Constitutive neural networks for main pulmonary arteries: Discovering the undiscovered

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Abstract

Accurate modeling of cardiovascular tissues is crucial for understanding and predicting their behavior in various physiological and pathological conditions. In this study, we specifically focus on the pulmonary artery in the context of the Ross procedure, using neural networks to discover the most suitable material model. The Ross procedure is a complex cardiac surgery where the patient's own pulmonary valve is used to replace the diseased aortic valve. Ensuring the successful long-term outcomes of this intervention requires a detailed understanding of the mechanical properties of pulmonary tissue. Constitutive artificial neural networks offer a novel approach to capture such complex stress-strain relationships. Here we design and train different constitutive neural networks to characterize the hyperelastic, anisotropic behavior of the main pulmonary artery. Informed by experimental biaxial testing data under various axial-circumferential loading ratios, these networks automatically discover the inherent material behavior, without the limitations of predefined mathematical models. We regularize the model discovery using cross-sample feature selection and explore its sensitivity to the collagen fiber distribution. Strikingly, we uniformly discover an isotropic exponential first-invariant term and an anisotropic quadratic fifth-invariant term. We show that constitutive models with both these terms can reliably predict arterial responses under diverse loading conditions. Our results provide crucial improvements in experimental data agreement, and enhance our understanding into the biomechanical properties of pulmonary tissue. The model outcomes can be used in a variety of computational frameworks of autograft adaptation, ultimately improving the surgical outcomes after the Ross procedure.

Keywords: constitutive artificial neural networks, automated model discovery, cardiovascular tissue, main pulmonary arteries, collagen fiber distribution

1 Introduction

Automated model discovery with constitutive artificial neural networks is an emerging technology aimed at improving the modeling of complex biological tissues (Linka and Kuhl, 2023; St. Pierre et al, 2024; Martonova et al, 2024). This method combines machine learning with traditional constitutive modeling techniques to automatically discover material laws that describe how biological tissues deform under various conditions. Cardiovascular tissues, such as arteries and heart

valves, are highly complex, exhibiting nonlinear and anisotropic behaviors. A priori selection of an appropriate traditional constitutive model to describe these behaviors requires a deep expert knowledge, which can introduce bias and limits successful modeling to a few well-trained individuals. In contrast, constitutive artificial neural networks leverage data from experiments or simulations to learn these relationships automatically. By training on experimental data, these networks are capable of capturing the intrinsic stress-strain relationships of cardiovascular tissues and, when done right, even generalize well to predict responses under previously unseen conditions.

Previous research has investigated anisotropic neural network models for human skin and healthy aortic arteries (Linka et al, 2023; Peirlinck et al, 2024b). Informed by biaxial extension tests, these networks inherently satisfied general kinematic, thermodynamic, and physical constraints. The results suggest that constitutive neural networks can robustly and consistently discover variations of arterial models from experimental data. Notably, the discovered models are generalizerable and interpretable, with the majority of network weights training to zero, while a small subset of non-zero weights defines the discovered model (Linka and Kuhl, 2024).

Artificial neural networks offer a key advantage in cardiovascular applications by automatically handling the complex, nonlinear nature of tissue mechanics without relying on oversimplified assumptions (Linka et al, 2021, 2022). This holds promise for personalized medicine, where models can be customized to patient data to individualize and improve surgical planning and device design (Peirlinck et al, 2021). The automated nature of this approach reduces the time and expertise needed for developing accurate models. Therefore, ongoing research will benefit from the tight integration of biomechanics, biomedical engineering, and physics-informed machine learning (Holzapfel and Ogden, 2017). Recent findings indeed suggest that neural networks could automate model discovery and parametrization, potentially transforming constitutive modeling and subsequent finite element simulations (Weiss et al, 1996; Peirlinck et al, 2024a,c). Moreover, the high-throughput results of neural networks allow for an in-depth analysis of the biological nature of the considered data, providing additional insights into the microstructural features of the input data.

The present work focuses on automated model discovery and the application of constitutive neural networks to main pulmonary artery experimental data, with the Ross procedure in mind. The Ross procedure is a surgical technique to treat aortic valve disease, particularly in young and active patients. In the 1960s, Dr. Donald Ross designed this intervention by taking the patient's own pulmonary valve and placing it in the aortic position to create a pulmonary autograft (Charitos et al, 2012; Chauvette et al, 2019; El-Hamamsy et al, 2022; Van Hoof et al, 2022). The new valve is alive and can adapt over time, making the Ross procedure the only aortic valve replacement technique that can restore long-term survival and maintain quality of life. Despite scientific consensus on its significant benefits, the Ross procedure still has a principal failure mode, linked to wall dilatation, which can lead to valve leakage and reoperation. Dilatation occurs due to the inability of the pulmonary autograft to adapt to the sudden increase in loading when exposed to the four- to fivefold increase in aortic pressures.

Here, we contribute to the broader picture of this research by further investigating the mechanical behavior of pulmonary tissue, which forms the baseline for the long-term outcomes of the autograft in the Ross procedure. Multiple computational modeling studies are currently investigating the growth and remodeling outcomes of the Ross procedure, ranging from analytical solutions to patient-specific finite element frameworks (Famaey et al, 2018; Vastmans et al, 2021; Vervenne et al, 2023; Maes et al, 2024). Ultimately, all of these models and results could make the Ross procedure the preferred solution for aortic valve replacement worldwide (Middendorp et al, 2024). At the very core of these frameworks are the constitutive models and parameters of the pulmonary autograft tissue. The sensitivity of the constitutive equations and mechanical properties considered cannot be underestimated, and the presented constitutive artificial neural networks aim to increase the overall biofidelity of these computer simulations.

We base our study on biaxial extension data from $n = 8$ pulmonary artery samples under different loading ratios. We perform sample-specific

model discovery both with and without regularization. Additionally, we systematically explore constitutive feature selection across all samples. This will allow us to identify a universal constitutive behavior through cross-sample feature selection regularization. To probe the anisotropic tissue response, we perform a fiber angle sensitivity analysis using a sweep of models with fixed fiber angles across the axial-circumferential domain. Finally, we compare our results with the traditional Holzapfel-Gasser-Ogden model, which considers strain-stiffening collagen fibers in an isotropic elastin matrix (Holzapfel et al, 2000). Ultimately, our discovered models and constitutive insights into main pulmonary arteries can inform and support computational studies, particularly in the context of aortic valve replacements through the Ross procedure.

2 Materials and Methods

This section will first provide an overview of the unpublished experimental mechanical biaxial extension data used to train the neural networks. We will then outline the constitutive equations, including the deformation gradient and its invariants. These invariants form the basis of the total strain energy density function that constitutes the core of the constitutive artificial neural network. We will design potential terms of this free energy density based on principles of thermodynamic consistency, material objectivity and symmetry, incompressibility, and polyconvexity. Subsequently, we will highlight the specific axial and circumferential first Piola-Kirchhoff stress calculations for planar biaxial extension tests. At the model input, we will also study the effects of varying collagen fiber angles and assess their influence on the discovered models. Finally, we will outline different variations of the neural network loss function used for training.

2.1 Experimental dataset

In the context of an animal study on the Ross procedure (Van Hoof et al, 2021), we performed planar biaxial tensile tests on squared samples (10 mm x 10 mm) of the ovine main pulmonary artery, as shown in Fig. 1. The intimal side, or inner surface, of the pulmonary artery was exposed through an axial cut between the anterior cusp (left side of the figure) and the left cusp (right side of the figure) (Thiene and Rizzo, 2023). Two main pulmonary artery samples (A and B), distal to the valve sinuses, were extracted from a total of four ovine pulmonary roots, bringing the total number of tested samples to $n = 4 \cdot 2 = 8$.

Five rakes were mounted on each side of the sample, with an initial distance of 7 mm between the rakes in both the axial and circumferential directions. Planar biaxial tensile testing (MessPhysik - Zwick/Roell) was performed at the Core Facility for Biomechanical Characterization, FIBEr, KU Leuven. Axial and circumferential stretch was increased stepwise until single-rake failure occurred. This procedure resulted in a complete dataset of increasing stretch levels at 5%, 10%, 20%, and 30%, with the latter considered representative of the *in vivo* condition. Three axial-to-circumferential stretch ratios (2:1, 1:1, 1:2) were applied through the displacement-driven actuators, for each stretch level. A 2:1 ratio means that the full stretch level was applied by the actuator in the axial direction, and half that stretch level in the circumferential direction. Four preconditioning cycles were applied for each loading and stretch ratio, and only the fifth cycle was considered for post-processing (Fehervary et al, 2016).

Here, we write the imposed stretch levels and ratios as applied by the actuators as λ^*_{ax} and λ^*_{circ}, which can be different from the resulting measured planar biaxial deformations in the tissue. Therefore, during testing, 2D digital image correlation (DIC) particle tracking was performed using VIC 2D (Correlated Solutions) to calculate the resulting tissue strains (Vander Linden et al, 2023). The central 25% of the sample area were considered to ensure uniform stresses and strains. The results from opposite actuators were averaged to obtain a single axial and circumferential curve. This resulted in the actual stretches λ_{ax} and λ_{circ} shown on the x-axes of our plots. Experimentally measured forces were converted to tissue stresses on the y-axes using initial load-free thickness and areal sample measurements, obtained before testing via a Micro Laser Scanner (Acacia Technology).

