petrini et al., 2004). A stent with high radial stiffness resists the compressive force of the artery (Rieu et al., 2002) and may be advantageous when treating calcified lesions. A stent with a high longitudinal resistance prevents it from becoming distorted under compressive or elongation forces during delivery and deployment (Ormiston et al., 2011).

### 2.6.2.3 Arterial metrics

Arterial metrics are concerned with the impact of the stent on the artery, with wall shear stress, drug elution and stent-to-artery ratio amongst the most commonly selected metrics (Migliavacca et al., 2002; Bedoya et al., 2006; Pant et al., 2011,
2012). Stresses on the arterial wall arise as a result of penetration upon expansion or due to shear stresses arising as a result of blood flow (Figure 2.11a). Drug elution (Figure 2.11b) measures the volume-averaged drug delivered into the tissue and can also provide an indication of the tissue volume that receives a less than therapeutic level of the antiproliferative drug (Pant et al., 2012). Stent-to-artery ratio (Figure 2.11c) measures the surface area of the stent \( (SA_{\text{stent, initial}}) \) in contact with the artery \( (SA_{\text{artery}}) \) and is commonly expressed as a ratio (Migliavacca et al., 2002).

![Image](image1.png)

(a) Arterial stress  (b) Drug elution  (c) Stent-to-artery ratio

**Figure 2.11.** Arterial metrics used to evaluate the performance of coronary stents including (a) arterial stress, (b) drug elution and (c) stent-to-artery ratio.

High values of arterial stress have been associated with restenosis and increased levels of neointimal hyperplasia and hence, it is desirable to minimise these stressed regions (Bedoya et al., 2006). Low values of elution mean the artery is not receiving adequate levels of the antiproliferative drug and can contribute to restenosis (Serruys et al., 2009; Pant et al., 2012). The amount of drug and its distribution is critical if the drug has a low toxic-to-therapeutic ratio (Hara et al., 2006). High values of stent-to-artery ratios have been associated with increased levels of thrombosis and myocardial infarction and hence, it is desirable to reduce this ratio (Serruys et al., 2016).
2.6.3 Improving the design of poly(L-lactic acid) stents

There are a broad range of technical requirements which must be met to ensure that a PLLA BRS is both deliverable and deployable. Mechanical testing, through *in vivo* or *in vitro* methods, and clinical trials are both commonly used to evaluate the safety and efficacy of stent designs. However, both of these testing methods are time-consuming and hence, computational analysis is commonly used to reduce the cost of testing. Through deployment and bench testing simulations, the performance metrics outlined herein may be improved. Improvements in stent design may be achieved through the combination of two factors: (i) enhancing mechanical properties of the platform material (PLLA) by tailoring the processing history and (ii) iteratively refining the stent’s shape by modifying key geometric features.

2.6.3.1 Effect of material properties on performance

The elastic modulus of the platform material, which governs the stiffness of the stent, may potentially be the most important parameter in polymeric BRS design (Pauck and Reddy, 2015). In terms of dilation metrics, a stiffer stent will be less compliant during deployment and may resist the tendency to dog-bone (Migliavacca et al., 2002). With respect to mechanical metrics, an increase in the elastic modulus will generate a stent with a higher degree of radial stiffness and longitudinal resistance (Bobel et al., 2015). Intuitively, a stiffer stent will be less flexible which is undesirable from a deliverability perspective. However, polymeric stents are typically more flexible than their metallic counterparts (Ang et al., 2017) and hence, an increase in stiffness at the expense of slightly reduced flexibility may be desirable. The influence of material properties on arterial metrics is less pronounced. In general, these metrics are more strongly influenced by the stent’s geometry. However, studies have shown the presence of bioresorbable polymer coatings may decrease stent thrombogenicity and enhance vascular healing after stent implantation, when compared to their metallic counterparts (Mani et al., 2007; Eppihimer et al., 2013).
Few studies have evaluated the influence of the elastic modulus on the mechanical performance of PLLA BRSs (Bobel et al., 2015; Pauck and Reddy, 2015). Pauck and Reddy (2015) performed computational bench testing on three commercially available stent geometries, whilst varying the elastic modulus of the platform material, PLLA. The authors concluded that a stent geometry similar to that of the Absorb BVS, with a strut thickness and a strut width of 100 μm, coupled with an elastic modulus of 9 GPa, has sufficient radial stiffness to meet the minimum collapse pressure requirement of at least 40 kPa (Agrawal et al., 1992). The elastic modulus of extruded PLLA is approximately 3 GPa (Bergström and Hayman, 2015), significantly lower than the proposed value of 9 GPa, and hence additional processing steps must be taken in order to improve upon this. Whilst a three-fold increase in the elastic modulus is difficult to physically attain, the inclusion of biaxial stretching has been shown to improve the mechanical properties of PLLA (Wu et al., 2013). Given that the relationship between elastic modulus and strut thickness has been shown to be nonlinear (Bobel et al., 2015), through careful matching of material properties to stent geometry, a physically attainable elastic modulus may be used to meet the radial stiffness threshold with a minimal increase in strut thickness (Alexy and Levi, 2013; Bergström and Hayman, 2015).

In addition to increasing the elastic modulus, increasing elongation to failure and yield strength of the platform material may improve the performance of PLLA BRSs. Currently, polymeric BRSs are prone to fracture (Iqbal et al., 2014; Elwany et al., 2017) highlighting a need for enhanced mechanical performance through material development and processing. Ductility has been identified as a significant root cause to fracture risk and increasing elongation to failure may reduce the likelihood of fracture (McMahon et al., 2018). Improving both the elongation to failure and the yield strength of PLLA may improve the ease-of-deployment of BRSs and improve their performance in treating complex or highly calcified lesions (Everaert et al., 2015).
2.6.3.2 **Effect of geometry on performance**

Stents have undergone numerous design iterations through the years with changes made to the platform material and the geometry. At their conception, they were often constructed from wire coils, however they were later superseded by slotted tube designs due to an inherent lack of radial strength. However, slotted tube stents suffer from a lack of flexibility and hence, modular ring designs (Figure 2.12) have become convention, providing improved flexibility with a minimal reduction in radial strength (Schmidt and Abbott, 2018). In a modular ring design, circumferential rings of ‘U’ shaped struts are linked together by flexible bridges. Flexible strut bridges ensure that the stent is able to be navigated through tortuous anatomy by the clinician. During dilation, the strut hoops effectively act as a plastic hinge which ensures that the stent retains its desired diameter following deflation (unloading).

![Diagram of stent components](image)

**Figure 2.12.** Various geometric features on a current generation bioresorbable coronary stent.

In order to further categorise modular ring stent designs, they are often classified as:
(a) closed or open cell; (b) having in-phase or out-of-phase circumferential rings; (c) having straight or curved bridges and (d) having a round or square cross section (Figure 2.13).
Figure 2.13. Schematic illustrating the various categorical geometric variables: (a) closed vs. open cell; (b) straight vs. curved bridges; (c) in-phase vs. out-of-phase and (d) round cross-section vs. square cross-section.

A more flexible, open-cell stent design is ideal for deliverability, especially during a surgical procedure that requires the surgeon to navigate tortuous anatomy. However, an open-cell stent design, constructed from a material with a lower yield stress — such as PLLA — may result in a more compliant stent which is heavily
prone to dog-boning (Schiavone and Zhao, 2015), and even more so if the distal ends of the stent are unsupported, i.e. if the stent is longer than the lesion (Liang et al., 2005). Comparative studies between out-of-phase stent designs with peak-to-peak connections and in-phase designs with peak-to-valley connectors have shown that the latter typically offer greater resistance to longitudinal compression (Ormiston et al., 2011; Prabhu et al., 2012). Curved bridges typically provide the stent with more flexibility when compared to straight bridges and can help mitigate the foreshortening during expansion. However, both CE approved PLLA stents (for coronary application), the Absorb BVS and the DESolve stent, are designed with straight bridges given their already improved flexibility when compared to metallic DESs (Ang et al., 2017). With regard to round vs square cross-sections, Hamuro et al. (2001) showed that the edge angle of the stent strut influenced the rate of endothelialisation. The authors noted that a smaller edge angle facilitates endothelialisation, demonstrating improvements over a square cross-section.

In addition to the classifications used to categorise modular ring stent designs in Figure 2.13, the stent’s geometry may also be parameterised in terms of strut thickness, strut width, strut length and number of struts per strut ring (Figure 2.14).

![Schematic illustrating the various numeric geometric variables: strut thickness, t; strut width, w; strut length, l and number of struts per ring, n.]

Figure 2.14. Schematic illustrating the various numeric geometric variables: strut thickness, t; strut width, w; strut length, l and number of struts per ring, n.

Increasing strut thickness has been shown to improve radial strength, radial stiffness and the recoil performance for PLLA BRSs, however this comes at the expense of deliverability and flexibility, and has also been shown to promote angiographic restenosis (Kastrati et al., 2001; Briguori et al., 2002; Pache et al., 2003). The
Intracoronary Stenting and Angiographic Results: Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO) trial was conducted with a group of 651 patients treated with two commercially available stents of comparable design but different strut thicknesses (50 μm and 140 μm), in order to assess whether a thinner strut design reduces the likelihood of angiographic restenosis. Evaluation of study results (after one year) revealed a 10% reduction in the incidence of angiographic restenosis for the thin-strut group compared to the thick-strut group, and a 5% reduction in reintervention rates (Kafrati et al., 2001). This study raised the issue as to whether strut thickness is a predictor of restenosis across different stent designs and prompted the follow-on ISAR-STEREO-2 trial, in which a group of 611 patients were treated with either a thin-strut (50 μm), open-cell stent or a thick-strut (140 μm), closed-cell stent. Study results showed an incidence of 17.9% in angiographic restenosis in the thin-strut group vs. 31.4% in the thick strut group. The results of this study were further supported in a study by Briguori et al. (2002), which performed retrospective analysis of 821 patients treated with 14 unique stent designs. The study results showed an angiographic restenosis rate of 28.5% for thin-strut designs (< 100 μm) vs. 36.6% for thick-strut designs (> 100 μm), and concluded that strut thickness was an independent predictor of angiographic restenosis.

Increasing strut width has a similar effect to increasing strut thickness in that radial stiffness and recoil are improved, based on a cross-comparison of the parametric studies conducted by García et al. (2012), Li et al. (2017), Migliavacca et al. (2002), Pant et al. (2012), Pant et al. (2011) and Timmins et al. (2007). Increasing strut width increased the level of plastic deformation within the strut hoops, which reduced the degree of elastic recoil and resisted the compressive forces typically exerted by the artery. Additionally, increasing strut width improved drug delivery due to the higher contact area with the artery. However, these improvements came at the expense of the stent-to-artery ratio, foreshortening and flexibility.
Decreasing strut length has been shown to improve radial stiffness and recoil, however this also negatively affects drug elution and foreshortening (Bedoya et al., 2006; Pant et al., 2012). Bedoya et al. (2006) also showed that the spacing between stent struts was the most dominant independent predictor of high arterial stresses and suggest that stent designs should incorporate large axial strut spacing, blunted corners at bends and high amplitudes of strut rings. However, Pant et al. (2012) showed that whilst strut length has an effect on flexibility, it does not influence this parameter as much as the strut width or the strut bridge geometry.

Reducing the number of struts per circumferential ring and number of strut-strut interactions has been shown to reduce thrombus formation and neointimal hyperplasia (Rogers and Edelman, 1995; Takebayashi et al., 2004). Garasic et al. (2000) examined the vascular response of rabbit iliac arteries (n = 28) to stent expansion, and after 28 days found that stents designed with 12 struts per circumferential ring had 50% less thrombus formation than identical stents with 8 struts per circumferential ring. A similar study on rabbit iliac arteries by Rogers & Edelman (1995) showed that a 29% reduction in strut-strut intersections (keeping stent mass and surface area constant) was enough to reduce vascular injury by 42%, thrombosis formation by 69% and neointimal hyperplasia by 38%.

2.7 Concluding remarks

2.7.1 Summary of literature reviewed

Bioresorbable PLLA stents are a promising technology and have shown some success at a clinical level. However, the increased strut profiles (compared to metallic DESs) of PLLA BRSs have been shown to promote thrombosis and myocardial infarctions following their implantation within the body. Emphasis must therefore be placed on improving the short-term (pre-degradation) performance of PLLA BRSs by reducing strut profiles and improving radial strength and stiffness. Improvements in PLLA stent design may be attained by: (i) enhancing mechanical
properties of the platform polymer by tailoring the biaxial stretching processing history and (ii) iteratively refining the stent’s shape by modifying key geometric features.

Stretch blow moulding can be used to improve the elastic modulus, yield strength and elongation to failure of PLLA, which may enable the design of stents with reduced strut profiles. The reviewed literature suggests that temperature, stretch ratio, strain rate, and deformation mode during biaxial stretching affect these mechanical properties. However, the interdependencies between these processing parameters and their effect on these mechanical properties have not been investigated for PLLA. Furthermore, the reviewed literature also suggests that PLLA’s post-processing mechanical response depends on temperature, strain rate and processing history. As a result, its physical behaviour is difficult to predict using simple constitutive models. From the reviewed literature, few models capture the anisotropic, rate-dependent and temperature-dependent nature of PLLA.

Computational simulations are used to assess the performance and efficacy of a given stent geometry across a series of metrics that capture the conflicting requirements for a stent. The reviewed literature suggests that strut thickness, strut width, strut length and the number of struts per strut ring all influence the performance of the stent during and immediately following deployment. Parametric optimisation studies have been used to refine stent geometry to optimise a subset of dilation metrics, mechanical metrics and arterial metrics. However, the influence of the material’s processing history, which in turn influences the material properties, is often ignored in these studies. Given that biaxial deformation has been shown to improve PLLA’s mechanical properties, it is hypothesised that the SBM processing history must not be neglected when optimising the design of a BRS. To the best of the author’s knowledge, no study has considered the combined effect of the biaxial stretching processing history and strut geometry on stent performance.
2.7.2 Aims and objectives

This thesis aims to address the challenge of designing mechanically effective but sufficiently thin PLLA stents through a parallel experimental and computational approach that optimises material properties and stent geometry. A flowchart of the research methodology within this thesis is presented in Figure 2.15, with key objectives discussed below:

(i) Replicate the biaxial stretching processing history of a PLLA coronary stent and evaluate the improvement in short-term (pre-degradation) mechanical properties against extruded PLLA. Evaluate the influence of biaxial stretching processing parameters on the mechanical properties of the stretched sheet, identify the most critical factor(s) and establish processing-property relationships (Chapter 3)

(ii) Perform experimental characterisation of post-biaxially stretched PLLA sheet for various combinations of processing parameters, temperatures and extension rates that are representative of those conditions typically experienced by a stent from processing through to deployment within the body. Calibrate a representative constitutive model based on the processing-property relationships established in Chapter 3 (Chapter 4)

(iii) Generate parametric PLLA stent designs by varying the biaxial stretching processing history and stent geometry. Perform finite element simulations for each design, using the constitutive model developed in Chapter 4, and evaluate key performance metrics. Establish a set of statistical surrogate models that relate performance metrics to the design parameters. Finally, perform multi-objective optimisation using these statistical models in order to identify an optimal stent design within a given set of constraints (Chapter 5)
Figure 2.15. Flowchart illustrating the research methodology used for the work conducted within this thesis.
3. Processing-property relationships of biaxially stretched poly(L-lactic acid)\(^1\)

3.1 Overview

The development of coronary stents from PLLA requires knowledge of its mechanical properties and the effects of manufacturing processes on those properties. Stretch blow moulding can be used to improve the mechanical properties of the polymer (Alexy and Levi, 2013). The SBM process imposes a state of biaxial strain on the parison and may be replicated using a biaxial tensile test machine that stretches polymer sheet in a planar configuration (Menary et al., 2012). The reviewed literature suggests that temperature, stretch ratio, strain rate, and deformation mode each affect biaxial deformation behaviour and the resultant mechanical properties of the stretched sheet. However, to the best of the authors’ knowledge, the interdependencies between these aforementioned processing parameters and their effect on the elastic modulus and yield strength of the post biaxially stretched sheet have not been investigated for PLLA. The aim of the present chapter is to replicate the processing history of a polymeric coronary stent and evaluate the improvement in short-term (pre-degradation) mechanical

\(^1\) A manuscript based on this work titled “Processing-property relationships of biaxially stretched poly(L-lactic acid) sheet for application in coronary stents” has been published in the Journal of the Mechanical Behavior of Biomedical Materials.
properties of extruded PLLA post biaxial stretching, in order to facilitate the design of high stiffness, thin strut polymeric stents.

