Neural operator learning of heterogeneous mechanobiological insults contributing to aortic aneurysms

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Thoracic aortic aneurysm (TAA) is a localized dilatation of the aorta that can lead to life-threatening dissection or rupture. In vivo assessments of TAA progression are largely limited to measurements of aneurysm size and growth rate. There is promise, however, that computational modelling of the evolving biomechanics of the aorta could predict future geometry and properties from initiating mechanobiological insults. We present an integrated framework to train a deep operator network (DeepONet)-based surrogate model to identify TAA contributing factors using synthetic finite-element-based datasets. For training, we employ a constrained mixture model of aortic growth and remodelling to generate maps of local aortic dilatation and distensibility for multiple TAA risk factors. We evaluate the performance of the surrogate model for insult distributions varying from fusiform (analytically defined) to complex (randomly generated). We propose two frameworks, one trained on sparse information and one on full-field greyscale images, to gain insight into a preferred neural operator-based approach. We show that this continuous learning approach can predict the patient-specific insult profile associated with any given dilatation and distensibility map with high accuracy, particularly when based on full-field images. Our findings demonstrate the feasibility of applying DeepONet to support transfer learning of patient-specific inputs to predict TAA progression.

1. Introduction

Thoracic aortic aneurysms (TAAs) are localized dilatations of the aorta that associate with a higher risk of life-threatening aortic dissection or rupture; they can initiate from diverse biomechanical and genetic factors, often developing over several years [1–6]. Treatment of TAAs may involve surgical replacement with a synthetic graft or repair via the placement of an endovascular stent [7,8]. Determination of the optimal approach and time of intervention depends on many factors, including the size, growth rate and location of the aneurysm, and the individual’s genetics [9]. Ultimately, to systematically improve prognosis and therapeutic design, there is a pressing need to understand the complex roles these factors play in the development of aneurysms [10].

Assessment of aortic health in the clinic is largely limited to in vivo anatomical information and haemodynamic measurements, with few biomarkers available. On the other hand, murine models of aortic aneurysm have provided valuable insight into the structural and biomechanical properties of the normal and diseased thoracic aorta via in vitro experimentation of excised tissue specimens [11,12] that complement in vivo studies. Several genetic mutations leading to compromised aortic structure and function have been identified as
critical predisposing factors driving aneurysm formation, including those affecting extracellular matrix integrity, smooth muscle contractile dysfunction, and aberrant intracellular signalling [2,13–16]. Although much has been learned from these studies, multiple contributors often coexist in vivo, rendering it challenging to identify relationships among different mechanisms. Nevertheless, characterization of the biomechanics of the aorta is necessary to gain a deeper knowledge of disease progression. Towards this end, computational models of aneurysm growth and remodelling (G&R) can facilitate mechanistic understanding by isolating the influence of individual biomechanical defects on subsequent progression [17–20]. A theoretical model with an ability to generate robust predictions of aneurysm progression from limited anatomical information can both generate synthetic datasets for analysis and lay the foundation for enriched diagnosis of aortic function beyond clinically available measurements.

Current advancements in modelling now provide the opportunity to leverage machine learning, which has emerged as an effective surrogate model for high-fidelity solvers, in order to overcome previous computational hurdles that would otherwise make such modelling intractable for clinically relevant time frames. Such surrogate models have demonstrated the potential for automated measurement of aortic geometry, patient risk stratification, and prediction of aneurysm growth and rupture [6,21–25]. Additionally, physics-informed neural networks (PINNs) [26–29] have been a promising advancement in the domain of scientific machine learning. However, one often needs to retrain a PINN to simulate multiple initial/boundary problems having different applied loading. Hence, it is critical to develop models that can learn the operator-level mapping between functions (that is, forecasting the physical system under a variety of initial/boundary circumstances) [30,31]. In this case, neural operators can learn nonlinear mappings between function spaces, providing a novel simulation paradigm for real-time prediction of complicated dynamics. A deep operator-based neural network (DeepONet) proposed in [32] is now popular for learning solutions from labelled input–output datasets consisting of varied initial/boundary conditions and different forcing functions. DeepONet is motivated by the Universal Approximation Theorem for Operators, which defines a new and relatively unexplored realm for deep neural network (DNN)-based approaches that map infinite-dimensional functional spaces rather than finite-dimensional vector spaces (functional regression). The computational model consists of two classes of DNNs; one encodes the input function at fixed sensor points (branch net) while the other accounts for the location of the output function (trunk net).

Here, we present an integrated computational platform for predicting contributing factors to TAA by melding a constrained mixture model of TAA enlargement with a DeepONet. Specifically, we use a previously established computationally efficient implementation of our mechanobiologically equilibrated constrained mixture model to describe the long-term evolution of TAAs. We propose two surrogate models to approximate aneurysmal initiating factors: the first framework admits sparse information to be encoded in the branch network, while the second encodes full-field greyscale images taking into account patient-specific characteristics [33]. The accuracy of each approach is evaluated for multiple types of simulated aneurysms arising from multiple contributors investigated in past studies, and several variations of the neural network design are explored to compare the relative performance of different architectures. Our findings demonstrate feasibility of this technique for future analysis of clinical images of the aorta. The key highlights are:

- A novel framework to predict TAA pathology by combining a constrained mixture model for arterial G&R with a DeepONet-based surrogate model.
- Three-dimensional finite-element simulations of TAA progression arising from randomly distributed losses of elastic fibre integrity and dysfunctional mechanosensing.
- The generalizable DeepONet can predict the solution with sufficient accuracy, even when provided with limited information.
- Performance is improved by employing convolutional neural networks (CNNs) rather than fully connected feed-forward neural networks (FNN) with sparse information.
- The preferred network architecture takes as input greyscale images of clinically relevant dilatation and distensibility to predict the insult profile.
- This approach can be extended to patient-specific medical images to provide patient-specific solutions.