The resulting engineering stress versus DIC stretch curves for the three ratios and post-preconditioning last loading cycle are presented

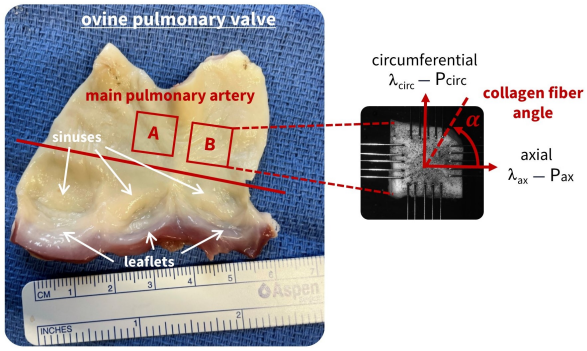

Fig. 1 Biaxial tissue extraction and mounting. From four ovine pulmonary roots, two main pulmonary artery squared samples per sheep were extracted. This resulted in a total of $n = 8$ samples, which were mounted in the biaxial test device through rake fixation. The main collagen fiber angle α is indicated in the figure and will be varied in the axial-circumferential plane during modeling.

for one representative sample in Fig. 2. The complete dataset for all $n = 8$ samples is available in the Supplementary Materials. The engineering stress curves do not start at zero stretch or zero stress. This is due to an applied preload of 0.1 N during testing, which is reasonable for aortic tissues but was considered excessive for pulmonary artery tissues. Therefore, we corrected the zero-strain state and considered the moment in time when all four actuators experienced positive forces as the new reference. Note that this force-driven prestretch correction differs in the stretch domain between the axial and circumferential directions, λ_{ax} and λ_{circ}, but uses the same 1:1 ratio offset, $\lambda^*_{\text{ax}} : \lambda^*_{\text{circ}} = 1 : 1$, for all three stretch ratios.

2.2 Constitutive modeling

In continuum mechanics, we can represent the initial configuration through a Lagrangian variable, $\mathbf{X}$, and the current or deformed configuration by a Eulerian variable, $\boldsymbol{x}$. A mapping function can transform one state into the other, $\boldsymbol{x} = \varphi(\mathbf{X})$. Locally, we use the deformation gradient tensor $\mathbf{F}$ to represent the change in infinitesimal line elements between both configurations, $d\boldsymbol{x} = \mathbf{F}(\mathbf{X})d\mathbf{X}$. We can then write

$$\mathbf{F} = \frac{\partial \boldsymbol{x}}{\partial \boldsymbol{X}} = \frac{\partial \varphi(\boldsymbol{X})}{\partial \boldsymbol{X}}. \tag{1}$$

The symmetric right Cauchy-Green deformation tensor $\mathbf{C}$ is defined as $\mathbf{C} = \mathbf{F}^T \cdot \mathbf{F}$. We can now indicate the Green-Lagrange strain as $\mathbf{E} = \frac{1}{2}\mathbf{C} - \mathbf{I}$, where $\mathbf{I}$ is the identity tensor (Mooney, 1940; Ciarlet, 1988; Holzapfel, 2002).
Yet another important continuum mechanics variable is the Jacobian $J = \det(\mathbf{F})$. The Jacobian expression itself is in the third invariant, $I_3 = \det(\mathbf{F}^T \cdot \mathbf{F}) = J^2$. Here, we assume a perfectly incompressible arterial tissue, thus characterized by a constant Jacobian equal to one, $I_3 = J^2 = 1$. For an anisotropic material, we can write the isotropic invariants I_1 and I_2 as well as anisotropic invariants I_4 and I_5 as functions of the deformation gradient (Spencer, 1971):

$$\begin{aligned} I_1 &= \left[\mathbf{F}^T \cdot \mathbf{F}\right] : \mathbf{I}, \\ I_2 &= \frac{1}{2}\left(I_1^2 - \left[\mathbf{F}^T \cdot \mathbf{F}\right] : \left[\mathbf{F}^T \cdot \mathbf{F}\right]\right), \\ I_4 &= \left[\mathbf{F}^T \cdot \mathbf{F}\right] : \mathbf{N} = \boldsymbol{n}_0 \cdot \left[\mathbf{F}^T \cdot \mathbf{F}\right] \cdot \boldsymbol{n}_0, \\ I_5 &= \left[\mathbf{F}^T \cdot \mathbf{F}\right]^2 : \mathbf{N} = \boldsymbol{n}_0 \cdot \left[\mathbf{F}^T \cdot \mathbf{F}\right]^2 \cdot \boldsymbol{n}_0. \end{aligned} \tag{2}$$

Here, $\boldsymbol{n}_0$ is the main fiber direction in the undeformed configuration, and $\boldsymbol{n}$ is its representation in the deformed configuration. As such, we can write $\boldsymbol{n} = \mathbf{F} \cdot \boldsymbol{n}_0$, with its associated structure tensor $\mathbf{N} = \boldsymbol{n}_0 \otimes \boldsymbol{n}_0$. Considering a collagen fiber angle α within the biaxial plane, we can then state that $\boldsymbol{n}_0 = [\cos\alpha,\ \sin\alpha,\ 0]^T$. This indicative fiber direction is indicated in Fig. 1.
In what follows, and in the context of large deformations, we introduce the first Piola Kirchhoff stress $\mathbf{P} = \mathbf{P}(\mathbf{F})$ as

$$P_{ij} = \frac{df_i}{T_j dS}, \tag{3}$$

where df_i is the force component in the deformed configuration acting on the corresponding initial surface area. The latter is defined by dS as the initial surface area on which the force acts, and with T_j representing the component of the unit normal vector in the j-direction in the reference configuration. For readability, we will use the term engineering stress as first Piola Kirchhoff stress alternate. Considering thermodynamic consistency, we imply this engineering stress $\mathbf{P}$ is equal to the derivative of the strain energy ψ with

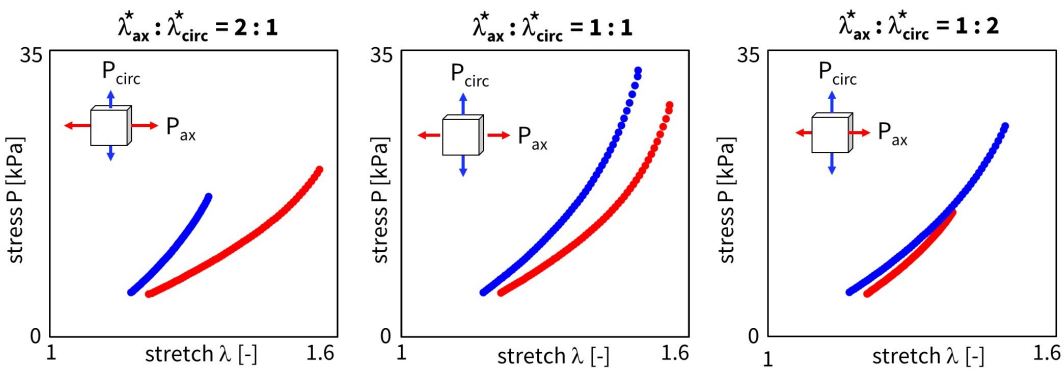

Fig. 2 Experimental stress-strain curves. We plot the engineering stress $\mathbf{P}$ versus the diagonal stretch component λ from the deformation gradient $\mathbf{F}$, in the axial (red) and circumferential (blue) directions. A representative dataset from a single main pulmonary artery biaxial extension test was selected. From left to right, the plots show the axial-to-circumferential ratios of 2:1, 1:1, and 1:2. The illustrated curves represent the 5th loading cycle at the 30% stretch level, with the preload correction applied to the stretch domain.

respect to the deformation gradient $\mathbf{F}$,

$$\mathbf{P} = \frac{\partial \psi(\mathbf{F})}{\partial \mathbf{F}}. \tag{4}$$

Next, material objectivity enforces that the constitutive equation does not depend on the external frame of reference, and we require that the free energy function ψ is a function of the right Cauchy-Green tensor $\mathbf{C} = \mathbf{F}^T \cdot \mathbf{F}$ (Noll, 1958):

$$\mathbf{P} = \frac{\partial \psi(\mathbf{C})}{\partial \mathbf{F}}. \tag{5}$$

Material symmetry for transversely isotropic materials now allows us to write:

$$\begin{aligned} \mathbf{P} &= \frac{\partial \psi(I_1, I_2, I_4, I_5)}{\partial \mathbf{F}} - p\mathbf{F}^{-T} \\ &= \frac{\partial \psi}{\partial I_1}\frac{\partial I_1}{\partial \mathbf{F}} + \frac{\partial \psi}{\partial I_2}\frac{\partial I_2}{\partial \mathbf{F}} \\ &\quad + \frac{\partial \psi}{\partial I_4}\frac{\partial I_4}{\partial \mathbf{F}} + \frac{\partial \psi}{\partial I_5}\frac{\partial I_5}{\partial \mathbf{F}} - p\mathbf{F}^{-T}, \end{aligned} \tag{6}$$

where we again assume perfect incompressibility, enforced by a hydrostatic pressure term $-p\mathbf{F}^{-T}$. We will be able to solve the latter from boundary conditions later on. Finally, if we consider polyconvexity of the free energy density function by ensuring that $\psi = \psi(I_1) + \psi(I_2) + \psi(I_4) + \psi(I_5)$, and by deriving the partial derivatives of equations 2 as

$$\begin{aligned} \frac{\partial I_1}{\partial \mathbf{F}} &= 2\ \mathbf{F}, \\ \frac{\partial I_2}{\partial \mathbf{F}} &= 2\ [I_1\mathbf{F} - \mathbf{F}\cdot\mathbf{F}^T\cdot\mathbf{F}], \\ \frac{\partial I_4}{\partial \mathbf{F}} &= 2\ \mathbf{F}\cdot\mathbf{N}, \\ \frac{\partial I_5}{\partial \mathbf{F}} &= \mathbf{F}\cdot[\mathbf{N}\cdot[\mathbf{F}^T\cdot\mathbf{F}] + [\mathbf{F}^T\cdot\mathbf{F}]\cdot\mathbf{N}], \end{aligned} \tag{7}$$

we can write:

$$\begin{aligned} \mathbf{P} = 2\Bigg[&\left(\frac{\partial \psi_1}{\partial I_1} + I_1\frac{\partial \psi_2}{\partial I_2}\right)\mathbf{F} - 2\frac{\partial \psi_2}{\partial I_2}\mathbf{F}\cdot\mathbf{F}^T\cdot\mathbf{F} \\ &+ \frac{\partial \psi_4}{\partial I_4}\mathbf{F}\cdot\mathbf{N} \\ &+ \frac{\partial \psi_5}{\partial I_5}\left(\mathbf{F}\cdot\mathbf{N}\cdot\mathbf{F}^T\cdot\mathbf{F} + \mathbf{F}\cdot\mathbf{F}^T\cdot\mathbf{F}\cdot\mathbf{N}\right)\Bigg] \\ &- p\mathbf{F}^{-T}. \end{aligned} \tag{8}$$