### 3.2 Material and methods

Pellets of PLLA (Tradename: Plurapol LX175) were donated by Corbion Purac (Amsterdam, The Netherlands). The pellets were dried for 12 h at 70 °C to remove the moisture prior to melt processing. Melt extrusion was performed using an E 25 M Dr Collin single screw extruder (Dr. Collin GmbH, Germany). During the extrusion process, the barrel temperature was set at 200 °C with a screw speed of 50 rpm and a CR 136/350 chill roll stack (Dr. Collin GmbH, Germany) temperature of 50 °C. Gel permeation chromatography (GPC) was performed on both pellets and extruded sheet in order to ensure that molecular weight did not significantly decrease during melt processing. An Agilent Technologies 1260 Infinity GPC system (Agilent Technologies, USA) with an eluent of tetrahydrofuran containing 2.0% v/ v triethylamine and 0.05% w/ v butylated hydroxytoluene inhibitor was used. Post-processing of the results was performed using Cirrus GPC software (Agilent Technologies, USA).

Poly(L-lactic acid) samples, each with dimensions of 76 mm x 76 mm x 1 mm were prepared for biaxial stretching, which was performed using a custom-built machine (Martin et al., 2005) that was designed to replicate the deformation behaviour of polymeric materials during SBM under controllable conditions (i.e. deformation mode, deformation temperature, and deformation rate). The biaxial stretching machine is capable of supplying a maximum stretch speed of 2400 mm/s, equivalent to an average nominal strain rate (ε) of 32 s⁻¹, and a maximum stretch ratio (λ) of 4.5 in both the machine direction (MD) and the transverse direction (TD). A constant temperature of up to 200 °C is attainable and the deformation mode may be varied from simultaneous (SIM) biaxial deformation to sequential (SEQ) biaxial
deformation (Figure 3.1) (Martin et al., 2005). Details of user-defined test conditions may be found in subsequent sections.

Uniaxial tensile testing was performed using an Instron 5564 Universal Material Testing machine (Instron, UK) to determine the elastic modulus and yield strength of both unstretched and biaxially stretched sheet. Uniaxial testing was conducted in accordance with the test protocol as outlined in ISO 527-2 Type 1BA (ISO, 1996). The samples (n = 3) tested were dumb-bell in shape; samples were punched from unstretched sheet in the extrusion direction (ED) and the TD, whilst samples were punched from biaxially stretched sheet in the MD and the TD. All samples were tested at room temperature (20 °C ± 3 °C) at an extension rate similar to that recommended for bioresorbable stent deployment (5 mm/min), according to published guidelines from Abbott (Abbott, 2012). Specimens were tested to a maximum strain of 0.05, by which point all specimens had yielded, and their elastic modulus (E) and yield strength (σ_y) were evaluated.

![Diagram](image)

**Figure 3.1.** Biaxial deformation parameters used to replicate SBM processing history for (a) simultaneous (SIM) biaxial deformation and (b) sequential (SEQ) biaxial deformation.

A design of experiments (DoE) approach was employed to identify the biaxial stretching processing parameters that most significantly affect the elastic modulus and yield strength of the stretched sheet. A one-half fraction of a six factor, two-
level factorial ($2^{k-1}$) randomised design was used with the following factors: stretch ratio in the MD ($\lambda_{MD}$), stretch ratio in the TD ($\lambda_{TD}$), deformation speed in the MD ($\dot{\varepsilon}_{MD}$), deformation speed in the TD ($\dot{\varepsilon}_{TD}$), temperature ($T$), and deformation mode. A $2^{k-1}$ fractional factorial is an example of a resolution VI design and, hence, main factors are aliased with five-way interactions (and above), whilst two-way interactions are aliased with three-way interactions (and above). Design of experiments screening permits the significant factors to be isolated from those that have minimal effect on the response variable(s). Preliminary testing was performed to identify upper and lower limits for the processing parameters evaluated under the DoE (Table 3.1). Samples were heated for 3 min prior to biaxial stretching in order to achieve uniform temperature distribution through the thickness. The temperature was held within the range 80–90 °C; below 80 °C the polymer behaved as a glassy solid whilst above 90 °C the polymer began to undergo cold-crystallisation. The strain rate was held within the range 1–16 s$^{-1}$, with faster rates leading to grip slippage during stretching. The maximum total area of deformation ($A_{total}$), defined as the product of the stretch ratios in the MD and the TD, which could be consistently achieved was 9, which was attainable through a 3 x 3 equibiaxial deformation — hence, the stretch ratio was held within the range 2-3. Response surface methodology (RSM) was employed to refine the design space of the significant factors, with multiple regression analysis performed on the results using R (version 3.4.0) (R Core Team, 2017) in order to provide an empirical correlation between biaxial stretching processing parameters and the mechanical properties of the stretched sheet.

Table 3.1. High and low levels for stretch ratio in MD ($\lambda_{MD}$), stretch ratio in TD ($\lambda_{TD}$), deformation speed in MD ($\dot{\varepsilon}_{MD}$), deformation speed in TD ($\dot{\varepsilon}_{TD}$), temperature ($T$) and deformation mode evaluated under the design of experiments (DoE).

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>$\dot{\varepsilon}_{MD}$ (s$^{-1}$)</th>
<th>$\dot{\varepsilon}_{TD}$ (s$^{-1}$)</th>
<th>$\lambda_{MD}$ (-)</th>
<th>$\lambda_{TD}$ (-)</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>SEQ</td>
</tr>
<tr>
<td>90</td>
<td>16</td>
<td>16</td>
<td>3</td>
<td>3</td>
<td>SIM</td>
</tr>
</tbody>
</table>
Differential scanning calorimetry (DSC) was conducted on both unstretched and biaxially stretched sheet to evaluate both the crystallinity and the thermal characteristics of the polymer. Test samples \( (n = 3) \) were taken from randomly selected sections over the PLLA sheet, weighing approximately 8 mg, and placed individually into an aluminium pan, sealed and subjected to a heating cycle of 10 °C/min between the limits of 30 °C and 180 °C, using a PerkinElmer DSC6 (PerkinElmer, USA). Post-processing of the results was performed using Pyris™ software (version 9.0) (Perkin-Elmer, USA) to identify crystallinity \( (X_c) \), glass transition temperature \( (T_g) \), cold-crystallisation temperature \( (T_{cc}) \), and the melting temperature \( (T_m) \) of the polymer. The crystallinity was calculated using (3.1) (Lovdal et al., 2017), in which the enthalpy induced by cold-crystallisation \( (\Delta H_{cc}) \) is subtracted from the enthalpy induced by melting \( (\Delta H_m) \) and measured relative to the enthalpy of fusion \( (\Delta H^o) \). The value of \( \Delta H^o \) was set to 93 J/g, based on the value for a 100% crystalline PLLA sample (Wunderlich, 1990).

\[
X_c (\%) = \frac{(\Delta H_m - \Delta H_{cc})}{\Delta H^o} \times 100\% 
\]  

(3.1)

### 3.3 Results

#### 3.3.1 Unstretched sheet

The mechanical and thermal properties for unstretched PLLA (Table 3.2) demonstrated that the polymer is relatively amorphous (approximately 4% crystallinity). A two-sample t-test showed no significant statistical difference \( (p > 0.05) \) between the moduli in the extrusion direction (ED) and the TD. Whilst yield strength showed a 14% difference between the ED and the TD, the polymer was assumed to have limited preferential orientation post-extrusion. The shape of the stress-strain curves resembled those shown in Figure 2.8b and Figure 2.8c, with a pronounced yield, immediately followed by softening. The results of GPC indicated that there was no significant reduction in molecular weight during melt
processing, with both the pellets and extruded sheet having a weight-average molecular weight and polydispersity index of approximately 230 kg mol$^{-1}$ and 2.0, respectively. It should be noted that whilst the PLLA tested in this chapter is intended for use packaging applications, its molecular weight and mechanical properties are similar to that of medical grade PLLA (Harper et al., 2012; Ahlinder et al., 2018). The properties outlined in Table 3.2 were used as comparative measures to evaluate the effect of the biaxial stretching process on the mechanical and thermal properties of the polymer at a macro- and microstructural level.

**Table 3.2.** Elastic modulus ($E$) and yield strength ($\sigma_Y$) for samples taken from the extrusion direction (ED) and transverse direction (TD), crystallinity ($X_c$) and thermal transitions ($T_g$, $T_{ce}$, $T_m$) for unstretched PLLA sheet.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{ED}$ (MPa)</td>
<td>2315 ± 137</td>
</tr>
<tr>
<td>$E_{TD}$ (MPa)</td>
<td>2181 ± 129</td>
</tr>
<tr>
<td>$\sigma_{Y,ED}$ (MPa)</td>
<td>55 ± 1</td>
</tr>
<tr>
<td>$\sigma_{Y,TD}$ (MPa)</td>
<td>48 ± 2</td>
</tr>
<tr>
<td>$X_c$ (%)</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>$T_g$ (°C)</td>
<td>62 ± 0.8</td>
</tr>
<tr>
<td>$T_{ce}$ (°C)</td>
<td>120 ± 0.3</td>
</tr>
<tr>
<td>$T_m$ (°C)</td>
<td>149 ± 0.1</td>
</tr>
</tbody>
</table>

### 3.3.2 Stretched sheet

Main effect plots (Figure 3.2a and Figure 3.2b) were generated based on the results from the 32-run DoE (Table 3.3) and describe the effect of each factor on the elastic modulus and yield strength, independent from all other factors. The steeper the slope of the line, the greater the magnitude of that main factor’s effect; the dotted line for each response variable represents the mean value across all runs. The elastic modulus and yield strength of the stretched sheet are, in general, most significantly affected by stretch ratio, with strain rate, temperature, and deformation mode each having a relatively lesser effect. The absolute effects of all main factors and two-way interactions on the elastic modulus and yield strength are annotated on half-normal probability plots (Figure 3.3a–d), with effects that are statistically significant ($p < 0.05$) highlighted on each graph. The effects of statistically insignificant factors (and interactions) describe a straight line on the plots, whilst the effects of
statistically significant factors (and interactions) are displaced from this line. The further the distance a factor or interaction is from the line, the more significant its effect. In general, two-way interactions are statistically insignificant, with stretch ratio in both the MD and the TD having the most dominant effect. An increased elastic modulus and yield strength in a given direction was obtained by increasing the stretch ratio in that direction, with a further increase attainable if the stretch ratio in the TD was reduced. Setting all factors to their optimum level increased the $E_{MD}$ and $E_{TD}$ by 49% and 62%, respectively when compared to all factors set at their pessimal level, and the $\sigma_{MD}$ and $\sigma_{TD}$ increased by 47% and 52%, respectively.

![Graph showing the relationship between E and $\lambda$](image1.png)

**Figure 3.2.** Main effect plots highlighting the dominance of stretch ratio in the machine direction (MD) and the transverse direction (TD) for (a) Elastic modulus ($E$) of PLLA sampled from the MD and the TD, $E_{MD}$ and $E_{TD}$, respectively; and (b) Yield strength ($\sigma_y$) in the MD and the TD, $\sigma_{y,MD}$ and $\sigma_{y,TD}$, respectively.
Table 3.3. Elastic modulus (E) and yield strength (σ) of specimens selected for the 32-run design of experiments (DoE) sampled from the machine direction (MD) and transverse direction (TD).

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Figure 3.3. Half-normal probability plots for main factors and two-way interactions highlighting the dominance of stretch ratio in the machine direction (MD) and the transverse direction (TD) for (a) Elastic modulus (E) in the MD, $E_{MD}$; (b) Elastic modulus (E) in the TD, $E_{TD}$; (c) Yield strength ($\sigma_Y$) in the MD, $\sigma_{Y,MD}$ and (d) Yield strength ($\sigma_Y$) in the TD, $\sigma_{Y,TD}$.

Although the $2^{6-1}$ fractional factorial design matrix permitted the evaluation of asymmetrical biaxial deformations such as 2 x 3 and 3 x 2, it was incapable of capturing the response of highly asymmetrical deformations, approaching that of a constant width deformation (where one axis is fully constrained). Response surface methodology was employed to refine the design space and provide an empirical correlation between stretch ratio and the mechanical properties of the polymer. The range of stretch ratios evaluated was modified from the DoE to include a low level of 1.5 and a high level of 3.5. Temperature was held constant at 80 °C, stretch speed
in MD and TD was also held constant at 16 s$^{-1}$ and a sequential deformation mode was used, with the aforementioned conditions providing the most repeatable deformation during biaxial tensile testing.

Multiple regression analysis of the RSM results (Table 3.4) was performed to generate 2D contour plots that relate both elastic modulus and yield strength to the stretch ratio (Figure 3.4a–d). The stepwise routine identifies a model containing the intercept, main factors, interaction and both squared terms. Empirical relations were generated from the regression analysis for both modulus and yield strength, including effects that were statistically significant ($p < 0.05$) with (3.2)–(3.5) achieving adjusted R-squared ($R^2_{adj}$) values of 0.97, 0.93, 0.98 and 0.87, respectively.

**Table 3.4.** Elastic modulus ($E$) and yield strength ($\sigma$) of specimens selected for the 12-run response surface methodology (RSM) sampled from the machine direction (MD) and transverse direction (TD).

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\[
E_{MD} = 1305 + 998\lambda_{MD} + 20\lambda_{TD} - 184\lambda_{MD}^2\lambda_{TD} \quad (3.2)
\]
\[
E_{TD} = 5499 - 2704\lambda_{MD} + 444\lambda_{TD} + 428\lambda_{MD}^2 \quad (3.3)
\]
\[
\sigma_{Y,MD} = 36.8 + 17.4\lambda_{MD} + 1.6\lambda_{TD} - 3.2\lambda_{MD}^2\lambda_{TD} \quad (3.4)
\]
\[
\sigma_{Y,TD} = 61.9 - 7.4\lambda_{MD} + 8.6\lambda_{TD} \quad (3.5)
\]
The thermal and microstructural properties of the RSM specimens are of particular interest when plotted against the $A_{\text{rel}}$, calculated as the product of $\lambda_{\text{MD}}$ and $\lambda_{\text{TD}}$ (Figure 3.5a–d). Results show that there was no statistical correlation between either $X_c$ or $T_m$ and $A_{\text{rel}}$, with $R^2$ values of 0.06 and 0.03, respectively. The $T_g$ and $T_\alpha$, both show correlation with $A_{\text{rel}}$, with $R^2$ values of 0.53 and 0.71, respectively.
Figure 3.5. Total area of deformation ($A_{\text{def}}$) plotted against (a) Crystallinity, $X_c$; (b) Glass transition temperature, $T_g$; (c) Cold-crystallisation temperature, $T_{cc}$; and (d) Melting temperature, $T_m$ for response surface methodology specimens.