2. Methods

To generate synthetic data for training the surrogate model, we employ a previously established constrained mixture model within a finite-element platform [34]. Finite-element simulations incorporating the initial geometry of the aorta, bulk mechanical properties of the vessel wall, and in vivo loading conditions (axial pre-stretch and intraluminal blood pressure), along with a prescribed mechanobiological insult to initiate TAA, allow predictions of local dilatation and distensibility fields (§2.2). These fields are converted into axial–azimuthal maps and randomly categorized into training and testing sets, which enable training of the DeepONet (§2.4) to predict the initial insult profile from a given dataset. Finally, prediction of the spatial distribution and severity of the insult profile is used to predict future TAA growth. The modelling pipeline is summarized in figure 1.

2.1. Constrained mixture model for arterial growth and remodelling

Over the past several years, we have developed a constrained mixture formulation to describe G&R of the aortic wall, which has been used to model the changing composition, structure, and mechanics in both animal and clinical studies [35–38]. We have recently implemented a computationally efficient three-dimensional finite-element framework for modelling the initiation, gradual evolution and long-term growth of TAA within a thick-walled cylindrical vessel segment [34]. In the following, we summarize the pertinent details of the modelling framework; further details can be found in the original papers [38,39].

2.1.1. Modelling framework

We model the arterial wall as a mixture of three primary load-bearing constituents: elastin-dominated matrix $e$, collagen fibre-dominated matrix $c$, and smooth muscle cells $m$, each of which can undergo changes in mass (grow) and microstructure (remodel) in response to biomechanical stimuli. These constituents $a = e, c, m$ are governed by mass density production rates $n^a(\tau)$
at the time of deposition $\tau$, removal (decay) functions $q^a(s, \tau)$, with $s$ denoting the current time, and stored energy density functions $W^a(s, \tau)$ that depend on the constituent-specific deformations relative to their evolving natural configurations $n(\tau)$ and thus describe the mechanical behaviours.

Because the extracellular environment is mechanoregulated by cells within the vessel wall, production and removal rates can be modulated by perturbations from the homeostatic state (i.e. a quasi-equilibrium where production balances removal, denoted by the subscript $o$). Production per unit volume at time $\tau$ is expressed using a potentially evolving nominal rate $m^a_0(\tau) > 0$ that is modulated by deviations in intramural stress $\sigma$ (induced by pressure and axial force) and wall shear stress $\tau_w$ (induced by blood flow) from homeostatic values, namely,

$$m^a(\tau) = m^a_0(\tau) \left( 1 + K^a_\sigma \Delta \sigma(\tau) - K^a_\tau \Delta \tau_w(\tau) \right) = m^a_0(\tau) \gamma^a(\tau), \quad \text{(2.1)}$$

where $K^a_\sigma$ and $K^a_\tau$ are gain-type parameters controlling the sensitivity to stress deviations $\Delta \sigma$ and $\Delta \tau_w$ from set points $\sigma_o$ and $\tau_{wo}$ summarized in the stimulus functions $\gamma^a$. Equation (2.1) is formulated to replicate experimental observations that increased wall stress and increased flow tend to heighten and reduce extracellular matrix production, respectively [17,38]. In this study, we define $\Delta \sigma = (\sigma - \sigma_o)/\sigma_o$ and $\Delta \tau_w = (\tau_w - \tau_{wo})/\tau_{wo}$, where $\sigma$ is one-third the trace of the Cauchy stress tensor, noting that the in-plane (circumferential and axial) components are tensile and more than an order of magnitude greater than the out-of-plane (radial) component that is compressive. It is important to note in this regard that the tissue behaviour is tractility, we assume that the stress depends only on passive forces.

Constituent removal between times $\tau$ and $s$ is modelled by a first-order kinetic decay-type relation,

$$q^a(s, \tau) = \exp \left( - \int_{\tau}^{s} k^a_\sigma \left( 1 + \omega(\Delta \sigma(t))^2 \right) dt \right), \quad \text{(2.2)}$$

where $k^a_\sigma$ is the (potentially evolving) basal removal rate, and $\omega > 0$ is a gain-type parameter for intramural stress capturing sensitivities to deviations in stress from homeostatic values. Note that, while increases in intramural stress can drive increased production, as stated above, they can also stimulate the removal of constituents through activation of matrix-degrading enzymes, as reflected in equation (2.2). With the above definitions, we then express the mass density per unit reference volume of each constituent $\rho^a_0$ by

$$\rho^a_0(s) = \int_{-\infty}^{s} m^a_0(\tau) q^a(s, \tau) d\tau, \quad \text{(2.3)}$$

where $m^a_0 = \text{int}^a$ is the referential (subscript $R$) mass density production rate, with $J = \sum \rho^a_0/\rho$ representing the volume ratio between the reference and current in vivo configurations of the tissue constituents.

We employ a hyperelasticity framework to describe the transient biomechanical properties of the vessel wall, which is modelled as a mixture of nonlinear, nearly incompressible, anisotropic materials. This allows the intramural stress-driven changes in production and removal to be defined in terms of stored energy density relations $W^a(s, \tau)$, which are functions of the multiaxial deformations of each constituent. The Cauchy stress at the tissue (mixture) level $\sigma$ includes passive contributions from each constituent, given by

$$\sigma(s) = -p(s) I + \frac{2}{\rho} \int_{s} F(s) \frac{\partial W^a(s)}{\partial C^a(s)} F^T(s), \quad \text{(2.4)}$$

where $p$ is a Lagrange multiplier that enforces the transient isochoric motions at a fixed G&R state, $I$ is the identity tensor, $F$ is the deformation gradient tensor for the tissue from reference to current configurations, $C = F^T F$ is the right Cauchy–Green tensor, $J = \text{det} F$ and $W_k = \sum W^a_k$ is the total stored energy of the mixture, where the constitutive relations are defined separately for $e, c$ and $m$. Further details are described in electronic supplementary material, appendix A. Note that, because many TAA contributing factors associate with diminished or absent smooth muscle contractility, we assume that the stress depends only on passive properties [40].