The engineering stress is now defined as a function of the deformation gradient and the derivative of the strain energy density function with respect to the four invariants (Hartmann and Neff, 2003; Ehret and Itskov, 2007).

2.3 Constitutive artificial neural network

Fig. 3 shows the constitutive artificial neural network framework with the relevant invariants for transversely isotropic, perfectly incompressible materials. The network has two hidden layers,

with four and eight nodes. The first layer generates powers $(\circ)$ and $(\circ)^2$ of the network input and the second layer applies the identity $(\circ)$ and exponential functions $(\exp(\circ))$ to these powers. The network is not fully connected by design to satisfy the condition of polyconvexity a priori. Explicitly, we can now write the resulting strain or free energy density $\psi(\mathbf{F})$ as a function of the considered invariants:

$$\begin{aligned}\psi = & w_1\ w_1^*\ [I_1-3]\ + w_2\ [\exp(w_2^*\ [I_1-3]\ )-1]\\ & + w_3\ w_3^*\ [I_1-3]^2 + w_4\ [\exp(w_4^*\ [I_1-3]^2)-1]\\ & + w_5\ w_5^*\ [I_2-3]\ + w_6\ [\exp(w_6^*\ [I_2-3]\ )-1]\\ & + w_7\ w_7^*\ [I_2-3]^2 + w_8\ [\exp(w_8^*\ [I_2-3]^2)-1]\\ & + w_9\ w_9^*\ [I_4-1]\ + w_{10}\,[\exp(w_{10}^*\,[I_4-1]\ )-1]\\ & + w_{11} w_{11}^*\,[I_4-1]^2 + w_{12}\,[\exp(w_{12}^*\,[I_4-1]^2)-1]\\ & + w_{13} w_{13}^*\,[I_5-1]\ + w_{14}\,[\exp(w_{14}^*\,[I_5-1]\ )-1]\\ & + w_{15} w_{15}^*\,[I_5-1]^2 + w_{16}\,[\exp(w_{16}^*\,[I_5-1]^2)-1]\,,\end{aligned} \tag{9}$$

corrected by the pressure term, $\psi = \psi - p\,[J-1]$. The network has a total of two times 16 trainable weights, with $2^{16} = 65,536$ possible combinations of terms. In other words, we can learn any strain energy function that follows from first- and second order, and identity and exponential additive combinatorics of the I_1, I_2, I_4, and/or I_5 invariants. Note that the growth condition corrections -3 and -1 for the isotropic and anisotropic terms, respectively, ensure that $\psi = 0$ in the undeformed state where $\mathbf{F} = \mathbf{I}$, and thus $I_1 = 3$, $I_2 = 3$, $I_4 = 1$, and $I_5 = 1$.

Planar biaxial extension testing

Through experienced mounting of the samples in the test device, as indicated in Fig. 1, we can state that the transversally isotropic pulmonary artery is stretched in two perfectly orthogonal directions, $\lambda_1 = \lambda_{\text{ax}}$ and $\lambda_2 = \lambda_{\text{cir}}$. Indeed, in a biaxial extension context, we use the stretch as a direction diagonal component of the deformation gradient $\mathbf{F}$, where $\lambda_1 = \mathbf{F}(1,1) = F_{11}$ represents the axial direction, and $\lambda_2 = \mathbf{F}(2,2) = F_{22}$ represents the circumferential direction. We assume that the tissue is perfectly incompressible, i.e., $I_3 = \lambda_1^2\lambda_2^2\lambda_3^2 = 1$, leading to $\mathbf{F} = \text{diag}\{\lambda_1, \lambda_2, (\lambda_1\lambda_2)^{-1}\}$. We can then rewrite equations 2 as

$$\begin{aligned} I_1 &= \lambda_1^2 + \lambda_2^2 + (\lambda_1\lambda_2)^{-2},\\ I_2 &= \lambda_1^{-2} + \lambda_2^{-2} + (\lambda_1\lambda_2)^{2},\\ I_4 &= \lambda_1^2\cos^2\alpha + \lambda_2^2\sin^2\alpha,\\ I_5 &= \lambda_1^4\cos^2\alpha + \lambda_2^4\sin^2\alpha,\end{aligned} \tag{10}$$

and their derivatives using equations (7) as

$$\begin{aligned} \frac{\partial I_1}{\partial \mathbf{F}} &= 2\ \text{diag}\{\lambda_1, \lambda_2, (\lambda_1\lambda_2)^{-1}\},\\ \frac{\partial I_2}{\partial \mathbf{F}} &= 2\ \text{diag}\,\{\lambda_1\lambda_2^2 + \lambda_1^{-1}\lambda_2^{-2}, \lambda_1^2\lambda_2\\ &\quad + \lambda_1^{-2}\lambda_2^{-1}, \lambda_1\lambda_2^{-1} + \lambda_1^{-1}\lambda_2\},\\ \frac{\partial I_4}{\partial \mathbf{F}} &= 2\ \text{diag}\{\lambda_1\cos^2\alpha, \lambda_2\sin^2\alpha, 0\},\\ \frac{\partial I_5}{\partial \mathbf{F}} &= 2\ \text{diag}\{\lambda_1^3\cos^2\alpha, \lambda_2^3\sin^2\alpha, 0\}.\end{aligned} \tag{11}$$

We can now insert equations (10) and (11) into the general invariant-based definition of the engineering stress (6). By assuming a zero engineering stress condition throughout the thickness, we can additionally say that $P_{33} = 0$ or $\mathbf{P} = \text{diag}\{P_{11}, P_{22}, 0\}$. The latter defines the boundary condition for the incompressibility requirement and leads to the following expression for the hydrostatic pressure term p:

$$p = 2\frac{1}{\lambda_1^2\lambda_2^2}\frac{\partial\psi}{\partial I_1} + 2\left(\frac{1}{\lambda_1^2} + \frac{1}{\lambda_2^2}\right)\frac{\partial\psi}{\partial I_2}. \tag{12}$$

Altogether, we can explicitly provide an analytical expression for the engineering stresses P_{11} and P_{22}, in terms of the applied biaxial stretches λ_1 and λ_2, the stretches in the axial and circumferential directions,

$$\begin{aligned} P_{11} &= 2\left(\lambda_1 - \frac{1}{\lambda_1^3\lambda_2^2}\right)\frac{\partial\psi}{\partial I_1} + 2\left(\lambda_1\lambda_2^2 - \frac{1}{\lambda_1^3}\right)\frac{\partial\psi}{\partial I_2}\\ &\quad + 4\lambda_1\cos^2(\alpha)\frac{\partial\psi}{\partial I_4} + 8\lambda_1^3\cos^2(\alpha)\frac{\partial\psi}{\partial I_5},\\ P_{22} &= 2\left(\lambda_2 - \frac{1}{\lambda_2^3\lambda_1^2}\right)\frac{\partial\psi}{\partial I_1} + 2\left(\lambda_1^2\lambda_2 - \frac{1}{\lambda_2^3}\right)\frac{\partial\psi}{\partial I_2}\\ &\quad + 4\lambda_2\sin^2(\alpha)\frac{\partial\psi}{\partial I_4} + 8\lambda_2^3\sin^2(\alpha)\frac{\partial\psi}{\partial I_5}.\end{aligned} \tag{13}$$

Note that we assume that the biaxial pulmonary tissue samples are mounted consistently and

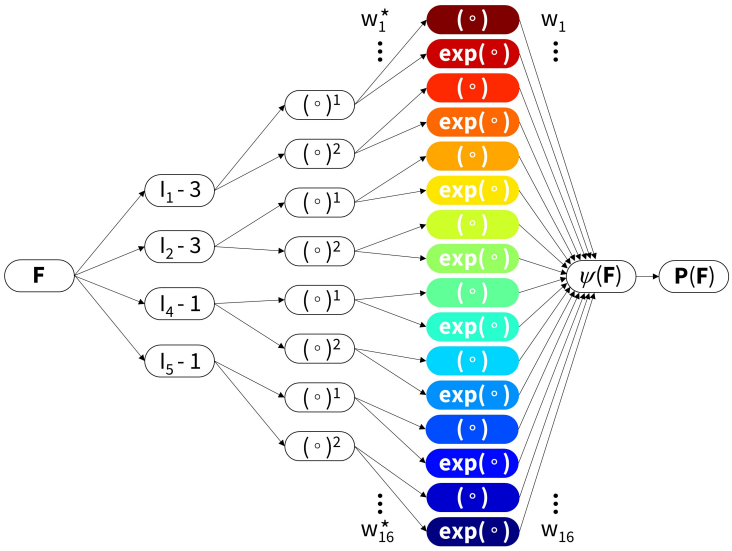

Fig. 3 Constitutive Artificial Neural Network. Transversely isotropic, perfectly incompressible, constitutive artificial neural network with two hidden layers for approximating the free energy function $\psi(I_1, I_2, I_4, I_5)$ as a function of the invariants of the deformation gradient $\mathbf{F}$ using sixteen terms. The first layer generates powers $(\circ)$ and $(\circ)^2$ of the network input and the second layer applies the identity $(\circ)$ and exponential functions $(\exp(\circ))$ to these powers. Adopted from (Linka et al, 2023). The chosen color code for the invariants in their specific forms will be respected throughout the continuation of the paper.

have two symmetrical collagen fiber families with respect to the axial and circumferential directions, both with identical properties. Therefore, we can combine their effects in the fourth- and fifth-invariants I_4 and I_5, and we multiplied their contribution in equations (13) by a factor of two.