3.4 Discussion

In this chapter, the processing history of a polymeric coronary stent was replicated using a custom-built biaxial tensile test machine, in order to evaluate the improvement in short-term (pre-degradation) mechanical properties of extruded PLLA post biaxial stretching. Given that the elastic modulus of the platform material is considered to be the most important parameter in bioresorbable stent design (Bobel et al., 2015; Pauck & Reddy, 2015), optimising processing conditions has the potential to facilitate the design of high stiffness, thin-strut polymeric stents for the application of coronary stents.
Results presented within this chapter show that biaxial deformation has the potential to enhance the elastic modulus and yield strength of extruded PLLA sheet by approximately 80% (maximum of 4093 MPa) and 70% (maximum of 84 MPa), respectively, with the aforementioned mechanical properties most significantly affected by stretch ratio during processing. An increased elastic modulus and yield strength in a given direction were obtained through increasing the stretch ratio, with a further increase attainable if the stretch ratio in the TD was reduced. Conversely, sequentially deformed sheets exhibited in-plane isotropy suggesting that the orientation developed during the first stretch was destroyed as a result of the second transverse stretch, supporting the hypothesis of Ou & Cakmak (2008). Intuitively, this is to be expected, as a highly asymmetrical biaxial deformation tending towards constant width deformation has been shown to enhance the mechanical properties in the direction of stretching for other semi-crystalline polymers (Marco et al., 2002). Strain rate, temperature, and deformation mode each had a lesser effect on the mechanical properties of the stretched sheet, when compared to that of stretch ratio. The deformation mode (SIM or SEQ) did not significantly affect the elastic modulus or yield strength in either the MD or the TD, suggesting that whilst the sequence in which the strain occurs during biaxial processing influenced crystal orientation (Løvdal et al., 2016; Ou & Cakmak, 2008), it has a limited effect on the resulting mechanical properties of the stretched PLLA sheet.

The results of DSC analysis showed there is no statistically significant relationship between crystallinity and total area of deformation, suggesting that molecular orientation may be more important than crystallinity to enhance elastic modulus and yield strength of biaxially stretched sheets. There exists an inverse relationship between $T_{\text{cc}}$ and the degree of amorphous orientation in semi-crystalline polymers (Gowd et al., 2004; Vasanthan et al., 2013). Results presented within this chapter showed that a similar relationship exists between $T_{\text{cc}}$ and total area of deformation. Furthermore, results showed an increase in glass transition temperature with total
area of deformation, which may be due to limited chain motion as a result of increased molecular orientation (Tsai et al., 2010). Such findings support the hypothesis of (Løvdal et al., 2016), who suggested that mechanical properties of PLLA are related to strain-induced amorphous orientation rather than strain-induced crystallinity. Results presented within this chapter showed that specimens subjected to an equibiaxial stretch ratio of 2 had a significantly lower value of crystallinity than those subjected to a stretch ratio of 2.5 (and above). Wu et al. (2013) observed a similar trend, suggesting that this may potentially be the critical level of elongation beyond which strain-induced crystallisation occurs. Such a hypothesis has already been proven for poly(ethylene terephthalate), with Marco et al. (2002) noting that crystallinity was increased beyond a stretch ratio of 2.

The empirical relations (3.2)–(3.5) and contour plots (Figure 3.4a–d) relate the mechanical properties of the stretched sheets to the stretch ratio during biaxial processing, with the intention that they may be used to aid in the design and process optimisation of coronary stents. However, defining a set of stretch ratios to provide optimum mechanical properties in both the MD and the TD is not possible, given that both factors directly counteract each other. Increasing stretch ratio in the MD will increase the elastic modulus in MD, however this will reduce the elastic modulus in the TD, and vice versa. The optimal solution will primarily be governed by the loading requirements experienced by a vascular stent in vivo. One concern for polymeric stents is that they do not possess the same degree of radial stiffness as that of a metallic stent. A stent must possess significant radial stiffness to provide support to the displaced arterial wall, which would suggest that it may be beneficial to process the polymer such that it has a preferential circumferential orientation. Increasing circumferential modulus (to increase radial stiffness of the stent) should result in reduced axial modulus (and thus flexural stiffness of the stent), enabling the design of flexible stents (for tortuous arterial morphologies) that possess sufficient radial stiffness. However, a reduced axial modulus also increases the
stent’s longitudinal compressibility (which can lead to stent malapposition) and hence, an optimal stent design will always be a trade-off.

Finally, the processing-property relationships presented in this chapter provide an understanding of the effect of processing parameters on the mechanical response of PLLA. However, the modulus and yield strength of the post biaxially stretched sheets were measured at room temperature (20 °C), at an extension rate of 5 mm/min. Literature has shown the mechanical response of PLLA to be dependent on both strain-rate and temperature (Løvdal et al. 2015). In the next chapter, the testing framework is adapted to account for this strain rate and temperature dependency, in order to calibrate a representative constitutive model.

3.5 Conclusion

The processing history of a polymeric coronary stent was replicated using a custom-built biaxial tensile test machine in order to assess the improvement in short-term (pre-degradation) mechanical properties of extruded PLLA. Results indicated that biaxial deformation has the potential to enhance the elastic modulus and yield strength of extruded PLLA sheet by approximately 80% and 70%, through selection of optimal processing conditions. The elastic modulus and yield strength of the biaxially stretched sheets were highly dependent on the stretch ratio during processing, with temperature, strain rate and deformation mode each having a comparatively less significant influence on these mechanical properties. Empirical equations have been proposed that relate these mechanical properties to the stretch ratio during processing. The highest values of elastic modulus and yield strength were obtained through highly asymmetrical biaxial deformation, tending towards pure constant width. The results of DSC suggest that this increase in mechanical properties is not directly attributable to crystallinity content, but instead due to amorphous orientation (based on the inverse relationship observed between the $T_c$ and the total area of deformation of biaxially stretched sheet).
4. Characterisation and constitutive modelling of biaxially stretched poly(L-lactic acid)$^2$

4.1 Overview

A PLLA stent is exposed to a variety of processing techniques, temperatures and environmental conditions during its lifecycle, from the manufacturing process, to crimping through to deployment within the body. The reviewed literature shows that comprehensive mechanical characterisation has been performed for PLLA in order to calibrate constitutive models that capture (i) the anisotropy as a result of the processing history (Pauck and Reddy, 2015); (ii) the temperature-dependent behaviour (Wang et al., 2017); and (iii) the rate-dependent behaviour (Debuschere et al., 2015). However, each has been shown to affect the mechanical properties of the polymer and should not be considered in isolation. A constitutive modelling framework must therefore be established such that the anisotropic, rate-dependent and temperature-dependent nature of the polymer may be accurately captured. To the best of the authors’ knowledge, the interdependencies between processing history and post-processing conditions, such as temperature and extension rate, have not

$^2$ A manuscript based on this work titled “Characterisation and constitutive modelling of biaxially stretched poly(L-lactic acid) sheet for application in coronary stents” has been published in the Journal of the Mechanical Behavior of Biomedical Materials.
been evaluated experimentally and hence, a representative constitutive model does not exist. The aim of the present chapter is to experimentally evaluate the effect of post-processing temperature and post-processing extension rate on the short-term (pre-degradation) mechanical and viscoelastic properties of biaxially stretched PLLA sheet, subjected to various processing histories. Following experimental characterisation, a representative constitutive model was calibrated to the results in order to facilitate the design of high stiffness, thin strut polymeric stents.

4.2 Materials and methods

The strain history achieved during SBM was replicated using the same custom-built biaxial tensile test machine (Martin et al., 2005) and extruded PLLA (Tradename: Plurapol LX175) as presented in Chapter 3. Biaxial deformation was performed using a sequential deformation mode (Figure 4.1), with specimens initially undergoing constant width deformation in the machine direction (MD), followed by a second (constant width) deformation in the transverse direction (TD). Specimens were heated to a temperature (T) of 80 °C for 3 min, and deformed at a speed of 16 s⁻¹ in the MD (ε_md) and the TD (ε_td). The aforementioned conditions provided the most repeatable deformation during biaxial tensile testing, based on the results presented in Chapter 3, in which the stretch ratio in the MD (λ_md) and the stretch ratio in the TD (λ_td), along with the aspect ratio (A_r) between the pair, defined as the ratio of λ_td to λ_md (4.1), were shown to have the most significant effect on both the elastic modulus (E) and yield strength (σ) of the polymer.

Figure 4.1. Sequential biaxial deformation technique used to replicate the SBM processing history.
$$A_t = \frac{\lambda_{TD}}{\lambda_{MD}} \quad (4.1)$$

Dynamic mechanical analysis (DMA) was conducted on the biaxially stretched sheet to evaluate the $T_g$ and the storage modulus ($E'$) of PLLA as a function of frequency (f) using a Tritec 2000 DMA (Triton Technology Ltd., UK), running Tritec 2000 DMA version 1.43.00 software. Samples of 10 mm x 4 mm (length x width) were punched from biaxially stretched sheet in the MD and the TD. Testing was performed under tension configuration, with all samples having a thickness of < 1 mm. Temperature scans were performed at a heating rate of 5 °C/min between the limits of 20 and 130 °C, at frequencies of 0.1, 1 and 10 Hz. These DMA frequencies were selected to induce strain rates in the specimen comparable to those induced during polymeric stent expansion ($10^4$–$10^4$ s$^{-1}$) (Bobel et al., 2016). The $T_g$ was identified by the onset of the drop in $E'$. Frequency scans were performed between the limits of 0.1 and 10 Hz at room temperature (20 ± 3.0 °C), body temperature (37 ± 3.0 °C) and a crimping temperature (55 ± 3.0 °C), which was selected based on the results of the temperature scans presented in the following section. A dynamic displacement of 0.005 mm was used for all tests, with preliminary testing performed to ensure that the linear viscoelastic regime of the polymer was not exceeded.

A DoE approach was employed to identify the biaxial stretching processing parameters and post-processing uniaxial tensile test conditions that most significantly affect the elastic modulus of PLLA in the MD and TD ($E_{MD}$ and $E_{TD}$) and the yield strength in the MD and the TD ($\sigma_{Y,MD}$ and $\sigma_{Y,TD}$). A three-level, three factor, full factorial ($3^3$) randomised design was used with the following factors: the $A_t$ of the biaxial deformation, temperature during uniaxial deformation, and extension rate during uniaxial deformation. The temperature and extension rate during uniaxial deformation refer to post-processing conditions, hereafter referred to as post-processing temperature ($T_{pp}$) and post-processing extension rate ($\dot{e}_{pp}$), and are not to be misinterpreted as the temperature and extension rate applied during
biaxial deformation. Preliminary testing was performed to identify upper and lower limits for the parameters evaluated under the DoE (Table 4.1). The $A_s$s of the biaxial deformation were selected to induce varying degrees of anisotropy based on the results presented in Chapter 3. Specifically, $3 \times 3 \ (\lambda_{MD} \times \lambda_{TD})$ equibiaxial deformation ($A_s = 1.0$), $2 \times 3$ asymmetrical deformation ($A_s = 1.5$) and $1.5 \times 3.5$ highly asymmetrical deformation ($A_s = 2.3$) were selected. It should be noted that for each of these $A_s$s, the value of either $\lambda_{MD}$, $\lambda_{TD}$, or both, is greater than 2, as this was shown to be the critical level of elongation beyond which mechanical properties improved.

The uniaxial tensile properties (i.e. $E$ and $\sigma_y$) of the biaxially stretched sheet was determined in accordance with ISO 527-2 Type 1BA (ISO, 1996) using an Instron 5564 Universal Material Testing machine (Instron, UK). The samples tested ($n = 3$) were dumb-bell in shape; samples were punched from biaxially stretched sheet in the MD and the TD. Uniaxial tensile testing was performed under room temperature ($20 \pm 3.0 \ ^\circ\text{C}$), body temperature ($37 \pm 3.0 \ ^\circ\text{C}$) and a crimping temperature ($55 \pm 3.0 \ ^\circ\text{C}$), using a 3119 Series Instron Environmental Chamber (Instron, UK). The values of $\dot{\varepsilon}$ selected were 1, 5 and 10 mm/min, based on the recommended deformation speeds for polymeric stent expansion (Abbott, 2012). Multiple regression analysis was performed on the results using R (version 3.4.0) (R Core Team, 2017) to provide an empirical correlation between the factors included in the DoE and the mechanical properties of the stretched PLLA sheet. Additionally, in order to gain insight into the mechanical response of PLLA during unloading, tensile tests were performed in which each specimen was loaded to a specified strain level before being subsequently unloaded at the same crosshead speed (under displacement control) to zero load. A subset of specimens was selected and tested to strain levels of 0.1 and 0.25. This test procedure replicates the deformation behaviour typically observed during the recoil (or springback) of a stent as the balloon is deflated.
Table 4.1. High, medium and low levels for the aspect ratio ($A_r$) of the biaxial deformation, post-processing temperature ($T_{pp}$) and post-processing extension rate ($\dot{\varepsilon}_{pp}$) evaluated under the DoE.

<table>
<thead>
<tr>
<th>$A_r$</th>
<th>$T_{pp}$</th>
<th>$\dot{\varepsilon}_{pp}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)</td>
<td>(°C)</td>
<td>(mm/min)</td>
</tr>
<tr>
<td>1.0</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>1.5</td>
<td>37</td>
<td>5</td>
</tr>
<tr>
<td>2.3</td>
<td>55</td>
<td>10</td>
</tr>
</tbody>
</table>

4.3 Experimental results

The results of the DMA (Figure 4.2a and Figure 4.2b) indicated there is a statistically significant relationship ($p < 0.05$) between the $T_g$ and f for samples taken from biaxially stretched PLLA sheet in both the MD and the TD. However, no such relationship was found between the $T_g$ and the $A_r$, based on the results of two-way analysis of variance (ANOVA). A two-sample t-test showed no significant statistical difference ($p > 0.05$) between the $T_g$ in the MD and the TD. Abbott’s patented method for crimping a polymeric stent onto a delivery balloon (Jow et al., 2017) states that the stent is to be crimped at a temperature between the $T_g$ and 15 °C below the $T_g$. Hence, 55 °C was used as a crimping temperature for the DoE.

Figure 4.2. Glass transition temperature ($T_g$) at a given frequency (f) and aspect ratio ($A_r$) of biaxially stretched PLLA sampled from (a) the machine direction (MD) and (b) the transverse direction (TD).
Main effect plots from the DoE (Figure 4.3a and Figure 4.3b) were generated based on the results of the 27-run DoE (Table 4.2) and describe the effect of each factor on each response variable (i.e. $E_{MD}$, $E_{TD}$, $\sigma_{Y,MD}$ and $\sigma_{Y,TD}$), independent of all other factors. The steeper the slope of the line between factor levels, the greater the magnitude of the effect; the dotted line for each response variable represents the mean value across all runs. In general, E and $\sigma_Y$ are most strongly affected by $A_r$ and $T_{pp}$, with $\hat{e}_{pp}$ having a relatively weaker effect. Furthermore, increases in $E_{TD}$ and $\sigma_{Y,TD}$ are obtained by increasing the $A_r$ beyond unity ($A_r > 1$), however this comes at the expense of a reduction in $E_{MD}$ and $\sigma_{Y,MD}$.