### 2.1.2. Mechanobiologically equilibrated constrained mixture model

In cases of TAA, where the characteristic timescale of G&R is frequently shorter than that of the biomechanical stimulus (e.g.
elastic fibre degradation with gradual hypertension), G&R can be assumed to reach a quasi-static mechanobiological equilibrium $\psi > 0$, thus allowing a time-independent approach at which production balances removal and where computation of the heredity integrals is not required. In particular, the stimulus function in equation \((2.1)\) reduces to

$$Y\theta(x_1, x_2, \Delta \eta_{\theta}) = 1,$$  \hspace{1cm} (2.5)

with $\eta$ denoting the evolved homeostatic state. Accordingly, rule-of-mixtures expressions can be used for stored energy ($W_{\text{st}} = \sum \phi_d \phi \eta_{\theta}$, where $\phi_{d\theta}$ are the evolved constituent mass fractions). Similarly, for the Cauchy stresses (equation \((2.4)\)),

$$\sigma_{\theta} = -p_b I + \sum d_{\theta}^\alpha \eta_{\theta}^\alpha,$$  \hspace{1cm} (2.6)

where $d_{\theta}^\alpha$ are the constituent-specific Cauchy stresses, and $p_b$ is the equilibrated Lagrange multiplier for the quasi-static G&R evolution (see electronic supplementary material, appendix A for more details).

2.2. Modelling TAA growth from prescribed mechanobiological insults

Although TAs typically exhibit an irregular diameter, eccentricity and thickness, it remains instructive to consider smoothly varying insult profiles prescribed on an initially straight cylindrical vessel, with in vivo geometry and mechanical properties derived from our previous studies on the mouse aorta (uniform wall thickness $h_x = 40 \mu m$ and luminal radius $r_0 = 647 \mu m$; see electronic supplementary material, appendix A). Here, aneurysms are initiated by prescribing an insult that emulates defects such as a localized breakage in elastic fibres or disruption at cellular integrin binding sites. We adopt a cylindrical coordinate system in the initial homeostatic state $(r_x, \theta_x, z_x)$, and two approaches for insult profile definitions are considered: analytical and randomly generated.

2.2.1. Analytically defined insult profiles

Insult profiles $\theta$ varying in the $z_x, \theta_x$ (axial–azimuthal) plane are defined analytically with the expression \[(34)\]

$$\theta(z_{\theta}, \theta_{\theta}) = \theta_{\Theta} + \left( \frac{\theta_{\Theta} \theta_{\Theta} - \theta_{\Theta} \theta_{\Theta}}{\theta_{\Theta} \theta_{\Theta}} \right) \exp \left( -\frac{z_{\theta} - z_{\Theta} \theta_{\Theta}}{z_{\Theta} \theta_{\Theta}} \right) \times \exp \left( -\frac{\theta_{\Theta} \theta_{\Theta} - \theta_{\Theta} \theta_{\Theta}}{\theta_{\Theta} \theta_{\Theta}} \right),$$  \hspace{1cm} (2.7)

where $z_{\theta} \in [0, l]$, $l$ is the initial axial length (15 mm), $\theta_{\Theta} \in [0, 2\pi]$, $z_{\Theta}$ and $\theta_{\Theta}$ are the axial and circumferential characteristic widths of the insult region, respectively, $v_{\eta}$ and $v_{\theta}$ govern the softness of the boundaries in the axial and circumferential directions, respectively, and $\theta_{\Theta}$ and $\theta_{\Theta}$ are values of the insult at the ends of the cylinder ($z_{\theta} = 0, l$) and the apex ($z_{\theta} = z_{\Theta} \theta_{\Theta}$, $\theta_{\Theta} = \theta_{\Theta}$) of the profile, respectively. The profile is normalized to the interval $[0, 1]$, with 1 indicating the maximum insult degree that varies depending on the insult type and severity. Example insult profiles and their corresponding remodelled vessels are shown in figure 2, and parameter ranges are listed in table 1.

2.2.2. Randomly generated insult profiles

In contrast to the definition above, we also model aneurysms initiated from insult profiles randomly distributed along the vessel wall to validate the DeepONet model against more natural (i.e. irregular) insults. These profiles are initially generated as ‘latent’ (i.e. unobserved) Gaussian random fields (GRFs), then nonlinearly transformed and censored on $[0, 1]$ to match physically meaningful metrics prescribed by the user. On an unbounded space, the latent insult profiles are thus sampled according to

$$\theta^* \sim \mathcal{G}(\mu, \theta_\star),$$  \hspace{1cm} (2.8)

The mean $\mu(z_{\theta}, \theta_{\theta})$ and covariance $\kappa(z_{\theta}, \theta_{\theta}, z_{\theta}', \theta_{\theta}')$ between two points $(z_{\theta}, \theta_{\theta})$ and $(z_{\theta}', \theta_{\theta}')$ can be parametrized to control the overall propensity of insult ($\phi$), the length scale of the insult(s) in the circumferential ($L_\phi$) and axial ($L_\alpha$) directions, and the softness of the boundaries between normal and insult regions (e). To enforce periodicity in the circumferential direction, we define the covariance function as

$$\kappa(z_{\theta}, \theta_{\theta}, z_{\theta}', \theta_{\theta}') = \theta^2 \exp \left( -\frac{1}{2} \left[ \frac{D_\phi(\theta_{\theta}, \theta_{\theta}')}{L_\phi} + \frac{D_{z\theta}(z_{\theta}, z_{\theta}')}{L_\alpha} \right] \right),$$  \hspace{1cm} (2.9)