2.4 Model discovery

We now explore the training of our constitutive artificial neural network in Fig. 3 using different learning schemes. In particular, we will consider single or multiple samples in the loss function, with or without L1 lasso regularization. Moreover, we will compare fixing or fitting the fiber angle α, influencing the contribution of the anisotropic terms I_4 and I_5. We will consistently train all networks for 8,000 epochs, with a batch size of 32. We allow for early stopping within 2,000 epochs of no accuracy change. The robust adaptive Adam algorithm is used for first-order optimization. The Glorot normal initializer is used for the identity functions, and an unseeded random uniform initialization is used for the exponential functions, with a minimum and maximum weight value of 0.0001 and 0.1 respectively. Finally, we assess the results in terms of the individual R^2 values in the axial and circumferential directions, for each applied ratio.

2.4.1 Sample-specific model discovery

With our set of weights $\boldsymbol{w} = \{w_1^*, ..., w_{12}^*, w_1, ..., w_{12}\}$ from equation (9), we perform a gradient descent learning on a weighted least-squared error loss function L, penalizing the error between the discovered model $\mathbf{P}(\mathbf{F}_i, \boldsymbol{w})$ and the data $\hat{\mathbf{P}}_i$:

$$L(\boldsymbol{w}; \mathbf{F}) = \frac{1}{n_{\text{data}}} \sum_{i=1}^{n_{\text{data}}} \left\| \frac{\mathbf{P}(\mathbf{F}_i, \boldsymbol{w}) - \hat{\mathbf{P}}_i}{P^{\max}_{\text{dir,rat}}} \right\|^2 + \alpha_{\text{reg}} \sum_{i=1}^{16} (|w_i^*| + |w_i|) \rightarrow \min_{\boldsymbol{w}}, \tag{14}$$

where n_{data} is the total number of data points of a specific sample, considering the three axial-vs-circumferential experimental loading ratios, $\text{rat} = \{2:1,\ 1:1,\ 1:2\}$ and the two axial and circumferential loading directions, $\text{dir} = \{\text{ax}, \text{circ}\}$. For our sample-specific neural networks, the number of discrete data points n_{data} thus corresponds to the single sample experimental results of Fig. 2, i.e., the preconditioned axial and circumferential curves of the last loading cycle for each of the three loading ratios. To account for all experiments equally, we weight the error with the maximum

engineering stress per ratio and per direction, $P^{\max}_{\text{smp,rat}}$.

We enforce the weights to always remain non-negative, $\boldsymbol{w} \geq 0$. L1 regularization, or lasso regularization, enables extra feature selection and induces sparsity by reducing some weights exactly to zero, which effectively reduces model complexity and improves interpretability (McCulloch et al, 2024). Here, we set the parameter α_{reg} to 0.01 when L1 regularization is activated.

2.4.2 Cross-sample feature selection

To include all $n = 8$ samples during training, we adapt the loss function as follows,

$$L(\boldsymbol{w}; \mathbf{F}) = \sum_{i=1}^{n_{\text{smp}}} \frac{1}{n_{\text{data}}} \sum_{i=1}^{n_{\text{data}}} \left\| \frac{\mathbf{P}(\mathbf{F}_i, \boldsymbol{w}) - \hat{\mathbf{P}}_i}{P^{\max}_{\text{smp,rat,dir}}} \right\|^2 + \alpha_{\text{reg}} \sum_{i=1}^{16} (|w_i^*| + |w_i|) \rightarrow \min_{\boldsymbol{w}}, \tag{15}$$

where we extend the loss function with n_{smp} to account for different samples, from different biaxial datasets. Instead of the extra summation, we could alternatively also use n_{all} instead of n_{data} equation (14), with n_{all} now equal to the total number of data points of all samples combined, for all ratios and in each direction. Note that we additionally calculate the maximum engineering stress $P^{\max}_{\text{smp,rat,dir}}$ for each sample, still per ratio and per direction. This updated loss function (15) allows us to discover a unique model or set of invariant features, while we can still fit sample-specific weights in a second iteration. Through cross-sample feature selection regularization, this one-size-fits-all approach can therefore find a universal constitutive behavior. We set the parameter α_{reg} to 0.001 when L1 regularization is activated.

2.4.3 Reduced model discovery

After training the networks by minimizing the loss functions (14) and (15), we reduce the complete strain energy density function of equation (9) to a select group of constitutive features, or, in other words, number of terms. Interestingly, we uniformly discover a two-term model for main pulmonary artery tissue with an isotropic exponential first-invariant term, $(\exp([I_1 - 3] - 1))$, and an anisotropic quadratic fifth-invariant anisotropic term, $([I_5 - 1]^2)$. By constraining all other weights to zero during training, we can use our constitutive neural network to perform a parameter identification for the following reduced strain energy density function,

$$\psi^{\text{red}} = w_2 \exp(w_2^*[I_1 - 3] - 1) + w_{15}^* w_{15} [I_5 - 1]^2. \tag{16}$$

Per sample, we now fit two distinct sets of weights, w_2^* and w_2 for the isotropic term, $\exp([I_1 - 3] - 1)$, and w_{15}^* and w_{15} for the anisotropic term, $[I_5 - 1]^2$.

2.4.4 Traditional model fitting

The traditional Holzapfel-Gasser-Ogden model for arterial tissue assumes strain-stiffening fibers embedded in an isotropic matrix (Holzapfel et al, 2000). Considering the invariants, $I_1 = \lambda_1^2 + \lambda_2^2 + (\lambda_1 \lambda_2)^{-2}$ and $I_4 = \lambda_1^2 \cos^2 \alpha + \lambda_2^2 \sin^2 \alpha$, the Holzapfel-Gasser-Ogden model combines the isotropic linear neo-Hookean term of the first-invariant $[I_1 - 3]$ with an anisotropic quadratic exponential term of the fourth-invariant $\exp([I_4 - 1]^2)$. The specific Holzapfel-Gasser-Ogden strain energy density function is then equal to

$$\psi^{\text{hgo}} = \frac{c_1}{2}[I_1 - 3] + \frac{k_1}{2k_2} \left(\exp(k_2 [I_4 - 1]^2) - 1 \right), \tag{17}$$

with the shear modulus c_1, the stiffness-like parameter $k_1 > 0$ and the non-dimensional coefficient $k_2 > 0$. The last parameter highlights the exponential stiffening of the collagen fibers. Again, these three material parameters are enriched by the structural fiber angle parameter α in the fourth-invariant term. From our constitutive artificial neural network and the generalized equation (9), we derive and learn the exact same material model with all other weights set to zero,

$$\psi^{\text{hgo}} = w_1^* w_1 [I_1 - 3] + w_{12} \left(\exp(w_{12}^* [I_4 - 1]^2) - 1 \right). \tag{18}$$

The learned weights of this model then relate one-to-one to the material parameters of the original Holzapfel-Gasser-Ogden model, equation (17) with $c_1 = 2\, w_1^*\, w_1$ and $k_1 = 2\, w_{12}^*\, w_{12}$ and $k_2 = w_{12}^*$.

2.4.5 Fiber angle direction

We initialize the main collagen fiber angle to a certain direction in the axial-circumferential plane

and then considered it either as fixed or as fitted during network training. The parameter α is mathematically present in the undeformed collagen fiber vector $\boldsymbol{n}_0 = [\cos\alpha,\ \sin\alpha,\ 0]^T$, and microstructurally visible in Fig. 1. Subsequently, this microstructural information propagates into the neural network through the anisotropic I_4 and I_5 invariants, and appears as $\cos^2(\alpha)$ for the axial direction and $\sin^2(\alpha)$ for the circumferential direction in the engineering stress calculations of equations (13). To initialize the fiber orientation, we rely on previous microstructural analyses for biologically inspired collagen fiber directions (Fata et al, 2013; Rolf-Pissarczyk and Terzano, 2023). Researchers have used multiphoton microscopy and second-harmonic generation imaging on similar main pulmonary arteries to measure probability density functions for the collagen fiber orientation. Although these probability density functions exhibit notable in-plane axial-circumferential spreads, we postulate that the collagen fibers have a predominantly circumferential orientation.