The two-way interaction plots from the DoE (Figure 4.4a–d) describe the dependency of one factor on the level of another factor for each response variable. The more parallel the lines on the plots, the weaker the interaction, whilst the more non-parallel the lines, the stronger the interaction. Analysis of variance was conducted to evaluate main factors and interactions that were statistically significant ($p < 0.05$), whilst multiple regression analysis of the results was performed to generate constitutive equations (4.2)–(4.5). Results showed that for each response variable, $A_r$ and $T_{pp}$ terms were statistically significant ($p < 0.05$), whilst $\hat{e}_{pp}$ and all interaction terms were not statistically significant ($p > 0.05$), with (4.2)–(4.5) achieving adjusted R-squared ($R^2_{adj}$) values of 0.79, 0.86, 0.85 and 0.93, respectively.

$$E_{MD} = 3869 - 433A_r - 36T_{pp} \quad (4.2)$$
$$E_{TD} = 3501 + 610A_r - 50T_{pp} \quad (4.3)$$
$$\sigma_{Y,MD} = 90 - 8.3A_r - T_{pp} \quad (4.4)$$
$$\sigma_{Y,TD} = 90 + 7.3A_r - 1.3T_{pp} \quad (4.5)$$

Results of the DMA frequency sweeps showed that the storage modulus ($E'$) remained relatively constant across the frequency range for all combinations of $A_r$ and $T_{pp}$, with the percentage increase never exceeding 3.4% (Table 4.3).
Figure 4.3. Main effect plots highlighting the influence of the aspect ratio ($A_r$) of the biaxial deformation, post-processing temperature ($T_{pp}$) and post-processing extension rate ($\dot{e}_{pp}$) on (a) the elastic modulus ($E$) of biaxially stretched PLLA sampled from the MD and the TD, $E_{MD}$ and $E_{TD}$, respectively; and (b) the yield strength ($\sigma_Y$) in the MD and the TD, i.e. $\sigma_{Y,MD}$ and $\sigma_{Y,TD}$, respectively.
Figure 4.4. Two-way interaction plots of the aspect ratio ($A_r$) of the biaxial deformation, post-processing temperature ($T_{pp}$) and post-processing extension rate ($\dot{\varepsilon}_{pp}$) on the elastic modulus ($E$) in the MD, $E_{MD}$; elastic modulus in the TD, $E_{TD}$; yield strength ($\sigma_Y$) in the MD, $\sigma_{Y,MD}$ and yield strength in the TD, $\sigma_{Y,TD}$. 
Table 4.2. Elastic modulus (E) and yield strength (σ_Y) of specimens selected for the 27-run design of experiments (DoE) sampled from the machine direction (MD) and transverse direction (TD).

<table>
<thead>
<tr>
<th>A_t (°C)</th>
<th>T_pp °C</th>
<th>( \dot{\epsilon}_{pp} ) (mm/min)</th>
<th>E_MD (MPa)</th>
<th>( \sigma_{Y,MD} ) (MPa)</th>
<th>E_TD (MPa)</th>
<th>( \sigma_{Y,TD} ) (MPa)</th>
</tr>
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<tr>
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<td>1</td>
<td>2769 ± 80</td>
<td>61 ± 1</td>
<td>2885 ± 151</td>
<td>61 ± 2</td>
</tr>
<tr>
<td>1</td>
<td>37</td>
<td>1</td>
<td>2553 ± 155</td>
<td>50 ± 2</td>
<td>2623 ± 195</td>
<td>51 ± 2</td>
</tr>
<tr>
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<td>55</td>
<td>1</td>
<td>1063 ± 50</td>
<td>21 ± 0</td>
<td>1123 ± 48</td>
<td>21 ± 0</td>
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<td>34 ± 3</td>
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<td>42 ± 1</td>
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<td>52 ± 2</td>
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<td>1</td>
<td>486 ± 61</td>
<td>13 ± 0</td>
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<td>20 ± 2</td>
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<td>2152 ± 97</td>
<td>54 ± 1</td>
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<td>76 ± 1</td>
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<td>15 ± 1</td>
<td>1277 ± 144</td>
<td>22 ± 2</td>
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<td>10</td>
<td>2165 ± 160</td>
<td>53 ± 1</td>
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</tr>
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<td>10</td>
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</tr>
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<td>10</td>
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<td>19 ± 2</td>
<td>1399 ± 117</td>
<td>22 ± 1</td>
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<td>3518 ± 126</td>
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<td>55</td>
<td>1</td>
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<td>79 ± 3</td>
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<td>41 ± 1</td>
<td>3601 ± 359</td>
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</tr>
<tr>
<td>2.3</td>
<td>55</td>
<td>5</td>
<td>1195 ± 84</td>
<td>22 ± 1</td>
<td>1976 ± 23</td>
<td>29 ± 2</td>
</tr>
<tr>
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<td>20</td>
<td>10</td>
<td>1956 ± 74</td>
<td>49 ± 2</td>
<td>3599 ± 78</td>
<td>74 ± 4</td>
</tr>
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<td>2.3</td>
<td>37</td>
<td>10</td>
<td>1704 ± 63</td>
<td>41 ± 1</td>
<td>3261 ± 230</td>
<td>60 ± 6</td>
</tr>
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<td>2.3</td>
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<td>10</td>
<td>1139 ± 30</td>
<td>21 ± 1</td>
<td>2176 ± 114</td>
<td>31 ± 1</td>
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<td>61 ± 1</td>
<td>2885 ± 151</td>
<td>61 ± 2</td>
</tr>
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<td>37</td>
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<td>2553 ± 155</td>
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<td>2623 ± 195</td>
<td>51 ± 2</td>
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<tr>
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<td>55</td>
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<td>1063 ± 50</td>
<td>21 ± 0</td>
<td>1123 ± 48</td>
<td>21 ± 0</td>
</tr>
<tr>
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<td>20</td>
<td>5</td>
<td>2889 ± 140</td>
<td>67 ± 4</td>
<td>2889 ± 243</td>
<td>66 ± 3</td>
</tr>
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</table>
Table 4.3. Maximum percentage increase in the storage modulus ($E'$) of biaxially stretched PLLA, sampled in the MD and the TD, during DMA frequency sweeps between 0.1 Hz and 10 Hz, at various temperatures for a given aspect ratio ($A_r$) of the biaxial deformation.

<table>
<thead>
<tr>
<th>$A_r$ (-)</th>
<th>$\Delta E'_{MD}$ (%)</th>
<th>$\Delta E'_{TD}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 °C</td>
<td>37 °C</td>
</tr>
<tr>
<td>1.0</td>
<td>1.6</td>
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<tr>
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<td>1.7</td>
<td>2.1</td>
</tr>
<tr>
<td>2.3</td>
<td>1.4</td>
<td>1.7</td>
</tr>
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</table>

4.4 Constitutive model calibration

Since $E$ and $\sigma_v$ were both affected by $A_r$ and $T_{pp}$ but were insensitive to $\dot{\epsilon}_{pp}$, a rate-independent, transversely isotropic, temperature-dependent, elastic-plastic constitutive model was used to capture the mechanical response of PLLA. The linear elastic material behaviour was assumed to be transversely isotropic, which implies that at each point within the material there exists an axis of rotational symmetry that is normal to a plane of isotropy (Staab, 2015). In transversely isotropic materials, there exists a plane in which the material properties are the same in all directions (plane of isotropy) perpendicular to the plane’s normal vector (axis of transverse isotropy). However, material properties differ in the axis of transverse isotropy relative to the plane of isotropy (Figure 4.5).

![Figure 4.5. Three-dimensional model of transverse isotropy for biaxially stretched sheet. The 1-3 plane represents the plane of isotropy, whilst the 2 axis represents the axis of transverse isotropy. The material properties are identical in the 1 and 3 directions but are different in the 2 direction.](image-url)
Considering a Cartesian coordinate system, in which the principal directions are
denoted using 1, 2 and 3, and assuming the 1–3 plane to represent the plane of
transverse isotropy, the generalised Hooke’s law may be simplified to (4.6) (Cho et
al., 2012; Hibbitt et al., 2016), where $\varepsilon$ denotes normal strain, $\gamma$ denotes shear
strain, $\sigma$ denotes normal stress, $\tau$ denotes shear stress and the subscripts 1, 2 and 3
define direction. This equation is characterised by five independent elastic constants:
E and $E^*$ (representing the elastic moduli in the plane of transverse isotropy and in
the direction normal to it, respectively), $\nu$ and $\nu^*$ (representing the Poisson’s ratios
characterising the lateral strain response in the plane of transverse isotropy to a
stress acting parallel or normal to it, respectively), and $G^*$ which represents the
shear modulus in planes normal to the plane of isotropy (Amadei, 1996). However,
using the Saint-Venant empirical approximation (Saint Venant, 1863) in (4.7), $G^*$
can be expressed as a function of E, $E^*$, $\nu$ and $\nu^*$ which reduces the number of
independent constants to four.

$$\begin{bmatrix}
\varepsilon_{11} \\
\varepsilon_{22} \\
\varepsilon_{33} \\
\gamma_{12} \\
\gamma_{13} \\
\gamma_{23}
\end{bmatrix} = \begin{bmatrix}
\frac{1}{E} & -\frac{\nu^*}{E^*} & -\frac{\nu^*}{E} & 0 & 0 & 0 \\
-\frac{\nu^*}{E} & \frac{1}{E^*} & -\frac{\nu^*}{E} & 0 & 0 & 0 \\
-\frac{\nu}{E} & -\frac{\nu^*}{E^*} & \frac{1}{E} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \frac{1}{G^*} \\
0 & 0 & 0 & 0 & 0 & \frac{2}{G^*} \\
0 & 0 & 0 & 0 & 0 & \frac{1}{G^*}
\end{bmatrix} \begin{bmatrix}
\sigma_{11} \\
\sigma_{22} \\
\sigma_{33} \\
\tau_{12} \\
\tau_{13} \\
\tau_{23}
\end{bmatrix}$$  

(4.6)

$$\frac{1}{G^*} = \frac{1}{E} + \frac{1}{E^*} + 2\frac{\nu^*}{E^*}$$  

(4.7)

The plastic behaviour was defined using the anisotropic yield function defined by
Hill (1948) (4.8). The coefficients $\alpha_i$, $\alpha_4$ may be written as a function of the yield
strength ratios (r) (4.9)–(4.14) which define the yield stress in a given direction with
respect to a reference (isotropic) yield stress (4.15) (Hibbitt et al., 2016b).

$$f = \sigma = \sqrt{\alpha_1 \sigma_{22} - \sigma_{33}^2 - \alpha_2 \sigma_{33} - \sigma_{11} - \sigma_{22}^2 + 2\alpha_4 \sigma_{22}} + 2\alpha_5 \sigma_{33}^2 + 2\alpha_6 \sigma_{11}^2$$  

(4.8)
\[ \alpha_1 = \frac{1}{2} \left( \frac{1}{r_{22}^2} + \frac{1}{r_{33}^2} - \frac{1}{r_{11}^2} \right) \]  \hspace{1cm} (4.9) \hspace{1cm} \alpha_2 = \frac{1}{2} \left( \frac{1}{r_{33}^2} + \frac{1}{r_{11}^2} - \frac{1}{r_{22}^2} \right) \]  \hspace{1cm} (4.10)

\[ \alpha_3 = \frac{1}{2} \left( \frac{1}{r_{11}^2} + \frac{1}{r_{22}^2} - \frac{1}{r_{33}^2} \right) \]  \hspace{1cm} (4.11) \hspace{1cm} \alpha_4 = \frac{3}{2r_{23}^2} \]  \hspace{1cm} (4.12)

\[ \alpha_5 = \frac{3}{2r_{13}^2} \]  \hspace{1cm} (4.13) \hspace{1cm} \alpha_6 = \frac{3}{2r_{12}^2} \]  \hspace{1cm} (4.14)

\[ r_{ij} = \begin{cases} \frac{\sigma_{ij}}{\sigma_Y} & \text{if } i = j \\ \frac{\sqrt{3}\sigma_{ij}}{\tau_Y} & \text{if } i \neq j \end{cases} \]  \hspace{1cm} (4.15)

In the above equations, \( \sigma_{ij} \) is a non-zero stress component, \( \sigma_Y \) the reference yield strength and \( \tau_Y \) is the reference shear strength.

The directional properties were defined such that the MD, the TD and the through-the-thickness direction, or Z-direction (ZD), correspond to the 1, 2 and 3 directions, respectively. The MD–ZD plane therefore represents the plane of transverse isotropy, whilst the TD represents the direction normal to the plane of isotropy. With respect to (4.6), the moduli may be written as \( E = E_{MD} \) and \( E^* = E_{TD} \). The Poisson’s ratios characterising the lateral strain response in the plane of transverse isotropy to a stress acting parallel or normal to it, \( \nu \) and \( \nu^* \), respectively, were both assigned a value of 0.35, based on typical datasheet specifications for PLLA (Farah et al., 2016). The yield strength ratios in the plane of transverse isotropy (in the MD and the ZD) were set to unity \( (r_{11} = r_{33} = 1) \) and there was no anisotropy defined for any of the shear stresses \( (r_{12} = r_{13} = r_{23} = 1) \). The yield strength ratio in the TD \( (r_{22} \text{ in the direction normal to the plane of isotropy}) \) was calculated as the ratio of \( \sigma_{Y,TD} \) to \( \sigma_{Y,MD} \). A piecewise linear hardening model was used to capture the behaviour of PLLA post-yielding through a series of stress-strain couples with the Ramer-Douglas-Peucker algorithm (Ramer, 1972; Douglas and Peucker, 1973) used to reduce the number of data points whilst preserving the shape of the stress-strain curve.
Constitutive model calibration was performed using Python (version 2.7.13) (Python Software Foundation, 2017) and Abaqus/Standard 2016 (Dassault Systèmes, France). A unit cube finite element simulation was performed in which the cube, assigned the custom constitutive model, was subjected to a pure uniaxial deformation (in both the MD and TD), a method commonly employed within the field of constitutive modelling (Yeoh, 1993; Cowin, 2013; Bergstrom, 2015). Given that the strains in the unit cube were large (> 5%), NLGEOM was activated within Abaqus to account for geometric nonlinearity. The residual sum of squares was used to provide a quantitative comparison between experimental data and simulation data using the NumPy (version 1.14.2) package (Oliphant, 2006), while the Matplotlib (version 2.2.2) package (Hunter, 2007) was used to provide a qualitative, visual assessment of the goodness of fit.

The constitutive model was calibrated using uniaxial tensile test data (at an extension rate of 5 mm/min) for samples punched from biaxially stretched sheet in the MD and the TD, for all permutations of $A_r$ and $T_{pp}$ under the DoE (Figure 4.6). Whilst the constitutive model was calibrated using a set of three unique $T_{pp}$ and $A_r$, it may be used to capture any $T_{pp}$ within the range 37–55 °C and any $A_r$ within the range 1–2.3 using linear interpolation. The elastic portion of the constitutive model was fitted first by identifying appropriate elastic moduli in the MD and the TD, after which the yield strength ratios were varied in order to fit the plastic portion of the model. It should be noted that an $A_r$ of 1 produced nearly identical stress-strain curves in the MD and the TD for all values of $T_{pp}$. As a result, the constitutive model was calibrated to the TD experimental data and the model parameters were defined such that the material behaved isotropically for these cases ($E_{MD} = E_{TD}$ and $r_{11} = r_{22} = 1$).
Table 4.3: Comparison of experimental (expt.) data to simulation (sim.) prediction using the transversely isotropic, temperature-dependent constitutive model. Nominal stress-strain (σ-ε) plots are shown for various aspect ratios (A_r) and post-processing temperatures for biaxially stretched PLLA sampled from the MD and the TD, tested at an extension rate of 5 mm/min.

Finally, in order to assess the quality of the constitutive model during unloading, a step was added to the unit cube finite element simulation to replicate the experimental load/unload test procedure. In this step, the cube (assigned the custom constitutive model) was unloaded to zero load from a strain level of 0.1 and 0.25. Unloading was performed at a rate of 5 mm/min at room temperature (20 °C) for a
sample punched from the TD of a sheet biaxially stretched to an $A_e$ of 2.3. The results of these simulations were compared against the equivalent experimental test and the results are shown in Figure 4.7. Results showed that, in both cases, the experimental curve closely matched the simulated curve for the majority of the unloading phase, however deviated towards the end due to viscoelastic recovery. This was not captured by the constitutive model, in which the unloading curve is parallel to the elastic modulus of the material.