where $\theta^2$ is the overall variance of the GRF. To satisfy the prescribed insult propensity $\phi$ and boundary softness $\epsilon$, the mean and variance of the GRF are defined as

$$\mu = \frac{1}{2} - \frac{1}{\sqrt{\pi}} \exp \left( -\frac{(1 - 2\phi)^2}{\epsilon^2} \right),$$  \hspace{1cm} (2.10)

and $\theta^2 = \frac{1}{2\sqrt{\pi}} \exp \left( -\frac{2(1 - 2\phi)^2}{\epsilon^2} \right),$

where $\exp(-\cdot)$ denotes the inverse of the error function. Note that we choose $\epsilon$ to be constant herein with respect to $z_x$ and $\theta_x$. The insult propensity $\phi$ corresponds to the fraction of $\theta^*$ values greater than 0.5, while $\epsilon$ corresponds to the slope of the cumulative distribution function (CDF) of $\theta^*$ at $\theta^* = 0.5$ (see electronic supplementary material, appendix B for the derivation of equation \((2.10)\)). In practice, to ensure stability of the finite-element simulations that follow, we constrain $\theta^*$ at the vessel boundaries to be low (e.g. two standard deviations below the mean), such that the censored insult profile values are zero at the boundaries. Note that $\theta^*$ is discretized on the finite-element mesh of the vessel; thus, the nodal values $\theta^*_m$ jointly follow (and can thus be sampled from) a multivariate Gaussian distribution with mean vector $\mu = \mu_1 \Sigma_1$ and covariance matrix $\Sigma$, where $\Sigma_{ij} = \Sigma_{ii} = \kappa(z_{\theta}, \theta_{\theta}, z_{\theta}', \theta_{\theta}')$. Partitioning the mesh into the set of interior nodes $n$ and the set of boundary nodes $b$, it is straightforward to condition the distribution of $\theta^*_m$ on the enforced value of $\theta^*_m$ using

$$\mu_n = \mu_n + \sum_{b_{\theta}} \Sigma_{b_{\theta} n}^{-1} (\theta^*_b - \mu_b) \mu_n = \mu_n + \sum_{b_{\theta}} \Sigma_{b_{\theta} n}^{-1} (\theta^*_b - \mu_b),$$  \hspace{1cm} (2.11)

and $\Sigma_n = 0$, $\Sigma_{b_{\theta}} = 0$, $\theta^*_n = 0$, $\theta^*_b = 0$.

Instead for sampling purposes. After $\theta^*_m$ is sampled from $N(\mu^*, \Sigma^*)$, we perform a CDF/inverse-CDF transformation, so that the overall distribution of $\theta^*$ values in each random instance of $\theta^*$ matches the desired $N(\mu^*, \Sigma^*)$ (see electronic supplementary material, appendix B for more details). Specifically, \[(12)\]

$$\theta^*_m = \Phi^{-1}(F(\theta^*_m); \mu^*, \Sigma^*),$$  \hspace{1cm} (2.12)

where $F$ is the CDF of the generated random field values (approximated via kernel density estimation) and $\Phi^{-1}$ is the inverse CDF (i.e. quantile function) of the normal distribution with mean $\mu$ and variance $\Sigma$. Finally, the insult field values are censored using $\theta = \min(\max(\theta^*_m), 0, 1)$. The randomly generated insult profiles (i.e. loss of elastic fibre integrity or loss of mechanosensing) correspond in turn to random patterns of dilatation along the vessel (figure 3), which are afterward used as input data for the DeepONet model to perform an inverse prediction of the insult profile. In electronic supplementary material, appendix B, we present a
sensitivity analysis to demonstrate how $w$, $\epsilon$, $L_u$, and $L_z$ jointly control the size, shape and appearance of randomly generated insults with high precision.

2.2.3. Insult contributors

In previous work, we performed *in silico* assessments of TAA progression resulting from five types of mechanobiological insults: loss of elastic fibre integrity, disrupted collagen cross-linking, compromised tissue-level smooth muscle contractility, and dysfunctional mechanosensing and mechanoregulation of matrix [34]. For this study, we focus on two contributors that emerge from a common underlying defect in fibrillin-1, as in Marfan syndrome: loss of elastic fibre integrity (analogous to a reduced half-life) and dysfunctional mechanosensing (representing an impaired ability of cells to sense changes in intramural...
stress). That is, compromised fibrillin-1 adversely affects elastic fibre homeostasis, as well as connections between the smooth muscle cells and elastic lamellae; hence, contrasting these two insults is expected to provide a stringent test of our surrogate model. Insult values ranging from mild to severe are simulated for each of these cases (table 1).

**Elastic fibre integrity.** Functional elastin plays a crucial role in the elastic energy storage capability of the aorta (i.e. compliance and resilience), and genetic disorders such as Marfan syndrome associate with loss of elastic fibre integrity from fragmentation or degradation. Regions of the aortic wall with compromised elastin are unable to recoil against distending intraluminal pressure, resulting in an altered mechanical state predisposing to aneurysm [42]. This is modelled with a user-defined reduction in the baseline value of the material parameter $C$, chosen to achieve a loss in mechanical properties consistent with previous biaxial testing of aortas from *Fbn1*−/− mouse models for Marfan syndrome [2,11,14].

**Dysfunctional mechanosensing.** Mechanical homeostasis of the aorta is regulated by intramural cells that sense the local microenvironment, primarily through integrin binding sites. When these cells cannot accurately detect deviations in stress from their homeostatic levels, whether through disruptions in extracellular matrix or impaired actomyosin activity, they tend to drive maladaptations within the aorta [15,43]. This is represented with the parameter $\delta \in [0, 1]$, with 0 indicating perfect mechanosensing, and the modified expression for deviations in intramural stress $\Delta \sigma = ((1 - \delta \sigma - \sigma_0) / \sigma_0)$ [34].