For a fixed fiber direction, we can also vary α stepwise, from a complete axial orientation of $\alpha = 0°$ towards a complete circumferential orientation of $\alpha = 90°$ as $\{0°,\ 10°,\ 20°,\ 30°,\ 40°,\ 45°,\ 50°,\ 60°, 70°,\ 80°,\ 90°\}$. We note that for $\alpha = 45°$, the fiber contributions to the axial and circumferential directions are identical. In a biaxial tensile test, such a scenario would lead to similar force readings in two directions, and as such a material that can be considered to showcase perfectly isotropic behavior. For the fitted fiber direction, we consider the same range of angles as a multi-start initialization or initial guess, but then learn the unknown fiber direction during training.

3 Results and Discussion

In this section, we illustrate the process of model discovery for one representative sample, corresponding to the dataset in Fig. 2. We distinguish four learning variations or categories:

- training with no regularization: $\alpha_{\text{reg}} = 0$, and fitted fiber angle α
- training with L1 regularization: $\alpha_{\text{reg}} > 0$, and fitted fiber angle α
- training with no regularization: $\alpha_{\text{reg}} = 0$, and fixed fiber angle α
- training with L1 regularization: $\alpha_{\text{reg}} > 0$, and fixed fiber angle α

Training the neural networks in this section took about 4 minutes on a standard laptop for a single sample, with one condition of regularization and one initial guess of fiber angle, either fitted or fixed during training. Inspired by microstructural analyses, we plot the results for initial collagen fiber direction $\alpha = 70°$, but subsequently train the network with a fixed or fitted angle (Rolf-Pissarczyk and Terzano, 2023). We do this not only for one sample, but for all $n = 8$ biaxially tested tissues. This corresponds to locations A and B in Fig. 1, originating from the four distinct ovine pulmonary roots. The discovered models and parameters for all $n = 8$ samples are summarized in the Supplementary Materials.

3.1 Sample-specific model discovery

Fig. 4 shows the discovered models and resulting engineering stress contributions of the trained weights for our selected sample, without regularization and with a fitted fiber angle. We discover a model in three terms, $\exp([I_1-3])$ and $\exp([I_5-1])$ and $[I_5 - 1]^2$, with an overall goodness of fit of $R^2 > 0.99$. The resulting fiber angle direction is equal to 49.8° after training. The latter reflects an almost perfectly isotropic behavior, slightly oriented towards the circumferential direction. Even without any regularization, the majority of weights already train to zero. This suggests that the architecture of our neural network in Fig. 3 naturally supports sparse solutions, likely because of its orthogonal activation functions.

When adding regularization to the exact same network through the L1 term ($\alpha_{\text{reg}} = 0.01$), but still allowing the collagen fiber angle to be free and included in the learning process, we observe the results in Fig. 5. In agreement with our intuition, now, even more weights train to zero until, in the extreme case, only a single term, $[I_5 - 1]^2$, remains. This model reduction comes at the price of a major drop in the goodness of fit, $\mathrm{R}^2 < 0.84$. In support of our unregularized solution, the fiber angle remains at $\alpha = 49.0°$, indicating a nearly isotropic behavior with a slight preference towards the circumferential direction. From a biological perspective, a one-term model in terms of only

the fifth-invariant is non-intuitive, especially considering the presence of both isotropic elastin and anisotropic collagen throughout the arterial wall. These observations suggest that, with the chosen regularization parameter α_{reg}, we have likely over-regularized the model discovery.

Fig. 6 shows the results for the same input data, but now with the collagen fiber angle fixed at 70° during training. We observe a good fit with $R^2 > 0.98$, and a clear, more substantial contribution of the isotropic terms and weights. Specifically, we discover the full range of first-invariant terms, $[I_1 - 3]$ and $\exp([I_1 - 3])$ and $[I_1 - 3]^2$ and $\exp([I_1 - 3]^2)$, while the anisotropic terms $[I_5 - 1]$ and $[I_5 - 1]^2$ now only have minor contributions.

We can again regularize the same network using L1 regularization (($\alpha_{\text{reg}} = 0.01$), while fixing the collagen fiber angle α at 70°. Fig. 7 clearly shows the expected reduction in the number of discovered terms. The isotropic exponential term, $\exp([I_1 - 3])$, and the anisotropic quadratic term, $[I_5 - 1]^2$, which emphasizes the circumferential direction, are now more evident. By comparing the regularized network with fixed angle in Fig. 7 with the regularized network with fitted angle in Fig. 5, we can clearly see a major isotropic I_1 presence and a minor circumferential anisotropic I_5 contribution when the fiber angle is fixed. When the angle direction is fitted, the model adapts towards a more isotropic angle, with larger, but microstructurally less relevant I_5 weights.

3.2 Cross-sample feature selection

Following section 2.4.2 on the regularization through cross-sample feature selection, and according to the updated loss function over all samples of equation (15), we train a network with all $n = 8$ samples combined. Naturally, all samples are now taken into account. To reduce uncertainty across the samples, we fix the fiber angle to 70°. Here, our objective is to discover one single model for all data sets. This implies that the magnitude of the weights for the individual samples is of secondary importance. The discovered features, without and with an additional L1 regularization, are as follows:

without regularization

$\exp([I_1 - 3])$ $[I_5 - 1]^2$ $\exp([I_5 - 1]^2)$

with L1 regularization

$[I_1 - 3]$ $\exp([I_1 - 3])$ $[I_5 - 1]^2$

Here, we have lowered the impact of the L1 regularization by reducing the regularization parameter to $\alpha_{\text{reg}} = 0.001$. Notably, we consistently discover an isotropic and an anisotropic term to describe all eight samples combined. Strikingly, out of more than 60,000 models, and without regularization, we discover the exact same constitutive behavior as previous studies for layers of healthy human aortas (Peirlinck et al, 2024b). More specifically, we observe an overlap of the same $\exp([I_1 - 3])$ and $[I_5 - 1]^2$ features, without and with regularization, respectively. Training this enlarged neural network for all $n = 8$ samples takes about 20 minutes per condition of regularization. As part of the network's design, we initially train the weights in a one-size-fits-all approach. This will be useful for representing the entire population of main pulmonary arteries, and will allow us to retrain the weights while constraining the network to the universally discovered feature invariants. The Supplementary Materials additionally present the cross-sample feature selection results for different initial fiber angle directions, both fixed or fitted during training.

3.3 Fiber angle analysis

Considering all individual $n = 8$ samples, we now train the network for a sweep of fixed fiber angles. As such, we can perform an in-depth sensitivity analysis on this collagen fiber angle, sweeping the entire axial-circumferential domain. Fig. 8 shows the results without L1 regularization, highlighting the predominantly discovered isotropic exponential term, $\exp([I_1 - 3])$. Clearly, a higher number of anisotropic terms are discovered when the fiber angle is fixed toward a more circumferential range of the sweep with $\alpha > 45°$. The latter corresponds to the observed increased non-linearity in the circumferential direction of our data. In other words, we observe a naturally occurring sparsity in the anisotropic invariants for the more compliant direction, while training in the stiffer direction picks up the anisotropic invariant terms. Fig. 9 shows the same training workflow across angles but now with L1 regularization applied. When comparing both histograms, we observe a clear sparsification of our regularization through a decrease in the number of discovered terms, along with a shift from isotropic to anisotropic terms. The anisotropic quadratic

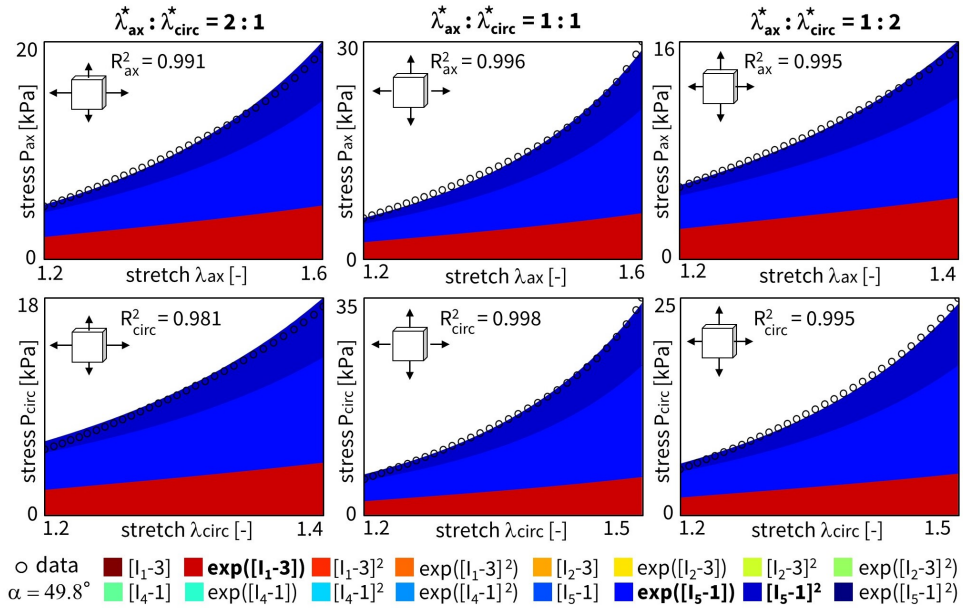

Fig. 4 No regularization - fitted angle. Automated model discovery for a single sample using a full network without regularization ($\alpha_{\text{reg}} = 0.01$). The legend highlights the discovered invariant terms in bold. The collagen fiber angle is *fitted* during training: 49.8°. $R^2_{\text{ax}} = 0.994$ and $R^2_{\text{circ}} = 0.991$.

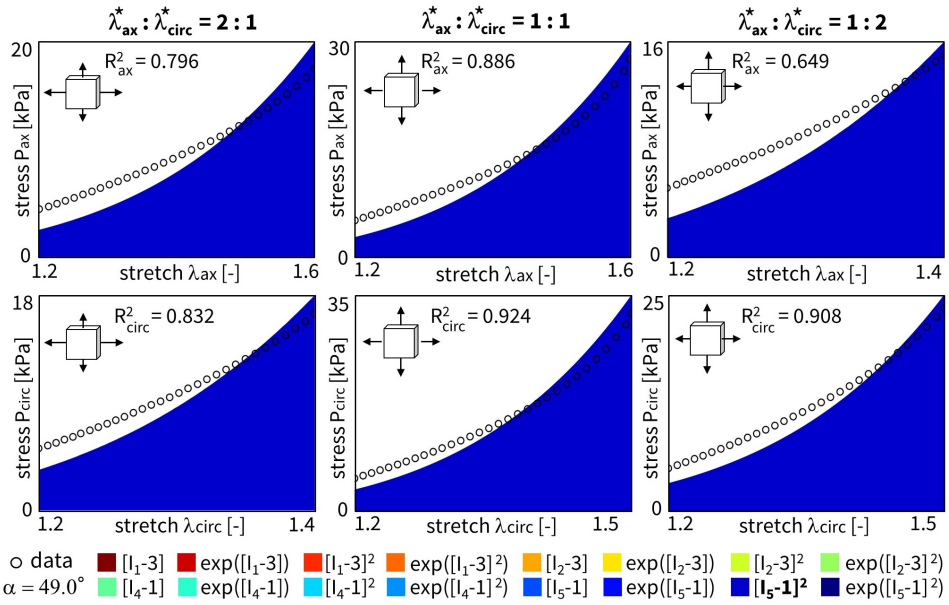

Fig. 5 L1 regularization - fitted angle. Automated model discovery for a single sample using a full network with L1 regularization ($\alpha_{\text{reg}} = 0.01$). The legend highlights the discovered invariant terms in bold. The collagen fiber angle is *fitted* during training: 49.0°. $R^2_{\text{ax}} = 0.777$ and $R^2_{\text{circ}} = 0.888$.

fifth-invariant term, $[I_5 - 1]^2$, becomes the most prevalent now. Again, we see an increased sparsity in the anisotropic terms for the axial range of fiber angles for $\alpha < 45°$. Interestingly, we observe a general shift from the isotropic first-invariant I_1 terms towards the more nonlinear isotropic second-invariant I_2 terms. Recent research has also shown that the second-invariant in the isotropic part of the strain–energy function can enrich the model

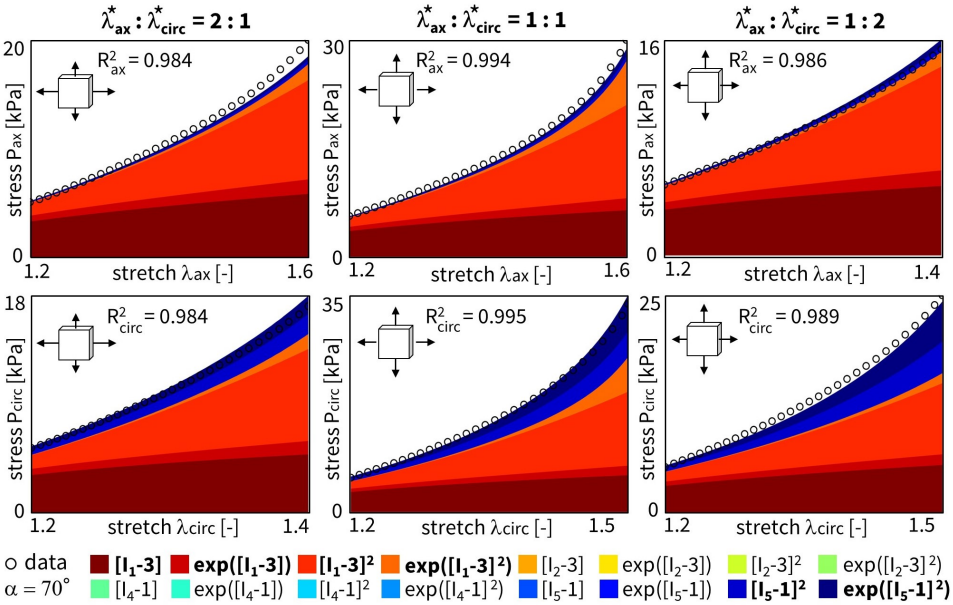

Fig. 6 No regularization - fixed angle. Automated model discovery for a single sample using a full network without regularization ($\alpha_{\text{reg}} = 0$). The legend highlights the discovered invariant terms in bold. The fiber angle is *fixed* towards the circumferential direction at 70° during training. $R^2_{\text{ax}} = 0.988$ and $R^2_{\text{circ}} = 0.989$.

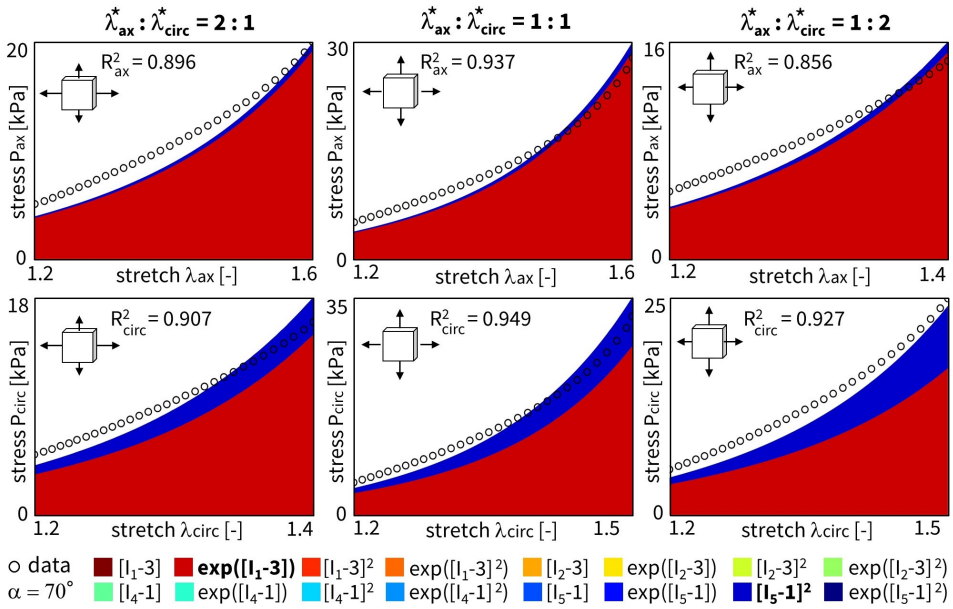

Fig. 7 L1 regularization - fixed angle. Automated model discovery for a single sample using a full network with L1 regularization ($\alpha_{\text{reg}} = 0.01$). The legend highlights the discovered terms in bold. The fiber angle is *fixed* towards the circumferential direction at 70° during training. $R^2_{\text{ax}} = 0.896$ and $R^2_{\text{circ}} = 0.928$.

discovery process (Kuhl and Goriely, 2024). Moreover, this is in agreement with similar neural network methods showing that cardiac tissue is best described by second-invariant models (Martonova et al, 2024).

An interesting constitutive insight when analyzing the range of fiber angles is to consider collagen fiber dispersion, as proposed in the dispersed Gasser-Ogden-Holzapfel model (Gasser et al, 2006):

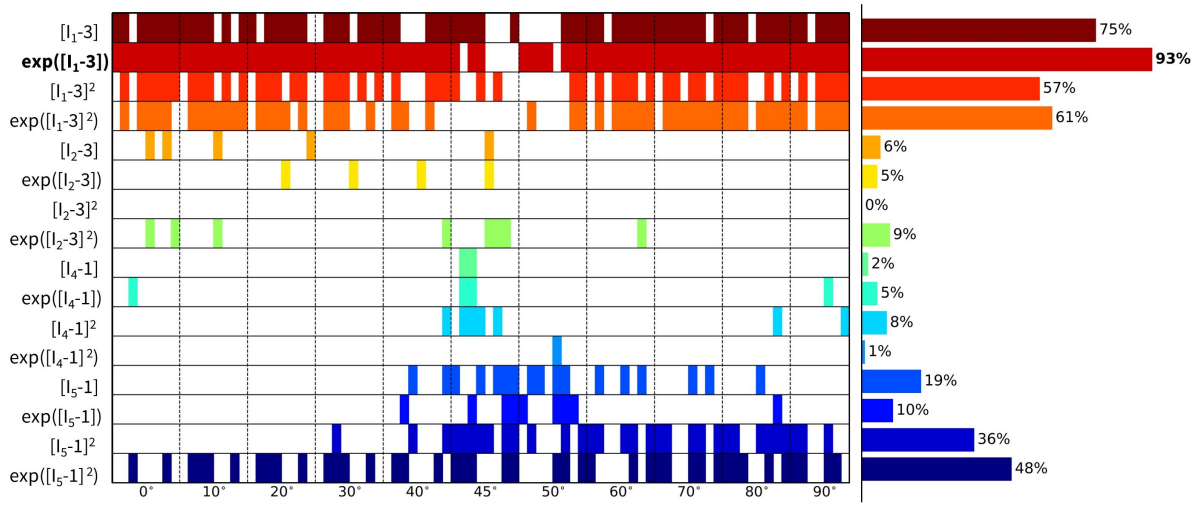

Fig. 8 Fixed fiber angle sweep - no regularization. Sweep of fixed collagen fiber angles, without regularization ($\alpha_{\text{reg}} = 0$). We vary the collagen angle in the following 11 steps: $\{0°, 10°, 20°, 30°, 40°, 45°, 50°, 60°, 70°, 80°, 90°\}$, where 0° represents the axial fiber direction, 45° indicates isotropic fiber behavior, and 90° corresponds to a perfect circumferential fiber direction. A separate network for each of the $n = 8$ samples has been trained in each collagen fiber angle category. The legend highlights the discovered terms and their prevalence across the whole 11 angles x 8 samples = 96 training routines spectrum, predominated by $\exp([I_1 - 3])$.