![Comparison of experimental (expt.) data to simulation (sim.) prediction for the load-unload tensile testing of biaxially stretched PLLA. Nominal stress-strain ($\sigma$-$\varepsilon$) plots are shown for samples taken from the TD of a sheet biaxially stretched to an $A_e$ of 2.3, tested at an extension rate of 5 mm/min and a temperature of 20 °C, up to a maximum strain of (a) 0.25 and (b) 0.1.](image)

**Figure 4.7.** Comparison of experimental (expt.) data to simulation (sim.) prediction for the load-unload tensile testing of biaxially stretched PLLA. Nominal stress-strain ($\sigma$-$\varepsilon$) plots are shown for samples taken from the TD of a sheet biaxially stretched to an $A_e$ of 2.3, tested at an extension rate of 5 mm/min and a temperature of 20 °C, up to a maximum strain of (a) 0.25 and (b) 0.1.

### 4.5 Discussion

In this chapter, the effect of biaxial processing history, along with the effects of temperature and extension rate (post-processing) on the short-term (pre-degradation) mechanical properties of biaxially stretched PLLA were evaluated. Subsequently, a transversely isotropic, temperature-dependent constitutive model
was calibrated to the experimental data. Given that a PLLA stent is exposed to
different processing techniques, temperatures, and environmental conditions during
its lifecycle, calibrating a representative material model that may be used during
preclinical simulation has the potential to facilitate the design of high stiffness, thin-
strut polymeric stents.

The DMA results show that the $T_g$ is dependent on frequency, often referred to as a
dynamic transition (Gracia-Fernández et al., 2010). Dynamic transitions are
commonly observed for semi-crystalline polymers, which generally see an increase in
the $T_g$ as the test frequency is increased (Menard, 2008). The patented method for
crimping a polymeric stent onto a delivery balloon (Jow et al., 2017) states crimping
should occur at a temperature between the lowest measured $T_g$ ($T_g$-low) and 15 °C
below the $T_g$-low. However, given the dynamic nature of the $T_g$, care should be
taken to match the crimping temperature to the time-scale of the procedure and, by
extension, the rate of deformation. As the deformation rate is decreased, the $T_g$ will
decrease and the undesirable situation may arise whereby the crimping temperature
exceeds the $T_g$ of the polymer, inducing significant changes in the polymer’s
molecular orientation and reducing its mechanical integrity (Jow et al., 2017).

Tensile test data showed that the mechanical response of PLLA is highly dependent
on the aspect ratio of the biaxial deformation and the post-processing temperature.
However, it was relatively insensitive to the post-processing extension rate. An
increased elastic modulus and yield strength in the TD were obtained by increasing
the aspect ratio of the biaxial deformation, at the expense of these properties in the
MD. This improvement in mechanical properties was attributed to the degree of
amorphous orientation induced during processing (Løvdal et al., 2016). The
processing history had a stronger influence on the modulus than the yield strength;
as the aspect ratio of the biaxial deformation was increased from 1 to 2.3, $E_{MD}$ and
$E_{TD}$ resulted in a 28% decrease and 34% increase, respectively, compared to the
respective 25% decrease and 20% increase in $\sigma_{Y,MD}$ and $\sigma_{Y,TD}$. In contrast, the post-
processing temperature exhibited a stronger influence on the yield strength; as the
temperature was increased from 20 °C to 55 °C, the $E_{MD}$ and $E_{TD}$ decreased by 55% and 54%, respectively, compared to the respective 62% and 65% decrease in $\sigma_{Y,MD}$ and $\sigma_{Y,TD}$.

The elastic modulus and yield strength exhibited slight rate-dependence with $E_{MD}$ and $E_{TD}$ undergoing a maximum increase of 8% and 6%, respectively, and $\sigma_{Y,MD}$ and $\sigma_{Y,TD}$ demonstrating a maximum respective increase of 12% and 9% across the range of extension rates tested (i.e. 1–10 mm/min). The results of DMA frequency sweeps were in agreement with the tensile test data and showed that the storage modulus remained relatively constant across the frequency range (i.e. 0.1–10 Hz) for all combinations of $A_\gamma$ and $T$, with a maximum percentage increase of 3.4%. The PLLA specimens subjected to load/unload testing exhibited slight viscoelastic recoveries of 18% and 10%, based on a comparison of (final) strain at zero load between experimental and simulated tests to strain levels of 0.1 and 0.25, respectively. This is typical behaviour for semi-crystalline polymers and has been observed in many studies investigating the strain-rate-dependence of PLLA (Eswaran et al., 2011; Debusschere et al., 2015; Bobel et al., 2016). However, the influence of post-processing extension rate was considerably less than that of post-processing temperature and aspect ratio, given that no significant interactions were observed between post-processing extension rate and either post-processing temperature or aspect ratio. Consequently, the polymer was idealised and assumed to be rate-independent across the range of strain rates tested (i.e. $10^{-4}$–$10^{-1}$ s$^{-1}$) resulting in the calibration of a rate-independent, transversely isotropic, and temperature-dependent constitutive model.

The empirical relations (4.2)–(4.5) and constitutive model presented herein may be used to augment the design and process optimisation of PLLA coronary stents. It is intended that during a PLLA stent’s initial design phase, these empirical relations may be used as a computationally inexpensive method to evaluate the influence of the biaxial processing history on the mechanical properties of the platform polymer. Furthermore, the constitutive model offers a finite element implementation of these
equations and may be used to evaluate the relationship between mechanical a stent’s processing history and its mechanical performance. To date, studies have performed parametric optimisation to refine the geometry of a stent (Bedoya et al., 2006; Wu et al., 2008; Pant et al., 2012; Li et al., 2017) or compared the influence of a particular material across common stent geometries (Schultze et al., 2008; Bobel et al., 2015; Pauck and Reddy, 2015). However, none of these studies considered the influence of biaxial stretching processing history and how it affects the design of the stent’s geometry. One of the most challenging aspects to overcome in the design of polymer-based stents lies in the significantly lower radial stiffness compared to their metallic counterparts, which is necessary to support the displaced arterial wall. By controlling the aspect ratio of the biaxial deformation and molecular orientation, it may be beneficial to process the stent such that the polymer has a preferential circumferential orientation. Matching the material processing to stent geometry through the use of the empirical relations and the constitutive model presented herein has the potential to generate polymeric stent designs with reduced strut profiles, which will be investigated in the subsequent chapter.

4.6 Conclusion

Results of an extensive experimental programme to characterise the post-processing material properties of PLLA indicated that the elastic modulus and yield strength of the biaxially stretched sheets were strongly influenced by the aspect ratio during biaxial deformation and post-processing temperature. In contrast, post-processing extension rate had relatively little influence on these mechanical properties. A transversely isotropic, temperature-dependent constitutive model was calibrated against experimental data using equations that relate the elastic modulus and yield strength of biaxially stretched sheets to the aspect ratio during processing and post-processing temperature (during uniaxial deformation).
5. Multi-objective optimisation of a poly(L-lactic acid) stent

5.1 Overview

Coronary stents for treating atherosclerosis are traditionally manufactured from metallic alloys. However, metal stents permanently reside in the body and may trigger undesirable immunological responses. Biodegradable polymer stents can provide a temporary scaffold that resorbs once the artery heals but are mechanically inferior, requiring thicker struts for equivalent radial support, which may increase thrombosis risk. The reviewed literature suggests that improvements in material processing, coupled with the correct matching of the stent’s geometry to the material may produce polymeric BRSs with reduced strut profiles that are comparable performance to current generation metallic DESs (Alexy and Levi, 2013; Pauck and Reddy, 2015; McMahon et al., 2018). To the best of the author’s knowledge, no study has considered the combined effect of the biaxial stretching processing history and stent geometry in order to optimise stent performance. In the preceding chapters, it has been shown that (i) biaxial stretching improves the mechanical properties of PLLA; and (ii) the mechanical response of PLLA can be written as a function of biaxial stretching processing parameters, in the form of a constitutive model. The aim of the present chapter is to use this constitutive model within computational bench testing simulations to facilitate the design of

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3 A manuscript based on this work titled “Multi-objective optimisation of material properties and strut geometry for poly(L-lactic acid) coronary stents using response surface methodology” has been published in PLoS ONE.
mechanically effective but sufficiently thin bioresorbable PLLA stents through multi-objective optimisation of processing parameters and stent geometry. By parameterising these design inputs and computationally evaluating the performance of a given stent design across a series of metrics (that capture the conflicting requirements for a stent), empirical relations were derived that relate both the stent’s processing history and geometry to its performance. Using these empirical relations, performance trade-offs were identified and an optimal design was established through multi-objective optimisation.

5.2 Material and methods

5.2.1 Process parameterisation

In Chapter 3, the SBM process (used during stent manufacture) was idealised and replicated using a custom-built biaxial tensile tester, to evaluate the mechanical properties of PLLA pre- and post biaxial stretching. The elastic modulus (E) and yield strength (σ_y) of extruded PLLA sheet increased by approximately 80% and 70% following biaxial stretching (Figure 5.1a). These mechanical properties were observed to be highly dependent on the stretch ratio in the machine direction (MD), λ_MD, and the stretch ratio in the transverse direction (TD), λ_TD, in addition to the aspect ratio (A_r) between the pair, defined as the quotient of λ_TD and λ_MD (Figure 5.1b). By tailoring A_r, biaxially stretched sheets were processed with direction dependent (anisotropic) mechanical properties. For A_r > 1, i.e. λ_TD > λ_MD, mechanical properties were improved in the TD at the expense of the mechanical properties in the MD. For A_r < 1, i.e. λ_TD < λ_MD, mechanical properties were improved in the MD at the expense of the mechanical properties in the TD. Therefore, it was hypothesised that if the MD and the TD were aligned with the stent’s axial and circumferential axes, respectively (Figure 5.1c), a stent may be made stiffer and stronger in a given direction by tailoring A_r.
Figure 5.1. Schematic diagram showing (a) the biaxial stretching process in the machine direction (MD) and transverse direction (TD); (b) the definition of aspect ratio ($A_r$), defined as the quotient of the stretch ratio in the TD ($\lambda_{TD}$) and the stretch ratio in the MD ($\lambda_{MD}$); and (c) the alignment of the MD and the TD with a stent’s axial and circumferential axes, respectively.

In Chapter 4, the $A_r$ was varied and uniaxial tensile testing was performed at comparable conditions to those experienced by a stent (Bobel et al., 2015). Results showed that the elastic modulus and yield strength were strongly dependent on temperature during uniaxial deformation, but were not heavily dependent on extension rate. Empirical relations were developed that related the elastic modulus and yield strength to $A_r$ and temperature (for $A_r \geq 1$). In this chapter, a constant body temperature was assumed (37 °C) and these equations were simplified for $A_r \geq 1$ (5.1)–(5.4) and rearranged for $A_r < 1$ (5.5)–(5.8). This set of empirical relations was used to generate a simplified transversely isotropic, rate-independent, elastic-plastic constitutive model, which neglects the softening following yield and assumes PLLA exhibits perfectly plastic behaviour, i.e. a change in strain causes no observable change in stress (Figure 5.2a–c). In the context of a stent, an $A_r = 1$ generated a design of equal strength and stiffness in both the axial and circumferential directions (Figure 5.2a). An $A_r < 1$ generated a design that was stiffer and stronger in the axial direction (Figure 5.2b), whilst $A_r > 1$ generated a design that was stiffer and stronger in the circumferential direction (Figure 5.2c). Given that one of the most challenging aspects to overcome when designing polymer-based stents lies in the significantly lower radial stiffness compared to their
metallic counterparts, it may be beneficial to process the stent such that it has a preferential circumferential orientation.

\[
\begin{array}{lcc}
  A_r \geq 1 & E_{MD} = 3062 - 555A_r & (5.1) & E_{TD} = 2196 + 618A_r & (5.2) \\
  & \sigma_{Y,MD} = 65 - 11A_r & (5.3) & \sigma_{Y,TD} = 46 + 10A_r & (5.4) \\
  A_r < 1 & E_{MD} = 2196 + \frac{618}{A_r} & (5.5) & E_{TD} = 3062 - \frac{555}{A_r} & (5.6) \\
  & \sigma_{Y,MD} = 46 + \frac{10}{A_r} & (5.7) & \sigma_{Y,TD} = 65 - \frac{11}{A_r} & (5.8)
\end{array}
\]

**Figure 5.2.** Simplified constitutive model stress-strain (\(\sigma-\varepsilon\)) curves for (a) \(A_r = 1\), which generated a stent design of equal strength and stiffness in both the axial and circumferential directions; (b) \(A_r < 1\), which generated a stent design that was stiffer and stronger in the axial direction; and (c) \(A_r > 1\), which generated a stent design that was stiffer and stronger in the circumferential direction.

### 5.2.2 Geometry parameterisation

The stent geometry was based on a conventional open-cell stent design with straight bridges, using SolidWorks 2016 (Dassault Systèmes, France) to generate the three-dimensional model Figure 5.3. The stent was designed in the crimped state with two repeating unit cells used to represent the full-length stent geometry, thereby
reducing computational cost. Parametric stent geometries were generated by varying strut width (w), strut thickness (t) and strut length (l).

Figure 5.3. Geometry parameterisation in terms of strut width (w), strut thickness (t) and strut length (l).

5.2.3 Performance metrics

Four performance metrics were extracted for each stent design, based on the results of deployment and bench test simulations: (i) the cross-sectional area post-dilation (CSA), (ii) foreshortening (FS), (iii) stent-to-artery ratio (SAR) and (iv) radial collapse pressure (RCP). Initially, an idealised quasi-static expansion procedure was simulated in Abaqus/Standard 2016 (Dassault Systèmes, France) using a displacement driven cylinder (meshed with S4R shell elements) and a deformable solid stent (meshed with C3D8R brick elements). The stent was designed in a pre-crimped state (Figure 5.4a) and constrained in both the axial and tangential directions (with respect to a user-defined cylindrical coordinate system) via three nodes forming an equilateral triangle in the central section. A radial displacement was prescribed to all nodes on the cylinder increasing the stent diameter from 1.8 mm to 3.5 mm using the smooth-step amplitude definition within Abaqus, with tangential and axial displacement prohibited (Figure 5.4b). Grogan et al. (2012) compared the simulation results of stents expanded using this idealised radial displacement deployment technique to those expanded using a computationally expensive wrapped balloon deployment technique, and showed comparable results based on the von Mises stress distribution and recoil values for the final (expanded) stent configuration. Frictionless surface-to-surface contact was assumed, and self-contact was enabled for the stent. Following expansion, the cylinder was contracted
during which the stent recoiled (Figure 5.4c). The time-frame typically required for polymeric stent expansion approaches one minute; according to published guidelines from Abbott (Abbott, 2012). However, given that a rate-independent material model is used, the time frame for expansion was reduced to 1 s.