### Table 1. G&R and mechanobiological insult profile parameters for normotensive and hypertensive simulations with analytically defined insults (equation (2.7)).

To avoid boundary effects, $z_{apex} = 7.5$ mm only for $z_{od} = 4.0$ mm. For randomly generated profiles, loss of elastic fibre integrity is varied from 6% to 60%, and dysfunctional mechanosensing ranges from 2.5% to 25% at normotensive conditions.

| parameter                              | variable | value       | value          |
|----------------------------------------|----------|-------------|----------------|
| axial characteristic width (mm)        | $z_{od}$ | 2.0, 3.0, 4.0 | normotensive   |
| circumferential characteristic width (°) | $\theta_{od}$ | 20, 100, 180, 260, 360 | hypertensive (33%) |
| axial placement (mm)                   | $z_{apex}$ | 6.0, 7.5, 9.0 | 4.75%–47.5%   |
| circumferential placement (°)          | $\theta_{apex}$ | 0, 90, 180, 270 |                      |
| loss of elastic fibre integrity        |          | 5.95%–59.5% | 4.75%–47.5%   |
| dysfunctional mechanosensing           |          | 1.84%–18.4% | 1.08%–10.8%   |
| G&R pressure (mmHg) [34]               |          | 105         | 105 → 140     |
| diastolic pressure (mmHg) [41]         |          | 99          | 129           |
| systolic pressure (mmHg) [41]          |          | 121         | 172           |

(1) Initialization: uniform pressurization and pre-stretch of the cylindrical vessel without insult to achieve the initial homeostatic state.
(2) G&R: computation of G&R in response to the gradually applied insult, at fixed pressure.
(3) Hyperelasticity: post-G&R computation of vessel deformation at normotensive diastolic and systolic pressures [41].

For analytically defined TAA cases, all combinations of insult profiles with variations in axial and circumferential location and extent were simulated for five levels of insult severity and for both insult types, yielding a total of 590 simulations at normotensive conditions. For randomly generated TAAs, 10 unique profiles sharing the same shape parameters were used to yield 100 cases.

#### 2.3.2. Superimposed hypertension

Uncontrolled hypertension (elevated blood pressure) is a critical determining factor in TAA growth [4,41]. Thus, each insult type in §2.2.3 is also simulated with superimposed hypertension, modelled by a gradual increase in the intraluminal pressure, concurrent with the prescribed insult. As a modification to the previously described simulation pipeline, hypertension cases are simulated as follows:

(1) Initialization: uniform pressurization and pre-stretch of the cylindrical vessel without insult to achieve the initial homeostatic state.
(2) G&R: computation of G&R in response to the gradually applied insult, concurrent with gradual increases in pressure by 33%.
(3) Hyperelasticity: post-G&R computation of vessel deformation at hypertensive diastolic and systolic pressures [41].

Cases of hypertension highlight how even a mild insult degree with modest dilatation under normotensive conditions can be exacerbated by increased pressure, yielding a maximum dilatation comparable to that produced by a severe insult under normotensive conditions (table 1). Five hundred and ninety additional simulations with hypertensive conditions are simulated for analytically defined profiles. Hypertensive conditions were not considered for randomly generated insults.
2.3.3. Post-processing training and testing data

In the initialization stage, the straight cylindrical vessel with inner radius $r_o$ is uniformly pressurized and pre-stretched according to normotensive in vivo conditions in one load step while maintaining a cylindrical geometry (figure 4a). In the G&R stage, an insult (analytically defined or randomly generated) is gradually applied over 10 subsequent load steps to compute the evolved post-G&R geometry, in which the homeostatic inner radius $r_h$ can be calculated with respect to the updated centreline. The luminal pressure is then adjusted to (c) diastolic and (d) systolic conditions to evaluate the local distension at diastole $A_D$ and systole $A_S$, respectively. (e) The distensibility is then computed with the relation $D = (A_S - A_D)/A_D$. Together, these steps yield the dilatation $A_D$ and distensibility $D$ maps (shown in the flattened $z$-$\theta$ plane). (f) Finally, the maps are converted into non-dimensionalized greyscale intensity maps and contrast enhanced. For illustrative purposes, this procedure is shown for an analytically defined insult (equation (2.7)) under normotensive conditions.

2.4. DeepONet

In this section, we describe the architecture of the surrogate model developed within the framework of DeepONet to predict mechanobiological insult profiles. The conventional unstacked DeepONet architecture consists of two deep neural networks (DNNs): one encodes the input function at fixed sensor points (branch net) while the other accounts for the locations of the output function (trunk net). The branch network input is customizable in a generalized setting and can take the shape of the physical domain, the initial or boundary conditions, constant or variable coefficients, source terms and so on, as long as the input function is discretized at sensor locations $n_{sen}$. For a regularly spaced discretization of the input function, a CNN can be used as the branch net, while for a sparse representation, one may also consider a feed-forward neural network (FNN), or even a recurrent neural network (RNN) for sequential data. A standard practice is to use an FNN in the trunk network to approximately 90% of the total number of datasets are used to train the model, and the remaining are used for validation. The mathematical foundation of DeepONet is provided in the neural network in the form of $z$-$\theta$ maps (figure 4e) as well as non-dimensionalized greyscale images (figure 4f).
The scalar distances $r$ sibility map ($U^s = U^p - U^a$) works under normotensive or hypertensive condition is normotensive or hypertensive. The five branch networks are used to account for the dilatation map at diastole ($U^d$). The DeepONet in this work considers multiple branch networks $2.4.1$. FNN-based architectures

The DeepONet in this work considers multiple branch networks to account for the dilatation map at diastole ($A_D$) and the distensibility map ($D = (A_S - A_D)/A_D$), as well as whether the loading condition is normotensive or hypertensive. The five branch networks $U^i$ for $i = 1, 2, \ldots, 5$ are formulated as FNNs with the following description:

- $U^1$: value of $A_D$ at $n_{sen}$.
- $U^2$: location of the maximum value in $A_D$.
- $U^3$: value of $D$ at $n_{sen}$.
- $U^4$: location of the minimum value in $D$.
- $U^5$: binary network to account for hypertension: normotensive = 0, hypertensive = 1.