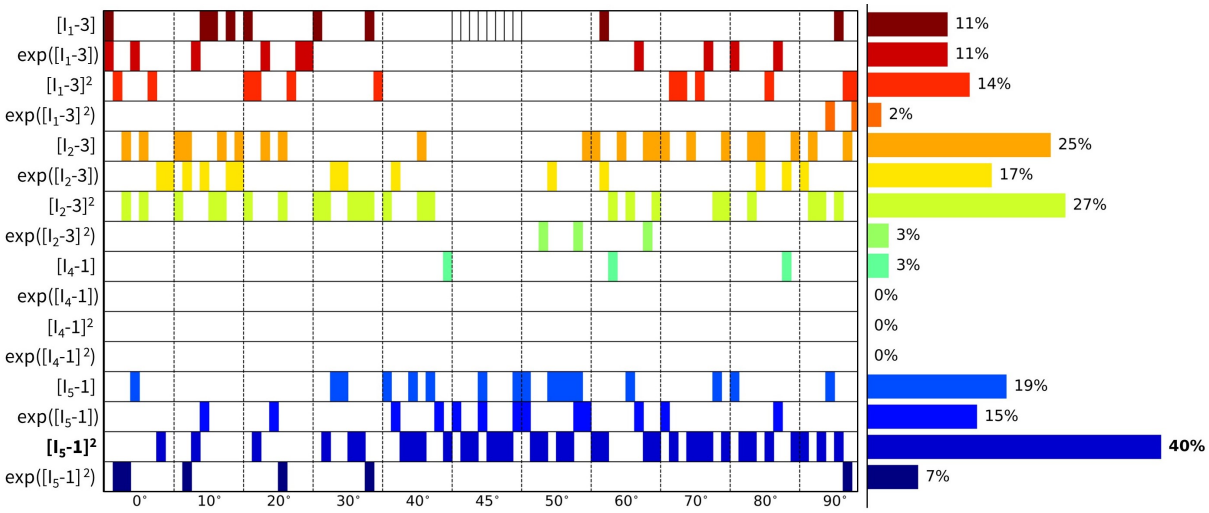

Fig. 9 Fixed fiber angle sweep - L1 regularization. Sweep of fixed collagen fiber angles with L1 regularization-($\alpha_{\text{reg}} = 0.01$). We vary the collagen angle in the following 11 steps: $\{0°, 10°, 20°, 30°, 40°, 45°, 50°, 60°, 70°, 80°, 90°\}$, where 0° represents the axial fiber direction, 45° indicates isotropic fiber behavior, and 90° corresponds to a perfect circumferential fiber direction. A separate network for each of the $n = 8$ samples has been trained in each collagen fiber angle category. The visual classification of the different samples per angle group is indicated in the cell of the first row, middle column. The legend highlights the discovered terms and their prevalence across the whole 11 angles x 8 samples = 96 training routines spectrum, predominated by $[I_5 - 1]^2$.

$$\psi_{\text{disp}}^{\text{goh}} = \frac{c_1}{2}[I_1 - 3] + \frac{k_1}{2k_2}\left(\exp[k_2[I_{1/4}^* - 1]^2] - 1\right), \tag{19}$$

where a mixed isotropic-anisotropic fiber invariant term expands as $I_{1/4}^* = \kappa I_1 + (1 - 3\kappa)I_4$, and the microstructural fiber dispersion parameter κ significantly influences the constitutive equation (Peirlinck et al, 2024a). When $\kappa = 0$, we have $I_{1/4}^* = I_4$, and the model reduces to the traditional Holzapfel-Gasser-Ogden model in equation (18), with no collagen fiber dispersion. When $\kappa = 1/3$, we have $I_{1/4}^* = I_1/3$, and the model reduces to a fully isotropic exponential model. The focus of this work is to discover a selected set of invariants with a clear distinction between isotropic and anisotropic terms, which is why we did not include a phenomenological fiber dispersion parameter κ. Alternatively, we could introduce multiple fiber families, each with different discrete fiber angles α_i. These collagen fiber families could then be incorporated into the constitutive artificial neural networks through multiple invariants $I_{4(ii)}$ and $I_{5(ii)}$ (Peirlinck et al, 2024a). This approach can be implemented in the Holzapfel-Gasser-Ogden model through a fiber-specific term E_i,

$$\psi_{\text{fib}}^{\text{hgo}} = \frac{c_1}{2}[I_1 - 3] + \sum_i \frac{k_1}{2k_2}\left(\exp[k_2[I_{1/4(ii)}^* - 1]^2] - 1\right), \tag{20}$$

either with or without dispersion (Sempertegui and Avril, 2024).

3.4 Reduced model discovery

Considering the results form the cross-sample feature selection and the fiber angle analysis in the previous Sections 3.2 and 3.3, we constrain our total neural network from Fig. 3 or general equation (9) to only two terms, $\exp([I_1 - 3])$ and $[I_5 - 1]^2$, resulting in the reduced equation (16). The trained weights of this novel constitutive model yield a balanced isotropic-anisotropic contribution, and a general goodness of fit of $R_2 > 0.99$, even with only two terms. The corresponding results are shown in Fig. 10. Obviously, network L1 regularization is obsolete here. Training this reduced neural network takes about 90 seconds. Note that the collagen fiber angle fitted in the current reduced model plots. As expected, we observe a slightly circumferential orientation of the fiber angle for the fifth-invariant term, but with no real pronounced anisotropy in the overall model ($\alpha = 50.9°$). Additionally, the mechanical data themselves display a more compliant behavior in the axial direction, with higher stretches after preload correction, and a stiffer behavior in the circumferential direction, with higher experimental forces, all in agreement with the discovered models here, and with previously published experimental data on similar tissue types.

3.5 Traditional model fitting

As a cross-comparison, we constrain our network to the traditional Holzapfel-Gasser-Ogden model of equation (18) with an isotropic linear first-invariant term, $[I_1 - 3]$, and an anisotropic quadratic exponential fourth-invariant term, $\exp([I_4 - 1]^2)$ (Holzapfel et al, 2000). Fig. 11 shows the resulting weights after training, with a fitted collagen fiber angle equal to 49.0°. L1 regularization is not applicable here, and we learn the fiber angle after initialization. Through equation (17), we report the known Holzapfel-Gasser-Ogden model parameters based on the learned weights, $c_1 = 1.95$ kPa and $k_1 = 0.77$ kPa and $k_2 = 0.145$. These parameters fall within expected stiffness ranges, and the fit can be considered fairly good. This is reasonable, as the Holzapfel-Gasser-Ogden model has been widely validated for a broad range of biological tissues. Alternatively, we derive the Holzapfel-Gasser-Ogden variables through a more traditional material parameter fitting approach, with a constitutively predefined optimization problem for non-dispersed fibers, and an objective function that minimizes the error between modeled and experimental engineering stresses (Fehervary et al, 2019). This results in $c_1^{\text{fit}} = 1.7$ kPa and $k_1^{\text{fit}} = 2.6$ kPa and $k_2^{\text{fit}} = 0.342$, and a fitted angle of 48.8° obtained through multi-start initialization. This highlights the overparametrized character of the whole framework, with multiple local minima, already for a two-term constitutive model with three material parameters and one structural parameter. Indeed, the latter traditional fitting approach gives rise to $\text{R}_{\text{ax}}^2 = 0.982$ and $\text{R}_{\text{circ}}^2 = 0.973$.

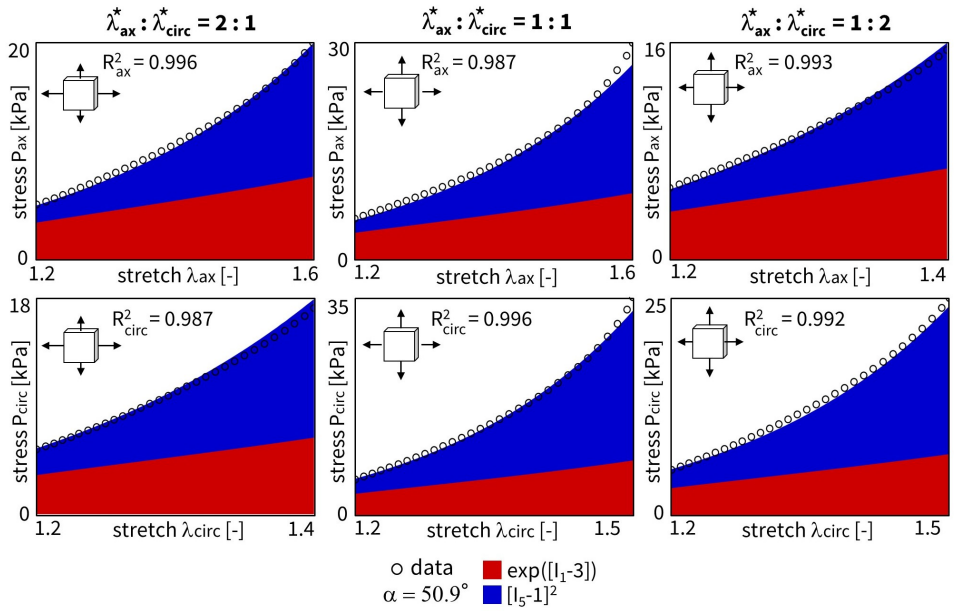

Fig. 10 Reduced constitutive neural network fit. Automated model discovery for a single sample using a reduced neural network. The *fitted* collagen fiber angle is equal to 50.9° after training. $R^2_{ax} = 0.993$ and $R^2_{circ} = 0.992$. The learned weights are $w_{1,2} = 0.185$, $w_{2,2} = 10.45$ kPa, $w_{1,15} = 0.462$, and $w_{2,15} = 0.274$ kPa.

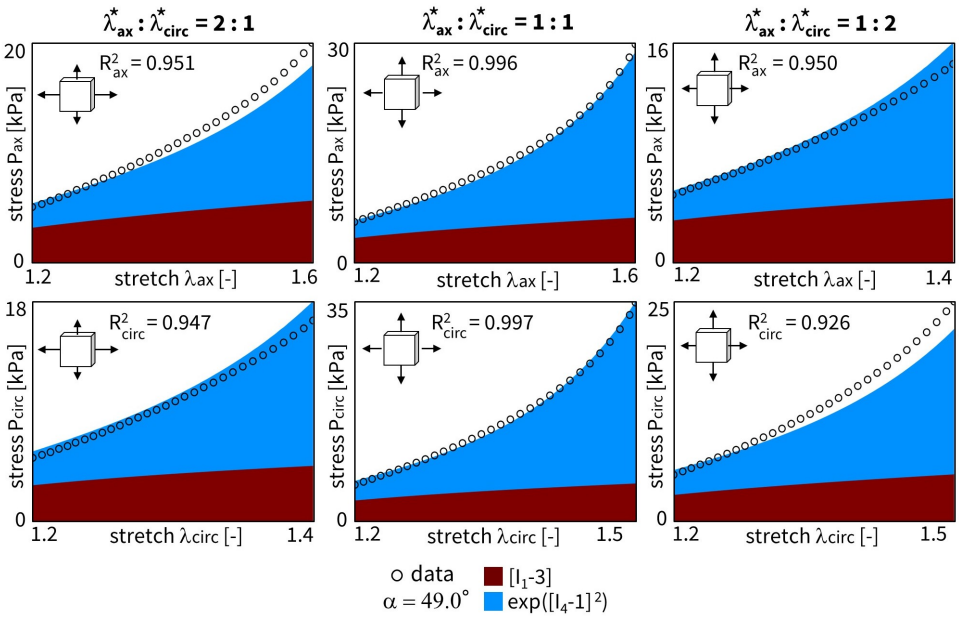

Fig. 11 Traditional Holzapfel-Gasser-Ogden fit. Model discovery for a single sample using the Holzapfel-Gasser-Ogden neural network. The *fitted* collagen fiber angle is equal to 49.0° after training. $R^2_{ax} = 0.965$ and $R^2_{circ} = 0.957$. The learned weights are $w_{1,1} = 0.838$, $w_{2,1} = 2.33$ kPa, $w_{1,12} = 0.413$, and $w_{2,12} = 2.66$ kPa.

Notably, we still observe a drop in R^2 compared to our newly discovered constitutive equation in Fig. 10 and equation (16). Strikingly, we rarely discover the characteristic exponential quadratic fourth-invariant term of the traditional Holzapfel-Gasser-Ogden model when sweeping the collagen fiber angles for all samples, as shown in Fig. 8 and Fig. 9, with a 1% and 0% occurrence without and with L1 regularization, respectively. Instead, the

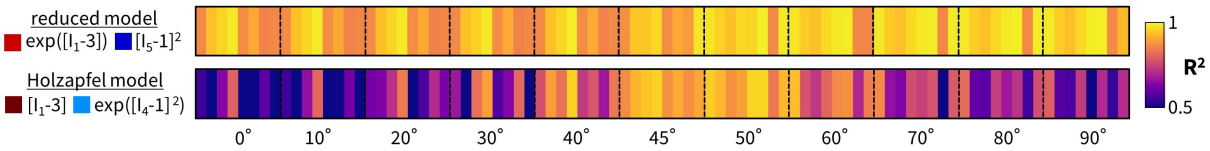

Fig. 12 Fitting accuracy - heat map comparison. Figure compares the reduced constitutive neural network fit with the traditional Holzapfel-Gasser-Ogden fit in terms of total R^2, averaged over the axial and circumferential direction, for all ratios. The restricted neural network was trained for each of the $n = 8$ samples in each imposed fiber angle category. We vary the fixed collagen angle in following steps: $\{0°, 10°, 20°, 30°, 40°, 45°, 50°, 60°, 70°, 80°, 90°\}$, where 0° represents the axial fiber direction, 45° indicates isotropic fiber behavior, and 90° corresponds to a perfect circumferential fiber direction.

anisotropic quadratic fifth-invariant term seems to better minimize the loss function of our network, and is therefore better suited to characterize the generally compliant and highly non-linear constitutive behavior of pulmonary arterial tissue. Accordingly, also an exponential first-invariant term seems to be the preferred learned isotropic part of the strain–energy function, instead of the traditional linear $[I_1 - 3]$.

To further quantify our results, Fig. 12 illustrates the averaged R^2 value for all of the $n = 8$ samples, with individual weights trained for the whole range of fixed collagen fiber angles. Heat map colors compare the fitting accuracy of the reduced model ($\exp([I_1-3])$ and $[I_5-1]^2$) to the Holzapfel-Gasser-Ogden model ($[I_1 - 3]$ and $\exp([I_4 - 1]^2)$). For a fiber angle in the range $45° \leq \alpha \leq 50°$, and fixed in this direction during learning, the traditional model fits the dataset well. However, we see a clear fitting improvement and model generalization for all fiber angles with our newly discovered constitutive equation. By combining an isotropic exponential first-invariant term with an anisotropic quadratic fifth-invariant term, we observe an $R^2 > 0.9$ over the whole collagen fiber spectrum, whereas the traditional model only performs well when the fixed angles are in the same range as the resulting fitted fiber angles (close to isotropy, tending towards the circumferential direction). The exact weights for all angles and for both models are provided in the Supplementary Materials.

Taken together, our invariant-based model discovery approach with more than 60,000 possible model terms, reduced to a select subset of constitutive behaviors, provides crucial insights into the biomechanics of the pulmonary arterial wall, that would be impossible to obtain with a traditional modeling approach.

4 Conclusion and outlook

In this work, we discovered a novel constitutive model for the main pulmonary arteries:

$$\psi = a_1 \left(\exp(a_2[\,I_1 - 3\,]) - 1\right) + b([I_5 - 1]^2),$$

characterized by three material parameters, a_1, a_2 and b, which aligns perfectly with our recently discovered material model for systemic arterial tissues (Peirlinck et al, 2024b). Specifically, we combined biaxial tensile testing of $n = 8$ pulmonary artery samples and automated model discovery using constitutive neural networks. Our constitutive neural network approximates the free energy function ψ using sixteen terms. Its first layer generates powers $(\circ)$ and $(\circ)^2$ of the four network invariants, I_1, I_2, I_4, I_5, while the second layer applies the identity $(\circ)$ and exponential function $(\exp(\circ))$ to these powers. From cross-sample feature selection regularization and an in-depth sensitivity analysis of the collagen fiber direction, we conclude that the constitutive behavior of pulmonary arteries is best characterized by a two-term model in terms of an isotropic exponential first-invariant term and an anisotropic quadratic fifth-invariant term.

Future work could address the uncertainty in the data through recently developed Bayesian constitutive artificial neural networks (Linka et al, 2024). This would alleviate the averaging assumptions of the presented cross-sample feature selection regularization. For example, we could explicitly learn the uncertainty in the fiber direction with a mean collagen fiber angle and a standard deviation that characterizes fiber dispersion, instead of using a purely phenomenological fiber dispersion parameter.

Similar artificial neural networks have recently enabled the robust discovery of anisotropic constitutive models for a wide variety of warp-knitted

fabrics (McCulloch and Kuhl, 2024). By considering different mounting orientations, the authors discovered interpretable anisotropic models that performed well in both training and testing. Such medical textiles, used in cardiovascular applications, can serve as external supports for the Ross procedure to prevent acute dilatation of the transplanted pulmonary tissue in the high-pressure aortic environment (Verbrugghe et al, 2013; Nappi et al, 2020; Vervenne et al, 2023). Many unknowns remain regarding the mechanocompatibility of these textiles and their interaction with the native tissue (Singh et al, 2015; Ramachandra et al, 2020). Textile stiffness should prevent short-term acute dilatation, while textile compliance should restore long-term blood pressure pulsatility. Once again, computational design solutions will critically depend on the models and parameters of the underlying pulmonary autograft tissue.

Our main take-home message is that the constitutive behavior of main pulmonary arteries can be best described by combining an isotropic exponential first-invariant term, $\exp([I_1 - 3])$, and with an anisotropic quadratic fifth-invariant term, $[I_5 - 1]^2$. Critical to discovering this sparse and interpretable model has been cross-sample feature selection and a thorough collagen fiber angle analysis sweep.

Supplementary Materials The source data, code, and results are available in KU Leuven's research data repository: https://doi.org/10.48804/almeep, and on https://github.com/LivingMatterLab/CANN.

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Declarations

Competing interests The authors have no competing financial or non- financial interests to declare that are relevant to the content of this article.

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