![Figure 5.4. Finite element deployment simulation showing the stent in its (a) initial crimped state; (b) deployed (expanded) state and (c) final (recoiled) state.](image)

The CSA following unloading was calculated based on the internal diameter of the stent ($D_{\text{unload}}$) (5.9) (Figure 5.5a). Cross-sectional area was selected as it accounts for both recoil and the thickness of the stent struts, and it has been shown to be a useful predictor of angiographic restenosis (Choi et al., 2012). During expansion, the opening of the strut hoops naturally cause the stent to contract in the axial direction (Figure 5.5b). The FS of a stent was defined as the percentage reduction between the stent length in its crimped state ($L_{\text{initial}}$) and the stent length following unloading ($L_{\text{unload}}$) (5.10). The SAR of the stent (Figure 5.5c) was calculated as the ratio between the external surface area of the stent in its crimped state ($SA_{\text{stent initial}}$) and the internal surface area of a compatible cylindrical artery ($SA_{\text{artery}}$) (5.11). The RCP of an expanded stent was evaluated through an additional virtual bench test in which eight rigid plates (meshed with R3D4 elements) (Figure 5.5d) were radially contracted using a displacement driven process to produce 10% diameter loss. The RCP was calculated as the quotient of the average reaction force acting on the plates ($RF_{\text{ave}}$) and the surface area of the stent post-recoil ($SA_{\text{stent unload}}$) (5.12). The smooth-step amplitude definition was used with frictionless surface-to-surface contact between the plates and the stent, and self-contact was enabled for the stent.
\[ \text{CSA} = \pi \left( \frac{D_{\text{unload}}}{2} \right)^2 \quad (5.9) \]

\[ \text{SAR} = \frac{S_{\text{stent}}^{\text{initial}}}{S_{\text{artery}}} \times 100\% \quad (5.11) \]

\[ \text{FS} = \frac{L_{\text{initial}} - L_{\text{unload}}}{L_{\text{initial}}} \times 100\% \quad (5.10) \]

\[ \text{RCP} = \frac{\text{RF}_{\text{ave}}}{S_{\text{stent}}^{\text{initial}}} \quad (5.12) \]

**Figure 5.5.** Schematic representations of tests for: (a) cross-sectional area (post-dilation), CSA; (b) foreshortening, FS; (c) stent-to-artery ratio, SAR and (d) radial collapse pressure, RCP.

### 5.2.4 Optimisation

The time required to perform the finite element simulations and calculate the performance metrics for a given parametric stent design exceeded one hour using five parallel processors. At these time scales, global optimisation processes become computationally inefficient and the majority of optimisation studies tend to adopt surrogate modelling approaches (Bressloff et al., 2016). Hence, response surface methodology (RSM) was employed in order to provide an empirical correlation between processing and geometry parameters, and the mechanical performance of the stent.
A design space was established using the limits for each of the design parameters (Table 5.1). The lower limit of $A_r$ generates stents that are stiffer in the axial direction whilst the upper limit generates stents that are stiffer in the circumferential direction. A lower limit of 100 µm was set for $w$ and $t$ to generate geometries that resembled a metallic stent, whilst an upper limit of 200 µm was set to generate geometries that resembled a polymeric stent. An upper limit of 1200 µm was set for $l$ to avoid self-contact between neighbouring circumferential rings, whilst a lower limit of 900 µm was set to prevent excessive plastic deformation. A baseline design was generated by setting $A_r$, $w$, $t$ and $l$ at the midpoint of their range.

**Table 5.1.** High and low levels for stent design parameters ($A_r$, $w$, $t$ and $l$).

<table>
<thead>
<tr>
<th>$A_r$ (-)</th>
<th>$w$ (µm)</th>
<th>$t$ (µm)</th>
<th>$l$ (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>100</td>
<td>100</td>
<td>900</td>
</tr>
<tr>
<td>2.3</td>
<td>200</td>
<td>200</td>
<td>1,200</td>
</tr>
</tbody>
</table>

Initially, 40 design points that uniformly filled the design space were selected using an optimised Latin hypercube (LHC) sampling technique (Morris and Mitchell, 1995). Parametric stent designs and finite element models were automatically generated using a combination of Python (version 2.7.13; Python Software Foundation) scripting, SolidWorks 2016 and the Abaqus CAE pre-processor. Deployment and bench testing simulations were performed in order to compute discrete values for each performance metric (CSA, FS, SAR and RCP). Multiple linear regression analysis was performed on the results using R (version 3.4.0) (R Core Team, 2017) to provide an empirical correlation between each performance metric and design parameters. The Matplotlib (version 2.2.2) package (Hunter, 2007) was used to generate three-dimensional response surface plots to provide a qualitative, visual assessment of the results.

Following the RSM, multi-objective least squares optimisation was performed in Python using the NumPy (version 1.14.2) (Oliphant, 2006) and SciPy packages (version 1.2.0) (Jones et al., 2001) to identify suitable options from non-dominated
Pareto designs. Each performance metric was normalised (scaled) to the same range \([0,1]\), based on its minimum and maximum attainable values, attained through single objective least squares minimisation. A single objective function (OF) was constructed (5.13) which combines these normalised CSA, FS, SAR and RCP terms. Each of these performance metrics have been shown to directly affect one (or more) of the commonly assessed clinical outcomes for a stent. A low CSA may restrict normal vasmotion (Iqbal et al., 2014), a high degree of FS may initiate restenosis (Lim et al., 2008), a high SAR may initiate thrombosis (Serruys et al., 2016), whilst a low RCP may prevent the stent from withstanding the compressive force of the artery (Ota et al., 2014). Hence, an equal weighting was applied to the normalised CSA, FS, SAR and RCP terms. The intention of this optimisation was to minimise FS and SAR whilst maximising CSA and RCP. Hence, negative sign convention was adopted for CSA and RCP so that lower values for absolute and normalised performance metrics indicate better designs. An inequality constraint was imposed that prevented RCP dropping below 40 kPa (5.14), which is commonly considered the minimum allowable collapse pressure for coronary stents (Agrawal et al., 1992). An additional inequality constraint was imposed that prevented \( t \) from exceeding the baseline value of 150 \( \mu m \) (5.15).

\[
\min \ OF = CSA + \overline{FS} + \overline{SAR} + \overline{RCP} \tag{5.13}
\]

\[
RCP \geq 40 \text{ kPa} \tag{5.14}
\]

\[
t \leq 150 \mu m \tag{5.15}
\]
5.3 Results

5.3.1 Baseline geometry

The baseline stent design parameters and its respective performance metrics are shown in Table 5.2. Cross-sectional area (post-dilation) is difficult to measure in vivo and hence, there is limited published data. However, the baseline designed recoiled by approximately 9% following dilation, which is comparable to commercial PLLA BRS (Schmidt et al., 2016). Given that the value of t is similar between the baseline design and a commercial stent, by extension the CSA will also be comparable. The baseline stent design values for FS and SAR of 5.7% and 35.5%, respectively, are comparable to the upper end of commercial the PLLA BRS range (Kawamoto et al., 2016; Schmidt et al., 2016). However, the baseline stent value for RCP of 20.9 kPa is approximately half of the minimum allowable collapse pressure for a coronary stent (Agrawal et al., 1992).

Table 5.2. Baseline stent design parameters (A, w, t, and l) and its respective simulated performance metrics (CSA, FS, SAR, and RCP).

<table>
<thead>
<tr>
<th>A</th>
<th>w</th>
<th>t</th>
<th>l</th>
<th>CSA (mm²)</th>
<th>FS (%)</th>
<th>SAR (%)</th>
<th>RCP (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.35</td>
<td>150</td>
<td>150</td>
<td>1050</td>
<td>-8.0</td>
<td>5.7</td>
<td>35.3</td>
<td>-20.9</td>
</tr>
</tbody>
</table>

5.3.2 Response surface methodology

The four performance metrics (CSA, FS, SAR and RCP) were computed for each of the 40 design points (Table 5.3).
Table 5.3. Design parameters (A, w, t and l) and respective performance metrics (CSA, FS, SAR and RCP) for each point considered under the optimised Latin hypercube sampling plan.

<table>
<thead>
<tr>
<th></th>
<th>(A)</th>
<th>(w)</th>
<th>(t)</th>
<th>(l)</th>
<th>CSA</th>
<th>FS</th>
<th>SAR</th>
<th>RCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.90</td>
<td>101</td>
<td>191</td>
<td>1166</td>
<td>-6.2</td>
<td>3.4</td>
<td>26.7</td>
<td>-6.8</td>
</tr>
<tr>
<td>2</td>
<td>0.47</td>
<td>134</td>
<td>161</td>
<td>1001</td>
<td>-8.1</td>
<td>6.8</td>
<td>30.9</td>
<td>-18.9</td>
</tr>
<tr>
<td>3</td>
<td>0.52</td>
<td>119</td>
<td>154</td>
<td>1144</td>
<td>-7.0</td>
<td>4.2</td>
<td>30.5</td>
<td>-8.5</td>
</tr>
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<td>134</td>
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<td>-7.6</td>
<td>5.5</td>
<td>29.9</td>
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</tr>
<tr>
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<td>2.23</td>
<td>146</td>
<td>169</td>
<td>1009</td>
<td>-8.4</td>
<td>5.8</td>
<td>33.6</td>
<td>-22.8</td>
</tr>
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Multiple linear regression analysis of the results was performed to generate constitutive equations that related each performance metric to the input parameters. A second-order model containing the intercept, main factors, two-factor interactions and quadratic terms (5.16) was used for CSA, FS, SAR and RCP. Using the constants in Table 5.4, each model predicts, with approximately 99.7% confidence, that all values lie within the mean prediction plus or minus three standard deviations (Figure 5.6). Model quality is assessed in Figure 5.7, in which the function values are predicted for a given performance metric, using the statistical model, and compared to their corresponding actual (measured) values extracted from finite element simulations. Linear behaviour was observed for CSA, FS, SAR and RCP, with the statistical models achieving R-squared ($R^2$) values of 0.950, 0.996, 0.999 and 0.996, respectively.

$$Y = \beta_0 + \beta_1 A_r + \beta_2 w + \beta_3 t + \beta_4 l + \beta_5 A_r w + \beta_6 A_r t + \beta_7 A_r l + \beta_8 wt + \beta_9 w l + \beta_{10} t l + \beta_{11} A_r^2 + \beta_{12} w^2 + \beta_{13} t^2 + \beta_{14} l^2$$

(5.16)

where $Y$ denotes the predicted response for a given performance metric i.e. CSA, FS, SAR and RCP.

| Table 5.4. Statistical model coefficients for CSA, FS, SAR and RCP. |
|----------------------------------|---|---|---|---|
| CSA | FS | SAR | RCP |
| Intercept | -2.6 | 44.9 | -1.1 | -25.3 |
| $A_r$ | 16.0E-1 | -26.6E-1 | -4.7E-1 | -69.2E-1 |
| $w$ | -55.7E-3 | 6.6E-3 | 96.3E-3 | -249.7E-3 |
| $t$ | -2.7E-3 | 25.3E-3 | 1.5E-3 | -422.3E-3 |
| $l$ | -7.1E-3 | -67.5E-3 | 3.1E-3 | 110.3E-3 |
| $A_r w$ | -3.8E-3 | -6.8E-3 | 1.5E-3 | -2.0E-3 |
| $A_r t$ | 7.1E-4 | 10.4E-4 | 3.3E-4 | 183.6E-4 |
| $A_r l$ | -10.6E-4 | 11.6E-4 | 1.7E-4 | -16.0E-4 |
| $w t$ | 2.6E-5 | 2.6E-5 | -1.1E-5 | -225.7E-5 |
| $w l$ | -2.3E-5 | -1.2E-5 | 15.9E-5 | 56.3E-5 |
| $t l$ | 9.8E-6 | -35.7E-6 | -4.2E-6 | 612.6E-6 |
| $A_r^2$ | -7.5E-2 | 48.5E-2 | 1.3E-2 | 251.7E-2 |
| $w^2$ | 2.2E-4 | 1.8E-4 | -2.0E-4 | -9.3E-4 |
| $t^2$ | -3.6E-5 | 5.8E-5 | 1.2E-5 | -22.5E-5 |
| $l^2$ | 7.3E-6 | 27.9E-6 | -1.3E-6 | -104.5E-6 |
Figure 5.6. Standardised residual vs. predicted response using the statistical model in (5.16) for (a) CSA; (b) FS; (c) SAR and (d) RCP.

Figure 5.7. Predicted response using the statistical model in (5.16) vs. actual (measured) response from finite element simulations for (a) CSA; (b) FS; (c) SAR and (d) RCP.
A comparison of absolute t-values (for coefficients) from multiple regression analyses for each performance metric is shown in Figure 5.8. Main factors, two-factor interactions and quadratic terms are considered statistically significant \((p < 0.05)\) if their absolute t-value lies above the dashed line.

**Figure 5.8.** Comparison of absolute t-values (for coefficients) from multiple regression analyses highlighting significant \((p < 0.05)\) main factors and two-way interactions for (a) CSA; (b) FS; (c) SAR and (d) RCP.

Response surfaces were plotted for all two-way interactions (Figure 5.9–Figure 5.14) which highlight the combined influence of any two design parameters \((A, w, t \text{ or } l)\) on each performance metric (CSA, FS, SAR and RCP). For each response surface, the performance metric was plotted against two dependent design parameters whilst the remaining two independent parameters were held constant at their baseline (midpoint) value. For each response surface, moving from the purple region to the yellow region indicates an improvement.
**Figure 5.9.** Response surfaces highlighting the combined influence of $A_r$ and $w$ on each performance metric (CSA, FS, SAR and RCP), holding $t$ and $l$ constant at their baseline values ($t = 150 \, \mu m$ and $l = 1050 \, \mu m$).

**Figure 5.10.** Response surfaces highlighting the combined influence of $A_r$ and $t$ on each performance metric (CSA, FS, SAR and RCP), holding $w$ and $l$ constant at their baseline values ($w = 150 \, \mu m$ and $l = 1050 \, \mu m$).

**Figure 5.11.** Response surfaces highlighting the combined influence of $A_r$ and $l$ on each performance metric (CSA, FS, SAR and RCP), holding $w$ and $t$ constant at their baseline values ($w = 150 \, \mu m$ and $t = 150 \, \mu m$).

**Figure 5.12.** Response surfaces highlighting the combined influence of $w$ and $t$ on each performance metric (CSA, FS, SAR and RCP), holding $A_r$ and $l$ constant at their baseline values ($A_r = 1.35$ and $l = 1050 \, \mu m$).
Figure 5.13. *Response surfaces highlighting the combined influence of w and l on each performance metric (CSA, FS, SAR and RCP), holding A, and t constant at their baseline values (A_v = 1.35 and t = 150 μm).*

Figure 5.14. *Response surfaces highlighting the combined influence of t and l on each performance metric (CSA, FS, SAR and RCP), holding A, and w constant at their baseline values (A_v = 1.35 and w = 150 μm).*

The Pareto fronts presented in Figure 5.15 highlight the trade-offs between each set of performance metrics, with better designs lying towards the bottom left corner. Trade-offs were observed for CSA vs. FS, CSA vs. SAR, FS vs. RCP and SAR vs. RCP, whilst no trade-offs were observed for CSA vs. RCP or FS vs. SAR. Trade-offs occurred as a result of conflicting requirements for stent design, i.e. geometric and/or material parameters that improve one metric often negatively affect at least one of the other metrics.
Figure 5.15. Trade-off curves for all permutations of the four performance metrics: (a) CSA vs. FS; (b) CSA vs. SAR, (c) CSA vs. RCP and (d) FS vs. SAR, (e) FS vs. RCP and (f) SAR vs. RCP.

5.3.3 Optimisation

In order to construct a single dimensionless objective function, each performance metric was normalised (scaled) to the same range [0,1] based on its minimum and maximum attainable values (Table 5.5), attained using least squares minimisation (5.17).

\[
\hat{Y} = \frac{Y - Y_{\text{min}}}{Y_{\text{max}} - Y_{\text{min}}}
\]  

(5.17)

where \( \hat{Y} \) and \( Y \) denote the predicted normalised and absolute responses, respectively, for a given performance metric, whilst \( Y_{\text{min}} \) and \( Y_{\text{max}} \) denote the minimum and maximum attainable values.