We perform two experiments to decide the optimal number of sensors for $U^1$ and $U^5$, detailed below.

**Experiment 2.1.** $n_{sen} = 5 \times 5$ single-spaced sensor locations.

In this experiment, a $5 \times 5$ lattice of points is employed for $U^1$ and $U^5$, centred at the location of maximum dilatation $U^d$ and the location of minimum distensibility $U^s$. The locations of the sensors are selected such that the input data are constrained within a fairly localized neighbourhood around the local extremum, dictated by the spacing of the nodes in the finite-element mesh (in other words, the sensor locations correspond to a uniform $5 \times 5$ grid of adjacent single-spaced nodes). The arrangement of sensor points is shown in figure 5a.

**Experiment 2.2.** $n_{sen} = 9$ double-spaced sensor locations.

In this experiment, only 9 sensor locations are employed for $U^1$ and $U^5$; however, locations are distributed with double the spacing in the axial and azimuthal directions compared with the single-spaced $5 \times 5$ locations, encompassing a neighbourhood roughly four times the size of that in Experiment 2.1. As above, the sensors for $U^d$ and $U^s$ are centred at the locations of maximum dilatation and minimum distensibility, respectively (figure 5b).

The trunk network (FNN) considers the locations of evaluation in a cylindrical coordinate system (i.e. $y = \{y_1, y_2, \ldots, y_6\} = (\theta, z_1), (\theta, z_2), \ldots, (\theta, z_6)$). Incorporating previous knowledge into the architecture of DeepONet often improves the generalization of the output. Here, we replace the $\theta$ component of the trunk net with appropriate basis functions in Cartesian coordinates. Thus, the trunk net input is modified as $y = (\cos \theta, \sin \theta, z_i)$. A schematic of the framework is shown in figure 6.

![Figure 5. Depictions of the sensor locations for §2.4.1 within a representative TAA case (10.1% loss of mechanosensing, $z_{od} = 2$ mm, $\theta_{od} = 20^\circ$, $z_{apex} = 6$ mm, $\theta_{apex} = 270^\circ$).](image)
2.4.2. CNN-based architecture

In this section, we discuss the DeepONet architecture considering greyscale images, converted from the \( \mathcal{A}_2 \) and \( \mathcal{D} \) maps and contrast enhanced, as input functions for the branch network. This approach considers three branch networks with the following descriptions:

- \( U^1 \): greyscale image for \( \mathcal{A}_2 \) using a CNN.
- \( U^2 \): greyscale image for \( \mathcal{D} \) using a CNN.
- \( U^3 \): binary network to account for hypertension using an FNN.

Note that, in contrast to the sparse sensor point arrays, we use full-field images for \( U^1 \) and \( U^2 \), which have a resolution of 21 × 20 pixels. A schematic of the DeepONet implemented with this framework is shown in figure 7. The mathematical foundation of our proposed architectures can be found in [44].

3. Results

3.1. Dilatation and distensibility in TAA

Locally applied insults in elastic fibre integrity and mechanosensing both lead to the development of dilatations, as well as aneurysms (defined as a 1.5-fold increase in normalized diameter from baseline) in cases of severe insults of elastic fibre integrity. In cases with less circumferential involvement of insult (\( \theta_{obs} < 180^\circ \)), the unaffected regions of the vessel help to attenuate dilatation within the insult area. Additionally, each factor is modelled in combination with superimposed hypertension (elevated blood pressure), emphasizing how even a mild insult with modest dilatation in normotensive conditions can be exacerbated by the presence of additional risk factors. In hypertensive cases, the dilatation also increases significantly, including in regions where there is no insult applied.

Overall, increased dilatation associated with mechanobiological insults correlate well with decreases in distensibility. However, there are distinct differences between distensibility maps resulting from loss of elastic fibre integrity and those resulting from dysfunctional mechanosensing. Whereas the location of maximum dilatation and minimum distensibility co-localize in elastic fibre integrity loss, the maximum dilatation in mechanosensing loss occurs on the opposite side of the vessel from the minimum distensibility, although the distensibility also decreases at the location of maximum dilatation. These findings confirm the need to evaluate both metrics for robust training of the DeepONet in all cases, especially in experiments considering multiple types of insults, even when resulting from a common underlying cause (e.g. compromised fibrillin-I).
3.2. Performance of the surrogate models

The effectiveness of the developed surrogate models is demonstrated through several experiments, put forward in this section. To evaluate performance, we compute the $L_2$ relative error of predictions, and we report its mean and standard deviation based on five independent training trials. In all cases presented here, the DeepONet is trained using a combination of Adam [45] and L-BFGS optimizers [46]. The implementation is carried out using the TensorFlow framework [47]. Throughout all examples, we initialize the weights and biases of the DeepONet using Xavier initialization. The experiments carried out in this work are listed in table 2.

The experiments establish the accuracy of the three surrogate models when trained with data generated for analytically defined insult profiles (cases 1–5) and for randomly generated insult profiles (case 6). In figure 8, we present the performance of the three surrogate models for representative analytically defined and randomly generated insults in elastic fibre integrity (cases 1 and 6). For each architecture, we compute an error between the true and predicted insult profiles by normalizing the absolute error by the maximum insult value throughout the $z$–$\theta$ plane. While each DeepONet architecture is able to predict the insult profile within 5% error, the design with $5 \times 5$ sensors tends to exhibit the greatest prediction errors, whereas the design based on greyscale images provides the most accurate prediction. This discrepancy is most clearly observed in figure 8b.

In table 3, we show the relative $L_2$ error of the surrogate model predictions, averaged over the $z$–$\theta$ domain, for the testing dataset compromised of mechanosensing insults under normotensive conditions (case 2). Additionally, we show the total number of trainable (i.e. learnable) parameters.

Table 2. Descriptions of the datasets considered for the experiments performed. Insult profiles include either analytically defined or randomly generated losses of elastic fibre integrity or mechanosensing, and pressure conditions are either normotensive or hypertensive, listed in parentheses. For cases 1 and 2, the training and testing data consist of a single insult type under normotensive conditions; for cases 3–6, the training and testing data consist of multiple insult types and pressure conditions.

| case no. | description |
|----------|-------------|
| case 1   | analytically defined elastic fibre integrity (normotensive) |
| case 2   | analytically defined mechanosensing (normotensive) |
| case 3   | analytically defined elastic fibre integrity or mechanosensing (normotensive) |
| case 4   | analytically defined mechanosensing (normotensive or hypertensive) |
| case 5   | analytically defined elastic fibre integrity or mechanosensing (normotensive or hypertensive) |
| case 6   | randomly generated elastic fibre integrity or mechanosensing (normotensive) |

Figure 7. Schematic of the DeepONet for §2.4.2. Each branch net is a CNN that takes as inputs the greyscale images of dilatation $\Lambda_D$ and distensibility $\mathcal{D}$ (branch nets: $U^1$ and $U^2$, respectively). Blood pressure information is fed to the FNN using a branch net: $U^3$ as normotensive (input = 0) or hypertensive (input = 1). The outputs of the branch and trunk networks are merged into the solution operator $G_\theta$, and minimization of the loss function $\mathcal{L}$ enables estimation of the insult profile.
for each surrogate model, which are the weights and biases of the networks optimized using back-propagation during the training process. In general, the total number of parameters learned during the training process for a CNN is less than that for an FNN. CNNs are very effective in reducing the number of parameters without losing the quality of models, as the learnable filters of the network encode the information to reduce the high-dimensional input data (here, greyscale images) to a lower latent dimension. This is also seen in our results, which show that the network with full-field greyscale images requires the lowest number of parameters while simultaneously achieving the highest predictive accuracy. Finally, we evaluate the performance of the surrogate model trained with greyscale images.

**Figure 8.** Performance of the surrogate models for the prediction of analytically defined and randomly generated insult profiles. Axial–azimuthal views of representative true and predicted (a) analytically defined and (b) randomly generated insult profiles are predicted using 5 × 5 sensors, 9 sensors and full-field greyscale maps. The insult prediction error, normalized by the maximum insult value over the axial–azimuthal domain, is shown for each architecture.

**Table 3.** Relative $L_2$ prediction error and the number of trainable parameters of the three surrogate models for $N = 545$ training data and $N_t = 45$ testing data consisting of compromised mechanosensing under normotensive conditions. The noise is added in the inputs of the testing dataset.

| method              | no. parameters | relative $L_2$ error | +5% noise |
|---------------------|----------------|----------------------|-----------|
| 5 × 5 sensors       | 234 800        | 3.906 ± 0.004%       | 44.27 ± 0.008% |
| 9 sensors           | 230 784        | 2.712 ± 0.007%       | 32.52 ± 0.009% |
| greyscale images    | 141 180        | 2.340 ± 0.010%       | 8.2 ± 0.020%  |
images on a noisy dataset that consists of the original testing dataset with 5% added uncorrelated Gaussian noise. Overall, among the surrogate models considered in this case, the CNN-based design again demonstrates improved computational efficiency, prediction accuracy and robustness against noise.

In table 4, we report the relative $L_2$ errors of the three model predictions, along with the robustness of each model to 5% added uncorrelated Gaussian noise. Error plots for three representative test cases are shown in figure 9. Columns 1 and 2 show the three-dimensional geometry and the unfolded axial–azimuthal view of the aorta, respectively, coloured by the insult profile (ground truth). Columns 3–5 depict the prediction error of Experiment 2.1 (using $5 \times 5$ sensors), Experiment 2.2 (using 9 sensors) and using greyscale images to train the network, respectively. Error is normalized with respect to the maximum insult value of each case. These findings further reinforce the improvements of the CNN-based approach in a variety of testing scenarios varying by insult type, pressure conditions and insult profile generation method.

### 4. Discussion

#### 4.1. Insult profile prediction with sensor point- and image-based approaches

This study uses a constrained mixture model for arterial G&R integrated with a DeepONet to predict factors contributing to TAA. The main challenge in applying deep learning-based frameworks to predict TAA enlargement is the limited availability of critical information, both in terms of number of

### Table 4. Relative $L_2$ prediction error of the three surrogate models with $N_t$ training data and $N_r$ testing data for the cases listed in table 2. The noise is added in the greyscale full-field image inputs of the testing dataset.

| case no. | $N_t$ | $N_r$ | $5 \times 5$ sensors | 9 sensors | greyscale images | $+5\%$ noise |
|----------|-------|-------|-----------------------|----------|----------------|--------------|
| case 1   | 545   | 45    | 4.79 ± 0.008%         | 4.29 ± 0.008% | 3.458 ± 0.011% | 7.80 ± 0.03% |
| case 2   | 545   | 45    | 3.91 ± 0.004%         | 2.71 ± 0.007% | 2.340 ± 0.010% | 8.20 ± 0.020% |
| case 3   | 500   | 90    | 7.10 ± 0.001%         | 6.75 ± 0.003% | 5.948 ± 0.006% | 10.69 ± 0.015% |
| case 4   | 500   | 90    | 2.88 ± 0.005%         | 2.62 ± 0.001% | 2.280 ± 0.005% | 7.30 ± 0.01% |
| case 5   | 720   | 180   | 3.65 ± 0.005%         | 2.65 ± 0.003% | 2.540 ± 0.018% | 7.18 ± 0.012% |
| case 6   | 90    | 10    | 7.74 ± 0.011%         | 7.20 ± 0.020% | 2.292 ± 0.002% | 15.96 ± 0.029% |
samples and information per sample. Additionally, due to the high complexity of the mechanobiology in patient-specific predictions of TAA (e.g. age, hypertension, diabetes, prescribed medications), making accurate predictions with even high-fidelity physical models remains a challenge. To enable accurate predictions, we have proposed and evaluated three frameworks of DeepONet that are distinguished based on the information available for training the network. The results shown in table 4 indicate that the proposed frameworks indeed provide effective predictions for both analytically defined and randomly generated insult profiles. Our observations are summarized as follows:

1. It has been shown that aortic geometry alone is not sufficient to predict TAA progression [22]. Many have thus sought to incorporate additional information such as biomechanical properties and patient-level variables to improve predictive capability. We find that accurate prediction of the insult profile can be achieved with the inclusion of dilatation and distensibility fields generated from measurements of diastolic and systolic phases of the cardiac cycle, similar to the approaches used by other groups [6,24].

2. Predicting insult profiles with information at $5 \times 5$ sensor locations is sufficiently accurate for cases with $\theta_{\text{offset}} < 260^\circ$ and relatively small $z_{\text{offset}}$. However, with a wider $\theta_{\text{offset}}$ and broader $z_{\text{offset}}$, limited information within a single-spaced neighbourhood near the maximum dilatation and minimum distensibility is insufficient; hence, for such cases, the relative error increases. We also observe an expected reduction in accuracy when multiple insult types are considered together in the training and testing datasets.

3. Overcoming the limitations of $5 \times 5$ sensor locations, the double-spaced arrangement of 9 sensors more accurately estimates the insult profile within a wider neighbourhood compared with that of the $5 \times 5$ sensor array. This observation is in line with the reduced prediction errors reported in table 4 (fourth and fifth columns), which depict this improvement in accuracy. This suggests that the range of variation within the network inputs captured by the sensor point domain, rather than the absolute number of sensors, is a greater determining factor in the predictive capability of the network.

4. FNNs have proven to work well with limited information and also to be robust to noisy testing inputs. However, in the case of sparse information, the network fails to generalize well for noisy inputs and reports a relative $L_2$ error of $44.27 \pm 0.008\%$ and $32.52 \pm 0.009\%$ for $5 \times 5$ and 9 sensors, respectively, when tested with 5% Gaussian noise added to the testing inputs of case 2 (compromised mechanosensing) (last column in table 3).

5. The robustness of the different network architectures is evident in cases of randomly generated insult profiles. As seen in the third and the fourth columns of figure 10, networks trained on sparse sensor point information often fail to achieve accurate predictions if there is more than one region of localized dilatation or if the dilatation boundary is irregular. In these cases, we observe that the model with nine double-spaced sensor locations achieves better prediction accuracy than the $5 \times 5$ single-spaced sensor locations.

6. The multiple caveats of the FNN-based frameworks (§2.4.1) motivate the development of a CNN-based framework, which takes as inputs greyscale images of dilatation and distensibility fields to more accurately predict the insult profile. The predictive accuracy of the framework proposed in §2.4.2 is clearly seen in table 4 (sixth column) and figure 9. Additionally, the model is more noise-tolerant than the sparse sensor-based frameworks (last column of table 4).

7. The computational cost of a network is directly related to the number of trainable parameters. Neural networks employ back-propagation algorithms to tune the network parameters, while trying to reflect the best-fit solution to the training data. Therefore, an FNN trained on real-life images is often computationally expensive. The choice of a CNN to train on greyscale images benefits the model in terms of not only predictive accuracy but also computational efficiency, as this framework requires fewer learnable parameters compared with the models employing FNNs (second column of table 3).
4.3. Summary

We have developed a novel framework to predict pathological insults that lead to TAA by integrating a constrained mixture model for arterial G& per with a deep neural network surrogate model. Three-dimensional finite-element simulations of TAA development arising from randomly distributed losses of elastic fibre integrity and dysfunctional mechanosensing provided stringent (related) synthetic training data for the surrogate model, which was yet capable of predicting insult profiles from dilatation and distensibility information. Finally, we demonstrated improved performance using convolutional neural networks in our DeepONet construction. This framework can ultimately be applied to construct patient-specific profiles for aneurysm growth, which will provide critical information to contextualize the predicted mechanobiological insult and forecast the short-term evolution of TAA imaged once in the clinic. Characterization of this progression could play an integral role in determining future patient risk and in designing improved therapeutic interventions.

Data accessibility. All scripts used in this study are openly accessible through https://github.com/somdattagoswami/Operator-Learning-for-aortic-aneurysms. Data and code are available from the authors upon request. Supplementary material is available online [49].

Authors’ contributions. S.G.: conceptualization, data curation, formal analysis, methodology, software, validation, visualization, writing—original draft, writing—review and editing; D.S.L.: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing—original draft, writing—review and editing; B.V.R.: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing—original draft, writing—review and editing; M.L.: methodology, software, writing, review— and editing; J.D.H.: conceptualization, funding acquisition, investigation, project administration, resources, supervision, writing—original draft, writing—review and editing; G.E.K.: conceptualization, funding acquisition, project administration, resources, supervision, writing—original draft, writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. The authors declare no competing interests.

Funding. This work was supported by the National Institutes of Health (grant nos. P01 HL134605 and U01 HL142518).

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