Table 5.5. Minimum and maximum values for each performance metric (CSA, FS, SAR and RCP).

<table>
<thead>
<tr>
<th></th>
<th>CSA (mm(^2))</th>
<th>FS (%)</th>
<th>SAR (%)</th>
<th>RCP (kPa)</th>
</tr>
</thead>
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<tr>
<td>Min.</td>
<td>-9.4</td>
<td>2.3</td>
<td>22.1</td>
<td>-72.6</td>
</tr>
<tr>
<td>Max.</td>
<td>-5.8</td>
<td>13.9</td>
<td>50.0</td>
<td>-0.7</td>
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</table>
Multi-objective optimisation produced a stent design superior to the baseline with $t = 150 \, \mu m$ and $w = 173 \, \mu m$ (Table 5.6), which are lower than some commercial polymeric stents (Kawamoto et al., 2016), whilst meeting the minimum allowable collapse pressure (Agrawal et al., 1992). A comparison between the baseline design and the optimised design is shown in Figure 5.16, in which each performance metric has been normalised. The RCP of the optimal design is approximately twice that of the baseline design with a less than 1% increase in SAR. The CSA has increased by 14% and whilst FS has increased, a value of 8% is comparable to stents in commercial use (Wang et al., 2006).

**Table 5.6.** Comparison between baseline (base.) and optimal (opt.) stent designs highlighting design parameters and their respective performance metrics.

<table>
<thead>
<tr>
<th></th>
<th>A (\text{-})</th>
<th>w (\mu m)</th>
<th>t (\mu m)</th>
<th>l (\mu m)</th>
<th>CSA (\text{mm}^2)</th>
<th>FS (%)</th>
<th>SAR (%)</th>
<th>RCP (kPa)</th>
</tr>
</thead>
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<td><strong>Base.</strong></td>
<td>1.35</td>
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<td>150</td>
<td>1050</td>
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<td>5.7</td>
<td>35.3</td>
<td>-20.9</td>
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<tr>
<td><strong>Opt.</strong></td>
<td>2.3</td>
<td>173</td>
<td>150</td>
<td>900</td>
<td>-9.1</td>
<td>8</td>
<td>35.7</td>
<td>-40</td>
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</table>

**Figure 5.16.** Visual comparison of normalized performance metrics and design parameters between the baseline design and the optimal design.
5.4 Discussion

In this chapter, a multi-objective optimisation framework is proposed that considers the combined effect of the biaxial stretching processing history and the geometric configuration when optimising the short-term (pre-degradation) mechanical performance of a PLLA coronary stent. Given that the ideal stent must fulfil a range of conflicting technical requirements, a multi-objective optimisation process that offers compromises between key performance metrics was conducted to develop a polymeric stent that offered improved performance relative to a baseline design for the same strut thickness (150 μm). Performance trade-offs were observed (Figure 5.15) and may be explained using the absolute t-value comparisons for coefficients (Figure 5.8) and the response surface interaction plots for each performance metric (Figure 5.9–Figure 5.14). The absolute t-value comparisons for coefficients highlight statistically significant ($p < 0.05$) factors for each performance metric whilst the response surface interaction plots provide a visual aid in understanding the interdependent effect between two factors on a given performance metric.

5.4.1 Cross-sectional area vs. foreshortening

The trade-off between CSA and FS was primarily due to the conflicting requirements for $w$ and $l$. Cross-sectional area was most strongly affected by $w$ and $w^2$ (Figure 5.8a), whilst FS was most strongly affected by $l$ and $l^2$ (Figure 5.8b). Increasing $w$ improved CSA as a wider strut increased plastic deformation in the hoops and reduced radial recoil, which is in agreement with the findings of Pant et al. (2012). Furthermore, the presence of a significant ($p < 0.05$) quadratic effect ($w^2$) in the model suggested a curvilinear relationship between CSA and $w$. This was evident from the interaction plots in which $w$ was plotted as one of the dependent variables (Figure 5.9a, Figure 5.12a and Figure 5.13a). A convex relationship was observed between CSA and $w$, i.e. CSA improved as $w$ increased but with diminishing returns. Decreasing $l$ further improved CSA and was evident from the interaction plot between $w$ and $l$. By increasing $w$ from 100 μm to 200 μm and
decreasing I from 1,200 µm to 900 µm, CSA improved by approximately 53%. However, this change caused an undesirable increase in FS from 3% to 11%. In contrast to the requirements for CSA, narrow, long struts were ideal for reducing FS, as the struts deformed less to achieve an equivalent level of plastic strain, thereby reducing the level of axial contraction. This is in agreement with Li et al. (2017) who acknowledged the contrasting requirements for I, based on the observed trade-off between recoil and FS. Strut thickness has the weakest effect on CSA—whilst a higher value of t reduced the degree of radial recoil post-inflation, it was not offset by the reduced CSA (as a result of the thicker struts) pre-inflation. In general, it was beneficial to design the stent such that it is stiffer in the circumferential direction as FS improved without negatively affecting CSA. Hence, a lower value of I and A, were desirable.

5.4.2 Cross-sectional area vs. stent-to-artery ratio

The trade-off between CSA and SAR was primarily due to the conflicting requirements for w. Although high values of w improved CSA, a wider strut increased the surface area of the stent which negatively affects SAR. Low values of I were correlated with improved CSA, and were also correlated with improved SAR as, intuitively, a shorter strut reduced the surface area of the stent. The interaction between w and I had the strongest effect on SAR (Figure 5.8c) and was evident from the response surface plot (Figure 5.13c). Stent-to-artery ratio was unaffected by t and A, and hence, it was beneficial to design the stent with high values of A, and t as these parameters improved CSA. High values of A, and t, combined with a low value of I are ideal for improving both CSA and SAR. By holding each of these design parameters constant at their optimal limits and increasing w from 100 µm to 200 µm, CSA improved by approximately 20%. However, SAR had an undesirable increase from 22% to 40%, which is significantly higher than the SAR for both polymer and metallic stents in clinical practice, and may contribute to increased levels of thrombosis (Kolandaivelu et al., 2011; Kawamoto et al., 2016).
5.4.3 Foreshortening vs. radial collapse pressure

The trade-off between FS and RCP was primarily due to the conflicting requirements for w, t and l. Radial collapse pressure was most strongly affected by the interactions between w and t, w and l and t and l, with each interaction considered statistically significant ($p < 0.05$) (Figure 5.8d). The response surface plots for each of these interactions (Figure 5.12d, Figure 5.13d and Figure 5.14d) showed that RCP improves with high values of t and w, combined with low values of l. This combination of parameters tended to induce higher levels of plastic deformation in the strut hoops. By increasing w and t from 100 µm to 200 µm and decreasing l from 1,200 µm to 900 µm, RCP improved from 8.8 kPa to 70 kPa, meeting the minimum allowable collapse pressure of 40 kPa (Agrawal et al., 1992). However, this change caused an undesirable increase in FS from 2.5% to 12%. In general, $A_r$ did not strongly affect RCP and was not considered statistically significant ($p > 0.05$). However, given that a higher $A_r$ improved FS, it was beneficial to design the stent such that it is stiffer in the circumferential direction.

5.4.4 Stent-to-artery ratio vs. radial collapse pressure

The trade-off between SAR and RCP is similar to the trade-off observed between SAR and CSA, and is primarily due to the conflicting requirements for w. High values of $A_r$ and t, combined with a low value of l are ideal for improving both RCP and SAR. By holding each of these design parameters constant at their optimal limits and increasing w from 100 µm to 200 µm, RCP had a more than three-fold increase. However, SAR had an undesirable increase of approximately 80%.

5.5 Conclusion

An optimisation framework has been proposed that considers the combined effect of the biaxial stretching processing history and the geometric configuration when optimising the mechanical performance of a PLLA coronary stent. Response surface
methodology combined with multi-objective optimisation produced an optimal PLLA stent design that offered improved performance relative to a baseline design for the same strut thickness (150 µm). The effects of each of the design parameters ($A_n$, $w$, $t$ and $l$) on individual performance metrics (CSA, FS, SAR and RCP) have been quantified and compared. For each of the design parameters, a main factor or two-way interactions term had a statistically significant ($p < 0.05$) effect on at least one of the performance metrics. Pareto fronts highlighted that a change in one design parameter that improves one metric often leads to a compromise in at least one of the other metrics with trade-offs observed for CSA vs. FS, CSA vs. SAR, FS vs. RCP and SAR vs. RCP. In summary, this chapter addresses key limitations in polymeric stent design and the methodology presented herein could be applied in the development of high stiffness, thin strut polymeric stents.
6. General discussion

6.1 Overview

Percutaneous coronary intervention is a widely adopted, highly successful procedure for the treatment of CHD and demand is expected to increase considerably in the future (World Health Organization, 2011; Ludman et al., 2015). Currently, the majority of PCI procedures use a metallic DES and whilst these devices have shown success, their long-term safety remains an issue, due to LST and delayed healing (Bavry et al., 2006; Van Beusekom et al., 2007). The potential benefits of PLLA BRSs include late lumen enlargement following the resorption process, a reduction in LST and fewer complications during revascularisation procedures (Onuma and Serruys, 2011). However, the lower elastic modulus of PLLA compared to metals commonly used in DESs, means that the strut profile of a PLLA BRS is bulkier (Kolandaivelu et al., 2011; Kawamoto et al., 2016), which has been shown to increase thrombosis risk and restenosis (Kastrati et al., 2001; Serruys et al., 2016).

Improvements in material processing and the correct matching of material processing to stent geometry were identified as two methods to reduce strut profiles and improve the design of BRSs (Alexy and Levi, 2013; Pauck and Reddy, 2015). This work has built on previous innovations in coronary stent design to improve the applicability of the methods to polymeric BRS design. This thesis presented an investigation into the improvements in mechanical properties of PLLA attainable from biaxial deformation and the subsequent multi-objective optimisation of a BRS using the processed polymer as the platform material. Specifically, this work investigated the feasibility of designing a PLLA BRS with thinner struts, through the combined optimisation of material processing parameters and stent geometry.
6.2 Summary of key findings

6.2.1 Processing-property relationships

The first objective of this work was to replicate the SBM processing history of a polymeric stent, in order to investigate the impact of the biaxial deformation procedure on the short-term (pre-degradation) mechanical properties of extruded PLLA. If PLLA is to be used as the platform material for BRS, it is important to process the polymer such that key mechanical properties that are desirable for coronary stents (e.g. elastic modulus and yield strength) are enhanced. Although the effect of the biaxial deformation procedure has been widely examined for semi-crystalline polymers such as polyethylene terephthalate, high-density polyethylene and poly(ether-ether-ketone) (Menary et al., 2012; McKelvey et al., 2018; Turner et al., 2019), there has been limited investigation into its effect on PLLA. The influence of biaxial processing parameters on the mechanical properties of PLLA was examined in Chapter 3, with DoE screening used to identify significant parameters and RSM used to generate empirical relations that relate the elastic modulus and yield strength to significant parameters. Stretch ratio had the most significant effect of the mechanical properties of biaxially stretched PLLA whilst temperature, strain rate and deformation mode had a comparatively lesser effect.

6.2.2 Characterisation and constitutive modelling

The second objective of this work was to calibrate a constitutive model for biaxially stretched PLLA. A PLLA stent is exposed to a variety of temperatures and environmental conditions during its lifecycle and it is therefore essential that the mechanical behaviour of PLLA at each of these conditions is understood (Schmidt et al., 2016). Capturing the mechanical response of PLLA in a constitutive model is particularly useful for finite element simulations and predictive modelling. Furthermore, few studies have characterised and calibrated a constitutive model for
PLLA that has undergone a similar biaxial processing history to a coronary stent. The effect of temperature and extension rate on the short-term (pre-degradation) mechanical properties of extruded PLLA post biaxial stretching were investigated across a variety of processing histories in Chapter 4. The results of this chapter suggested that the mechanical response of PLLA was highly dependent on processing history and post-processing temperature, however was comparably less dependent on post-processing extension rate. The experimental data was used to calibrate a rate-independent, transversely isotropic, temperature-dependent, elastic-plastic constitutive model for finite element implementation.

6.2.3 Multi-objective optimisation

The third (and final) objective of this work was to assess if the correct matching of material processing conditions to stent geometry could reduce strut profiles (with respect to strut thickness and strut width) and ultimately improve the design of PLLA BRSs. Previous studies have suggested that the mechanical performance of a PLLA BRS is dependent on both its material properties, which are affected by the processing history, and its geometric configuration (Alexy and Levi, 2013; Pauck and Reddy, 2015; McMahon et al., 2018). A framework was proposed in Chapter 5 that sought to optimise both material properties and the geometry of a PLLA stent, through finite element analysis and the constitutive model proposed in Chapter 4. The results presented within this chapter suggested that key performance metrics, used to evaluate the efficacy of a stent design, were affected by both the biaxial stretching processing history and the geometric configuration of the stent. A surrogate modelling approach was used to generate constitutive equations that related each performance metric to the design parameters.
6.3 Clinical relevance of the work

It is intended that the optimisation framework developed herein would be predominantly used during the preclinical design phase. There are a number of advantages to using such a framework. Firstly, it is both robust and transferable, and can cater for different materials and alternate stent geometries. For example, whilst PLLA was investigated as the platform material in this thesis, it could potentially be replaced with any semi-crystalline polymer that can be biaxially processed. Likewise, whilst a traditional open-cell stent design was investigated in this thesis, it could be replaced with any geometry that can be parameterised. Hence, even with foreseeable advancements in polymer synthesis and changes in BRS geometry, the proposed methodology can still be used to evaluate these more abstract material/geometry combinations.

Secondly, there are a number of advantages to having empirical relations that correlate the mechanical properties to processing parameters. These relations can help an engineer identify a suitable set of processing parameters that meet the needs of a given stent geometry early in the design process. Additionally, implementing empirical relations for the elastic modulus and yield strength into a constitutive model which is capable of predicting the mechanical response of the polymer over a wide range of processing histories is particularly useful when the engineer is performing pre-clinical simulations.

Thirdly, the surrogate modelling approach used for the multi-objective optimisation drastically reduces solution time when compared to traditional methods. In an era where the concepts of patient specific and/or lesion specific stents are becoming more feasible, one of the primary drawbacks is the computational power required to run large cohorts of potentially suitable stent designs. Once the empirical coefficients of the surrogate models have been established and the criteria for optimality has been identified, a solution can be obtained within minutes, as opposed to the days/weeks it would take using a more traditional method of
optimisation. Furthermore, this surrogate modelling approach offers flexibility, whereby the objective function and constraints can be changed without affecting computational cost, making it a viable tool for pre-clinical design.

Finally, the performance metrics are related to both the platform material’s processing history and the stent’s geometry. In the context of a medical device manufacturer, this modelling approach generates a link between the engineer investigating potential processing windows for the platform material and the engineer investigating potential geometric configurations for the stent. It is intended that this link would reduce the degree of trial and error in the design process, allowing an optimal stent design to be established more efficiently and result in a more streamlined design process, culminating in a reduced time to market.

### 6.4 Critical assessment of the work

The proposed methodology for the experimental characterisation, constitutive modelling and multi-objective optimisation of PLLA BRSs incorporates a number of important features and design considerations. Nevertheless, there have been a number of simplifications made throughout the development of this framework and these limitations must be considered when assessing results. Furthermore, a brief discussion of the limitations of the framework is key to identifying suitable direction for future work.

#### 6.4.1 Experimental characterisation limitations

Throughout this thesis, it has been assumed that the state of biaxial deformation induced during planar (sheet) deformation is directly comparable to the state of biaxial deformation induced during a typical SBM process for a tube. Whilst studies have confirmed this (Menary et al., 2012), it should be noted that during the SBM process for a tube, the stretch ratio of the inside wall is significantly higher than the
stretch ratio of the outside wall. For example, in order to stretch blow mould a 3.5 mm diameter tube with 150 μm wall thickness, from which a stent can be laser cut, a preform with external and internal diameter of approximately 1.5 mm and 0.5 mm, respectively, may be used (Ramachandran et al., 2018). In this scenario, the external and internal circumferential stretch ratios will be approximately 2.3 and 6.7, respectively. Given that both the elastic modulus and yield strength have been shown to be dependent on stretch ratio, this could lead to a variation in mechanical properties through the thickness. In this thesis, the largest stretch ratio evaluated in any given direction was 3.5, with the custom-built biaxial tensile test machine limited to a maximum stretch ratio of five (Martin et al., 2005). Future work should therefore endeavour to replicate the biaxial deformation mode that a tubular preform experiences during SBM and investigate stretch ratios beyond 3.5. Additionally, the effect that the through-thickness variation in mechanical properties has on the performance of a stent should be investigated. If the through-thickness mechanical properties are shown to have significant influence, the transversely isotropic constitutive model proposed herein could be adapted to a fully anisotropic model.

The mode of deformation selected to calibrate the constitutive model was uniaxial and tensile, which is only partially representative of the mode of deformation that a typical coronary stent experiences during manufacture and in service. During both crimping and expansion, stent rings experience a combination of compression, tension and bending (Migliavacca et al., 2005; Karanasiou et al., 2017) that may not be adequately captured by the constitutive model presented herein. The films produced by biaxial stretching ranged in thickness from 100-300 μm. Therefore, whilst uniaxial tensile testing was feasible for sample thicknesses in this range, conventional macro-based test methods for compression and bending were not. Hence, future work should focus on using micro-based test methods, such as micro-compression and micro-bending, in order to characterise the material. Additionally, during characterisation, a dry oven was used to simulate body temperature (and
crimping temperature) during tensile testing. There may be justification for the inclusion of an environment chamber that uses water or a simulated body fluid, such as phosphate-buffered saline (PBS), to better replicate ‘wet’ in vivo conditions. However, studies have shown that PLLA experiences a minimal deterioration in mechanical properties when submersed in water or PBS for 4-6 weeks (Zilberman et al., 2005; Tanaka et al., 2013). Hence, replication of ‘wet’ in vivo conditions may only be required for long-term studies where degradation is of interest.

Uniaxial load/unload tensile tests were performed on a subset of specimens selected from the DoE in Chapter 4 to evaluate the viscoelastic recovery upon the removal of load, which occurs during the balloon deflation phase of a typical stent deployment. Specimens were subjected to a single (post-processing) temperature, (post-processing) extension rate and were punched in the TD from a single biaxially stretched sheet. Whilst the viscoelastic recovery was minimal for the set of conditions analysed, the effect of temperature, extension rate, processing history and direction that the specimen is punched in (in terms of MD and TD) must each be evaluated to ensure that factors (and the interactions between factors) do not have a significant effect on PLLA’s viscoelastic response. Hence, there may be justification to include this as a metric in the DoE, suggesting an area for future work.

Finally, elongation to failure was not considered as a performance metric during uniaxial tensile testing. Elongation to failure is highly dependent on the specimen geometry and any material imperfections induced during processing and/or preparation. For example, in Chapter 4, elongation to failure ranged from approximately 3% to 70% depending on the processing, temperature and strain rate used during tensile testing. As a result, a large sample size is necessary in order to get an accurate measurement of elongation to failure for a given set of test conditions. This made it a prohibitive metric for multi-factor design of experiments testing. Ideally, elongation to failure should be considered when designing a stent, given that strains of up to 50% may be experienced during deployment (Bobel et al.,
However, a significant proportion of the samples in Chapter 3 and Chapter 4 fractured prior to this level of strain being reached. The introduction of a biocompatible plasticiser (e.g. polyethylene glycol) in a concentration of approximately 10–20% w/w with the PLLA has been shown to increase elongation beyond this threshold whilst maintaining a high degree of stiffness and strength (Martin and Averous, 2001; Shibata et al., 2007; Farah et al., 2016). Alternatively, annealing at temperatures close to the $T_g$ promotes a brittle-to-ductile change in the fracture behaviour of PLLA and increases elongation-to-break with minimal reduction in mechanical properties (Kfoury et al., 2013). Given that biaxial deformation increases elongation-to-break compared to the unstretched PLLA (Wu et al., 2013), it is hypothesised that combining annealing with the introduction of a plasticiser could produce a polymer that is capable of consistently achieving these strain levels, suggesting an area for future work.

### 6.4.2 Computational modelling limitations

The constitutive model (developed in Chapter 4) was unable to capture the viscoelastic recovery observed during the experimental uniaxial load/unload tensile tests. The viscoelastic recovery was minimal for the conditions tested and hence a rate-independent elastic-plastic constitutive model was deemed acceptable. However, it has been suggested in the preceding section that specimens should be tested (experimentally) across a wider range of conditions. Should the viscoelastic recovery increase as temperature, extension rate or processing history are varied, there may be justification for introducing rate-dependency in the constitutive model.

For the deployment and performance testing simulations in Chapter 5, stents were designed in a pre-crimped state. Whilst crimping has been shown to impart residual stresses on the stent prior to deployment, Schiavone et al. (2017) showed, for a similar PLLA stent geometry to the one considered in Chapter 5, that neglecting these residual stresses has a minimal influence on recoil, stress distribution and
maximum stress in the stent following deployment. Hence, the crimping process was neglected in order to reduce computational time. However, a recent experimental study by Ailianou et al. (2016) found that the microstructural transformations induced during crimping improved strength and ductility of PLLA stents. Whilst these microstructural transformations improved the performance of the stent during crimping, they can also act as sites for crack initiation and fracture. The procedural complications with fracture can result in reduced support at the lesion and can trigger vessel injury and restenosis (Yamada et al., 2008; Manola et al., 2010; Sun et al., 2014). Poly(L-lactic acid) is a relatively brittle polymer (Todo et al., 2007) and given that PLLA BRSs can experience strains of up to 50% during crimping and deployment (Bobel et al., 2015), there may be an increased risk of cracking and fracture. Further developments to this work should therefore include the development of a micromechanical based constitutive model and consider the potential for stent fracture during crimping and deployment.

Stent geometries were based on a conventional open-cell design with straight bridges, which has proved ideal for metallic drug-eluting stents. However, this does not guarantee compatibility when using a polymer such as PLLA as the platform material, given that it exhibits an entirely different stress-strain response. Modifying the bridge geometry, strut cross-section and hinge profile have all been shown to influence the mechanical performance of stents (Pant et al., 2012; Grogan et al., 2013) and the inclusion of these parameters may permit the evaluation of unconventional (or unorthodox) geometries that are better suited to polymeric stents. In addition to increasing the number of design parameters, the inclusion of a stenosed artery into the finite element model would permit additional performance metrics to be evaluated. Modelling the expansion of a stent in a stenosed artery could provide an indication of high risk areas in the stented region and may also be used to evaluate the stent’s susceptibility to fracture.

There is limited information in literature on clinically acceptable values for the performance metrics evaluated within the optimisation framework, such as
foreshortening and stent-to-artery ratio. Identification of operational limits for these metrics is essential, as these limits can be used as constraints for the multi-objective optimisation procedure to tailor stent designs for a particular lesion or patient geometry, suggesting an area for future investigation.

Finally, the impact of the framework could be considerably improved by the experimental validation of the computational simulations. It is hypothesised that PLLA tube extrusion could be performed under similar conditions used for the sheet extrusion in Chapter 3. Following tube extrusion, the SBM process could be performed using a similar custom set-up to Løvdal et al. (2016) which consists of a cylindrical mould, heating elements, pressurised air and a linear actuator. Following SBM, the stent geometry may be formed by laser cutting a pattern on the stretch blow moulded polymeric tube (Grabow et al., 2015). Following laser processing, the stent should be crimped (at 55 °C) on to a folded angioplasty balloon using a benchtop stent crimping head that converts linear actuation to radial displacement. Deployment of the stent should be performed in a water (or simulated body fluid) bath at 37 °C (Meng et al., 2006). Cross-sectional area and foreshortening of a stent (post-dilation) can be measured using a digital calliper (Lanzer, 2007). Stent-to-artery ratio is a function of the stent’s surface area which is known prior to deployment and can be measured post-deployment using stereo-microscopy (Károly et al., 2013). Radial collapse pressure simulations can be experimentally replicated using a benchtop stent crimping head that records the radial force for a given displacement (Luo et al., 2014).

\[ \text{6.4.3 Degradation modelling limitations} \]

The emphasis of this work was placed on improving the short-term performance of a PLLA BRS and hence, long-term performance was neglected. The reasoning for this emphasis was that if the strut profile of a PLLA BRS cannot be reduced such that it is capable of performing its intended function in the short-term, then it cannot
hope to improve its performance in the long-term as the platform material degrades and the stent’s mechanical integrity begins to decay.

Degradation of the platform polymer may influence the geometric design of the stent. For example, a strut width that is optimal for short-term performance may not suffice for long-term performance, especially if the stent is unable to provide sufficient radial resistance to the compressive force of the arterial wall as a result of degradation. However, it may be possible to tailor the degradation profile of the platform polymer using biaxial stretching. In this thesis, biaxial stretching was shown to change the microstructure and crystallinity of the stretched polymer. Given that the rate of degradation of PLLA is a function of crystallinity (Vieira et al., 2011), as well as the magnitude of the applied stress (Grijpma and Pennings, 1994), biaxial stretching may potentially be used to tailor the degradation profile of the polymer. Significant work has been conducted into evaluating and modelling the degradation behaviour of PLLA (Muliana and Rajagopal, 2012; Khan and El-Sayed, 2013; Soares and Moore, 2016), however to the best of the author’s knowledge, no study has investigated the influence of biaxial stretching on the degradation profile of the polymer. Future iterations of this framework should therefore consider both the mechanical response of the platform material and the performance metrics used to assess the efficacy of a stent design as a function of time.
7. Conclusions

A framework for the multi-objective optimisation of a bioresorbable coronary stent was developed. The development required the author to perform the following actions: Initially, the effect of the biaxial stretching process on the mechanical properties of PLLA was investigated using design of experiments and response surface methodology. Secondly, the effects of processing history, post-processing temperature and post-processing extension rate on the mechanical response of PLLA were evaluated and a transversely isotropic, temperature-dependent elastic-plastic constitutive model was proposed. Finally, a multi-objective optimisation framework was developed to optimise the design of a high stiffness, thin-strut stent constructed from biaxially stretched PLLA, through the combined refinement of processing parameters and stent geometry. Successful implementation of this methodology suggested the following conclusions:

- Biaxial deformation has the potential to enhance the elastic modulus and yield strength of extruded PLLA sheet by approximately 80% and 70%, through selection of optimal processing conditions.
- These mechanical properties were highly dependent on the stretch ratio and the aspect ratio of the biaxial deformation, along with the temperature during uniaxial deformation (post-processing); but are not heavily dependent on extension rate (post-processing).
- The improvement in these mechanical properties as a result of biaxial deformation is not directly attributable to crystallinity, but may be attributable to the degree of amorphous orientation.
• A transversely isotropic, temperature-dependent, elastic-plastic constitutive model is capable of capturing the mechanical response of PLLA below its glass transition temperature.

• With regard to the multi-objective optimisation framework, a change in one design parameter that improves one metric often leads to a compromise in at least one of the other metrics with trade-offs observed for CSA vs. FS, CSA vs. SAR, FS vs. RS and SAR vs. RS.

• Correct matching of material processing to stent geometry produced an optimal PLLA stent design that offered improved performance relative to a baseline design for the same strut thickness (150 μm).

• Finally, this thesis addresses key limitations in polymeric stent design and the methodology proposed herein may be used to aid development of high stiffness, thin strut polymeric stents.
8. Future Work

A brief overview of the limitations of the work conducted within this thesis has suggested the following areas for future research.

- A number of possible improvements to the multi-objective optimisation framework can be made: (a) increase the number of parameters used to define the geometry of the stent — the inclusion of which may permit the evaluation of unconventional geometries that are better suited to polymeric stents; (b) simulate the crimping process and evaluate the risk of fracture prior-to and during stent deployment; (c) introduce a model artery and evaluate the interaction between stent struts and the surrounding tissue and (d) run a larger sample of finite element simulations to improve the accuracy of the response surface models.

- The constitutive model and the multi-objective optimisation framework would benefit from the inclusion of time-dependent parameters and metrics. This would permit the long-term performance of the stent (as it degrades) to be evaluated. Additionally, the biaxial stretching procedure may have a significant effect on the degradation profile of PLLA and to the best of the author’s knowledge, this has yet to be investigated.

- Finally, the multi-objective optimisation framework produced an optimal stent design based on computational deployment and bench test simulations. The impact of the framework could be considerably improved by the experimental validation of these simulations. A key part of the future development of this work should focus on developing test apparatus that accurately replicates the simulated test protocols.
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Appendix A. Code

All computational code used within this thesis has been submitted as supplementary information to Queen’s University Belfast and is available upon request. In addition, all computational code has also been made publically available using the links provided within this section.

A.1 R

Design of experiments, response surface methodology and regression analyses in Chapter 3, Chapter 4 and Chapter 5 were performed using R (R Core Team, 2017). The data files (.dat) and R files (.r) are available from the following links:

Chapter 3

Design of experiments (data):

Design of experiments (R):

Response surface methodology (data):

Response surface methodology (R):
Chapter 4

Design of experiments (data):

Design of experiments (R):

Chapter 5

Response surface methodology (data):

Response surface methodology (R):

A.2 Abaqus

The constitutive model finite element calibration simulations in Chapter 4 were performed using Abaqus/Standard 2016 (Dassault Systèmes, France). The input files (.inp) for each constitutive model are available from the following directory:

Chapter 4

Constitutive models:
A.3 SolidWorks

The three-dimensional model of the stent in Chapter 5 was generated using SolidWorks 2016 (SolidWorks Corporation, USA). The model part (.prt) file is available from the following link:

Geometry:

A.4 Python

A.4.1 Abaqus

The deployment and radial compression bench testing finite element simulations were performed using Abaqus/Standard 2016 (Dassault Systèmes, France). Finite element models were generated using a combination of Python (version 2.7.13; Python Software Foundation) and the Abaqus CAE pre-processor. The ‘para_des’ Python file (.py) generates forty unique stent designs, parameterised with respect to material properties and stent geometry, and modifies the ‘PLLA.py’ constitutive model file for each design. All Python files denoted with the suffix ‘_in’ are intended to be read by the Abaqus pre-processor in order to generate input files (.inp) for Abaqus/CAE to solve. All Python files denoted with the suffix ‘_out’ are intended to be read by the Abaqus post-processor in order to extract performance metrics (i.e. cross-sectional area post-dilation, foreshortening, stent-to-artery ratio and radial collapse pressure) from the Abaqus output database files (.odb). The aforementioned code is available from the following links.

Parametric designs

Generate parametric designs

para_des.py
Constitutive models
Poly(L-lactic acid) constitutive model (pre-processing):

Deployment
Simulation (pre-processing):
Cross-sectional area (post-processing):
Foreshortening (post-processing):
Stent-to-artery ratio (post-processing):

Radial compression
Simulation (pre-processing):
Radial collapse pressure (post-processing):
A.4.2 Optimisation

Multiple linear regression analysis was performed on the results presented in Chapter 5 (using R) in order to establish a set of statistical response surface models. Multi-objective least squares optimisation was performed on these statistical models using Python. The optimisation Python file (.py) is available from the link below:

Optimisation: