A comparison of hyperelastic constitutive models applicable to brain and fat tissues

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August 20, 2015

Abstract

In some soft biological structures such as brain and fat tissues, strong experimental evidence suggests that the shear modulus increases significantly under increasing compressive strain, but not under tensile strain, while the apparent Young’s elastic modulus increases or remains almost constant when compressive strain increases. These tissues also exhibit a predominantly isotropic, incompressible behaviour. Our aim is to capture these seemingly contradictory mechanical behaviours, both qualitatively and quantitatively, within the framework of finite elasticity, by modelling a soft tissue as a homogeneous, isotropic, incompressible, hyperelastic material and comparing our results with available experimental data. Our analysis reveals that Fung and Gent models, which are typically used to model soft tissues, are inadequate for the modelling of brain or fat under combined stretch and shear, and so are the classical neo-Hookean and Mooney-Rivlin models used for elastomers. However, a sub-class of Ogden hyperelastic models are found to be in excellent agreement with the experiments. Our findings provide explicit models suitable for integration in large-scale finite element computations.

Keywords: constitutive models; elastic moduli; large strain; brain tissue; brain tumours; fat tissue.

1 Introduction

Obtaining reliable constitutive models for the behaviour of tissues under loads is of the utmost importance when studying the response and evolution of organs in physiological and pathological conditions. For instance, the computational analysis of traumatic brain injury due to shocks or blast waves in sports, combats, or accidents relies on large finite element codes based on the constitutive properties of brain tissues. Similarly, an understanding of how brain tumours change the mechanical and neurological environment during growth depend on the mechanical responses of both healthy tissue and tumours [8]. The response of adipose tissue to external loads is also a growing area of interest in clinical research, for example in treating patients with impaired mobility and in pharmaceutical industry, particularly for the design of needle-free drug-delivery systems [7].

Recent experimental evidence [14,22,28] shows that soft biological tissues such as brain, gliomas, liver, and fat have some unusual mechanical properties under loads, namely:

(i) The shear modulus increases sharply as compression in the direction orthogonal to the shear direction increases;

(ii) The shear modulus remains almost constant or may decrease as tension in the direction orthogonal to the shear direction increases;

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The elastic modulus increases or remains almost constant when compression increases.

In particular, the shear modulus of normal brain can be increased nearly four times by compressive stresses. In addition, although at low strains, glioma brain tumours have similar elastic moduli as normal brain tissue (unlike other tumour types arising in breast tissue, for example [21]), at large strains, glioma tissue stiffens more strongly under compression than normal brain. However, while the shear modulus increases significantly when axial strain increases, the elastic modulus increases only slightly or not at all under increasing axial strain. During experimental tests, tissue samples exhibited a predominantly isotropic behaviour and their volume was reported to remain virtually constant.

![Figure 1: Graphical illustration of (a) brain and (b) fat tissues.](image)

Our aim is to capture these seemingly contradictory mechanical behaviours, both qualitatively (theoretically) and quantitatively (numerically), within the framework of finite elasticity, by modelling a soft tissue as a homogeneous, isotropic, incompressible, hyperelastic material. First we demonstrate analytically that, in large strain deformations, conditions (i)-(iii) can be satisfied simultaneously by Mooney-Rivlin models, but not by the neo-Hookean, Fung, and Gent models. The neo-Hookean model can be derived from first principles and is suitable for materials with entropic elasticity and a Gaussian distribution of chains with quadratic strain energy. While the neo-Hookean model can be seen as a general second-order approximation of a strain-energy density, the Mooney-Rivlin model for incompressible system is its third-order approximation and is known to be better suited than the neo-Hookean model to describe shear deformations in elastomers [4,9]. Fung model was developed initially to capture the response of tissues with a high content of collagen fibres, such as skin and arterial walls [3,29]. This model exhibits a typical dramatic strain-stiffening response in uniaxial loading characterising the extension of stiff crimped collagen fibres. The Gent model further penalises this extension by limiting the strain to a finite value, similar to worm-like chain models used in polymer physics [12]. As such, both Gent and Fung models are suitable for tissues which derive their elasticity from a mixture of a soft elastic matrix and stiff fibres. However, aggregate of cells found in brain and in fat tissues are approximately equiaxed in structure with a large lipid content, and this accounts for their almost isotropic, incompressible properties, which likely originate from their cellular structure rather than fibres [1,13,22,25,26] (Figure 1 and Supplemental Figure 1).

In this study, we provide a set of model examples for which we compare the values of the shear modulus under increasing compression or tension with experimental data for brain and fat tissues. The visco-elasticity of brain and adipose tissues was measured following the protocol described in [22]. The dynamic shear storage modulus $G'$ was measured as a function of time for increasing tensile or compressive strain (from 0% to 40%). Details are given in Appendix A.

A hyperelastic constitutive material has a unique stress-strain relationship, independent of strain rate. However, the stress-strain response for visco-elastic materials changes with strain rate, and a strain-energy density function does not exist for these materials. Nonetheless, for many soft tissues, the shape of the nonlinear stress-strain curve is typically invariant with respect to
strain rate. In this case, at fixed strain rate, the shear modulus may be captured by a nonlinear hyperelastic model (an example of this approach for fat tissues can be found in [2]).

The usual practice in constitutive modelling is to fit uniaxial data obtained under controlled compression, and less commonly under tension, with standard material models. This is due to the general experimental (and partly analytical) limitations to carry out proper assessment of stresses and deformations in multiple loading situations. This approach has been particularly successful for tissues that operate mostly under axial loading conditions, such as tendons or ligaments. However, soft tissues such as fat or brain, operate in highly varying and complex loading environment and exhibit responses that cannot be easily modelled by such an approach. The elasticity of these material can be probed by subjecting samples to multiple loadings and, indeed, our study of the shear modulus under combined stretch and shear demonstrates that different constitutive models behave very differently under combined deformation, even though some of them may respond very similarly in axial deformation alone.

From our numerical results, we infer that the shear modulus for the Mooney material is too small compared to the experimental values at similar strains, but appropriate Ogden models are found which are in excellent agreement with the experiments, and thus conditions (i)-(ii) are satisfied by the corresponding shear modulus. The newly identified models are robust and suitable for use in large-scale finite element computations. Furthermore, for the Mooney, Fung, Gent, and Ogden models analysed here, the elastic modulus increases or remains almost constant as compression increases, and therefore condition (iii) is satisfied numerically, whereas for the neo-Hookean material, this modulus decreases under increasing compression.

For the hyperelastic models under consideration, the associated strain energy functions and their ability to satisfy the conditions (i)-(iii), either theoretically or numerically, are summarised in Table 1. The numerical results are shown at a glance in Figures 3-4.

2 Nonlinear Elastic Modulus and Shear Modulus Relations

The homogeneous (affine) deformations analysed here are universal and controllable in the sense that they can be maintained in every homogeneous, incompressible, isotropic, elastic material by application of suitable surface tractions [10, 11, 20, 27, 30]. If the material is described by a strain energy function $W$, the associated Cauchy (true) stress has the Rivlin-Ericksen representation:

$$\sigma = -pI + \beta_1 B + \beta_{-1} B^{-1},$$

where $p$ is the arbitrary hydrostatic pressure, $B$ is the left Cauchy-Green strain tensor with the principal invariants $I_1, I_2, I_3$, and

$$\beta_1 = 2 \frac{\partial W}{\partial I_1}, \quad \beta_{-1} = -2 \frac{\partial W}{\partial I_2},$$

are the material response coefficients. Equivalently, in terms of the principal stretches $\lambda_1, \lambda_2, \lambda_3$:

$$\beta_1 = \lambda_1^3 \frac{\partial W}{\partial \lambda_1} + \lambda_2^3 \frac{\partial W}{\partial \lambda_2}, \quad \beta_{-1} = \lambda_3^3 \frac{\partial W}{\partial \lambda_1} + \lambda_3^3 \frac{\partial W}{\partial \lambda_2}.$$

Henceforth, we assume that these material responses are consistent with the Baker-Ericksen (BE) inequalities stating that the greater principal stress occurs in the direction of the greater principal stretch, and the pressure-compression (PC) inequalities stating that each principal stress is a tension or a compression according as the corresponding principal stretch is an elongation or a contraction [15–17].

2.1 The Elastic Modulus in Finite Tension or Compression

We first consider a unit cube of incompressible hyperelastic material subject to the uniaxial tension or compression in the second direction:

$$x = \frac{1}{\sqrt{a}} X, \quad y = a Y, \quad z = \frac{1}{\sqrt{a}} Z,$$  \hspace{1cm} (2.1)
| Material Model       | Strain Energy Function $W(\lambda_1, \lambda_2, \lambda_3)$ | Conditions (i)-(iii) Satisfied (✓)/ Failed (×) |
|----------------------|---------------------------------------------------------------|--------------------------------------------------|
| neo-Hookean [24]     | $C_2 (\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3)$       | (i)×; (ii) ✓; (iii) ×                            |
|                      | $C$ independent of deformation                              |                                                  |
| Mooney-Rivlin [18]   | $C_1 (\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3) + C_2 (\lambda_1^{-2} + \lambda_2^{-2} + \lambda_3^{-2} - 3)$ | (i) ✓; (ii) ✓; (iii) ✓                          |
|                      | $C_1, C_2$ independent of deformation                       |                                                  |
| Fung [5]             | $\frac{C}{2\alpha}\left[\alpha(\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3) + e^{\alpha(\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3)} - 1\right]$ | (i) ✓; (ii) ×; (iii) ✓                          |
|                      | $C, \alpha$ independent of deformation                     |                                                  |
| Gent [6]             | $-\frac{C}{2\beta}\ln\left[1 - \beta(\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3)\right]$ | (i) ✓; (ii) ×; (iii) ✓                          |
|                      | $C, \beta$ independent of deformation                      |                                                  |
| Ogden $N$ [19]       | $\sum_{p=1}^{N} \frac{C_p}{2m_p}(\lambda_1^{2m_p} + \lambda_2^{2m_p} + \lambda_3^{2m_p} - 3)$ | (i) ✓; (ii) ✓; (iii) ✓                          |
|                      | $C_p, m_p$ independent of deformation                      |                                                  |
where \((x, y, z)\) and \((X, Y, Z)\) are the Cartesian coordinates for the current and the reference configuration, respectively, and \(a > 1\) (tension) or \(0 < a < 1\) (compression) is constant.

For the deformation (2.1), the left Cauchy-Green strain tensor takes the form:

\[
\mathbf{B} = \begin{bmatrix}
\frac{1}{a} & 0 & 0 \\
0 & a^2 & 0 \\
0 & 0 & \frac{1}{a}
\end{bmatrix},
\]

and the non-zero components of the associated Cauchy stress are:

\[
\begin{align*}
\sigma_{xx} &= \sigma_{zz} \\
\sigma_{yy} &= \sigma_{zz} + \left( a^2 - \frac{1}{a} \right) \left( \beta_1 - \frac{\beta_{-1}}{a} \right) \\
\sigma_{zz} &= -p + \frac{\beta_1}{a} + a\beta_{-1}.
\end{align*}
\]

We define the nonlinear elastic modulus in the second direction as the ratio between the Cauchy (true) stress \(\sigma_{yy}\) and the logarithmic (true) strain (the sum of all the small strain increments) \(\ln \frac{B_{yy}}{B_{yy}^{1/2}}\) [20, p. 118]:

\[
E(a) = \frac{\sigma_{yy}}{\ln B_{yy}^{1/2}}. \tag{2.2}
\]

If \(\sigma_{xx} = \sigma_{zz} = 0\), then (2.2) takes the form:

\[
E(a) = \frac{1}{\ln a} \left( a^2 - \frac{1}{a} \right) \left( \beta_1 - \frac{\beta_{-1}}{a} \right), \tag{2.3}
\]

and if \(\sigma_{xx} = \sigma_{zz} \neq 0\), then by the PC inequalities, \(\sigma_{zz} < 0\) when \(1/a < 1\), and \(\sigma_{zz} > 0\) when \(1/a > 1\), hence:

\[
E(a) = \frac{\sigma_{zz}}{\ln a} + \frac{1}{\ln a} \left( a^2 - \frac{1}{a} \right) \left( \beta_1 - \frac{\beta_{-1}}{a} \right) < \frac{1}{\ln a} \left( a^2 - \frac{1}{a} \right) \left( \beta_1 - \frac{\beta_{-1}}{a} \right). \tag{2.4}
\]

### 2.2 The Shear Modulus for Finite Shear Superposed on Axial Stretch

We further examine a unit cube material sample deformed by the combined stretch and shear:

\[
x = \frac{1}{\sqrt{a}} X + kaY, \quad y = aY, \quad z = \frac{1}{\sqrt{a}} Z, \tag{2.5}
\]

where \((x, y, z)\) and \((X, Y, Z)\) are the Cartesian coordinates for the deformed and the reference configuration, respectively, and \(a\) and \(k\) are positive constants representing the axial stretch and the shear parameter, respectively (see Figure 2).

For the deformation (2.5), the left Cauchy-Green strain tensor takes the form:

\[
\mathbf{B} = \begin{bmatrix}
\frac{1}{a} + k^2a^2 & ka^2 & 0 \\
ka^2 & a^2 & 0 \\
0 & 0 & \frac{1}{a}
\end{bmatrix},
\]

and the non-zero components of the associated Cauchy stress are:

\[
\begin{align*}
\sigma_{xx} &= \sigma_{zz} + \beta_1 k^2a^2 \\
\sigma_{yy} &= \sigma_{zz} + \left( a^2 - \frac{1}{a} \right) \left( \beta_1 - \frac{\beta_{-1}}{a} \right) + \beta_{-1}k^2a \\
\sigma_{zz} &= -p + \frac{\beta_1}{a} + a\beta_{-1}, \\
\sigma_{xy} &= ka^2 \left( \beta_1 - \frac{\beta_{-1}}{a} \right).
\end{align*}
\]
For the deformed cube, the shear strain on the inclined faces and the associated shear traction are, respectively:

\[ B_t = \frac{k}{a(1+k^2)}, \quad \sigma_t = \frac{k}{a(1+k^2)} \left( \beta_1 - \frac{\beta_{-1}}{a} \right). \]

We define the **nonlinear shear modulus** as the ratio between the shear traction \( \sigma_t \) and the logarithmic shear strain \( \ln(B_t + 1) \), i.e.:

\[
\mu(k, a) = \frac{\sigma_t}{\ln(B_t + 1)} = \frac{B_t}{\ln(B_t + 1)} \left( \beta_1 - \frac{\beta_{-1}}{a} \right). \tag{2.6}
\]

Then the shear modulus (2.6) is independent of the hydrostatic pressure \(-p\) and is positive if and only if \( \beta_1 - \beta_{-1}/a > 0 \).

When the shear strain is small, the shear modulus (2.6) takes the form:

\[
\mu_0(a) = \lim_{k \to 0} \mu = \beta_1 - \frac{\beta_{-1}}{a}, \tag{2.7}
\]

where:

\[ \beta_1 = \lim_{k \to 0} \beta_1, \quad \beta_{-1} = \lim_{k \to 0} \beta_{-1}. \]

Assuming that \( \sigma_{zz} = 0 \), we also define:

\[ N_0(a) = \lim_{k \to 0} \sigma_{yy} = \left( a^2 - \frac{1}{a} \right) \left( \beta_1 - \frac{1}{a} \beta_{-1} \right), \]

and obtain:

\[
\frac{N_0}{\mu_0} = a^2 - \frac{1}{a}. \tag{2.8}
\]

Therefore, as the axial stretch \( a \) increases, the magnitude of the normal force \( N_0 \) relative to the shear modulus \( \mu_0 \) also increases. This is a **universal relation** [23], which holds independently of the material responses \( \beta_1 \) and \( \beta_{-1} \), and is analogous to **Rivlin’s formula** for a cylinder deformed by combined stretch torsion [30, p. 192]. Then, by (2.3) and (2.8):

\[
\frac{E}{\mu_0} = \frac{1}{\ln a} \left( a^2 - \frac{1}{a} \right), \tag{2.9}
\]

i.e. the ratio between the elastic modulus \( E \) and the shear modulus \( \mu_0 \) is also independent of the material parameters, and \( E/\mu_0 \to 3 \) as \( a \to 1 \).

If \( \sigma_{zz} \neq 0 \), then by the PC inequalities, \( \sigma_{zz} < 0 \) when \( 1/a < 1 \), and \( \sigma_{zz} > 0 \) when \( 1/a > 1 \). In this case:

\[ N_0(a) = \lim_{k \to 0} \sigma_{zz} + \left( a^2 - \frac{1}{a} \right) \left( \beta_1 - \frac{\beta_{-1}}{a} \right), \]
hence
\[ \frac{N_0}{\mu_0} < a^2 - \frac{1}{a} \quad \text{if} \quad a > 1 \quad \text{and} \quad \frac{N_0}{\mu_0} > a^2 - \frac{1}{a} \quad \text{if} \quad a < 1. \]

Then, by (2.4):
\[ \frac{E}{\mu_0} < \frac{1}{\ln a} \left( a^2 - \frac{1}{a} \right). \]

### 2.3 The Behaviour of Nonlinear Hyperelastic Models

For the hyperelastic materials listed in Table 1, we examine the elastic modulus (2.3) and the shear modulus (2.7) as the magnitude of the compressive or tensile strain \( b = \ln a \) increases. In view of the subsequent comparison with experimental data, we restrict our attention to the case when \( b \in (-0.5, 0.5) \).

- For the neo-Hookean model, the shear modulus (2.7) is equal to:
  \[ \mu_0 = C \]
  and is independent of strain. \textit{Hence condition (ii) is satisfied, but not (i).}

  Applying (2.9), the corresponding elastic modulus takes the form:
  \[ E = \frac{C}{b} \left( e^{2b} - e^{-b} \right) \]
  and increases as \( b \in (-0.5, 0) \) increases. \textit{Thus condition (iii) is not satisfied.}

- For the Mooney-Rivlin model, the shear modulus takes the form:
  \[ \mu_0 = C_1 + C_2 e^{-b} \]
  and, if \( C_1 > 0 \) and \( C_2 > 0 \), then this modulus decreases as \( b \) increases. \textit{Hence conditions (i) and (ii) are both valid.}

  By (2.9), the elastic modulus is equal to:
  \[ E = \frac{1}{b} \left( e^{2b} - e^{-b} \right) \left( C_1 + C_2 e^{-b} \right) \]
  and, if \( 0 < C_1 \ll C_2 \), then this modulus decreases as \( b \in (-0.5, 0) \) increases. \textit{Thus condition (iii) is valid as well.}

- For the Fung model:
  \[ \mu_0 = C \left[ 1 + e^{\alpha (e^{2b} + 2e^{-b} - 3)} \right] \]
  and, if \( C > 0 \) and \( \alpha > 0 \), then this modulus decreases as \( b \in (-0.5, 0) \) increases and increases as \( b \in (0, 0.5) \) increases. \textit{Hence condition (i) is satisfied, but not (ii).}

  For this model, by (2.9), the elastic modulus is:
  \[ E = \frac{C}{b} \left( e^{2b} - e^{-b} \right) \left[ 1 + e^{\alpha (e^{2b} + 2e^{-b} - 3)} \right], \]
  and there exists \( b_0 \in (-0.5, 0) \), such that this modulus decreases as \( b \in (-0.5, b_0) \) increases and increases as \( b \in (b_0, 0) \) increases. \textit{Thus condition (iii) is not satisfied.}

- Similarly, for the Gent model:
  \[ \mu_0 = \frac{C}{1 - \beta (e^{2b} + 2e^{-b} - 3)} \]
  and, if \( C > 0 \) and \( \beta > 0 \), then this modulus decreases as \( b \in (-0.5, 0) \) increases and increases as \( b \in (0, 0.5) \) increases. \textit{Hence condition (i) is satisfied, but not (ii).}
By (2.9), the corresponding elastic modulus is:

\[ E = \frac{C \left( e^{2b} - e^{-b} \right)}{b \left[ 1 - \beta \left( e^{2b} + 2e^{-b} - 3 \right) \right]}, \quad (2.13) \]

and there exists \( b_0 \in (-0.5, 0) \), such that this modulus decreases as \( b \in (-0.5, b_0) \) increases and increases as \( b \in (b_0, 0) \) increases. Hence condition (iii) is not satisfied.

- For the Ogden model:

\[ \mu_0 = \frac{1}{\lambda_1^2 - \lambda_2^2} \sum_{p=0}^{N} C_p \left( \tilde{\lambda}_1^{2m_p} - \tilde{\lambda}_2^{2m_p} \right), \]

where:

\[ \tilde{\lambda}_1^2 = \lim_{k \to 0} \lambda_1^2 = \frac{e^{2b} + e^{-b} + \sqrt{(e^{2b} + e^{-b})^2 - 4e^b}}{2}, \quad \tilde{\lambda}_2^2 = \lim_{k \to 0} \lambda_2^2 = \frac{e^b}{\lambda_1^2}. \]

For this model, a general conclusion about the monotonicity of the shear modulus cannot be drawn, and particular cases need to be examined individually. We do this in the following section where hyperelastic models are treated numerically.

### 3 Numerical Results

In this Section, we compare the mechanical performance of the neo-Hookean, Mooney, Fung, Gent, and Ogden materials described above when fitted to available experimental data for the shear modulus of brain and fat tissues. According to the experimental measurements, the shear modulus increases strongly under increasing compression, while in tension, it remains almost constant or decreases slightly at first, then begins to increase, but much less than in compression. In particular, for brain tissue, the shear modulus is essentially constant up to 10% tensile strain, while for lean and obese fat, this modulus appears almost constant up to 30% and 20% tensile strain, respectively. The experimental data for brain and fat tissues are marked by the (red) circles in the plots shown in Figure 3 (a) and Figure 4 (a), respectively.

| Material Model          | Non-Zero Parameter Values |
|-------------------------|---------------------------|
| neo-Hookean             | \( C = 333.28 \)          |
| Mooney-Rivlin           | \( C_1 = 0.28, C_2 = 333 \) |
| Fung                    | \( C = 166.64, \alpha = 2.4974 \) |
| Gent                    | \( C = 333.28, \beta = 0.9918 \) |

The values of the constant parameters for the hyperelastic models fitted to brain and fat data are recorded in Tables 2-3 and Tables 4-5, respectively. For the neo-Hookean, Mooney-Rivlin,
Table 3: The non-zero parameters for Ogden models fitted to shear modulus data for brain tissue at 2% shear superposed on up to 40% compression or tension.

| Material Model | Non-Zero Parameter Values |
|----------------|--------------------------|
| Ogden\textsubscript{3} (brain) | $C_1 = -3543$, $m_1 = 1$, $C_2 = -2723$, $m_2 = -1$ |
| | $C_3 = 654$, $m_3 = 2$ |
| Ogden\textsubscript{4} (brain) | $C_1 = -5877$, $m_1 = 1$, $C_2 = -5043$, $m_2 = -1$ |
| | $C_3 = 1161$, $m_3 = 2$, $C_4 = 501$, $m_4 = -2$ |
| Ogden\textsubscript{5} (brain) | $C_1 = -34399$, $m_1 = 1$, $C_2 = -18718$, $m_2 = -1$, $C_3 = 14509$, $m_3 = 2$ |
| | $C_4 = 2947$, $m_4 = -2$, $C_5 = -2349$, $m_5 = 3$ |
| Ogden\textsubscript{6} (brain) | $C_1 = 1189$, $m_1 = 1$, $C_2 = 16855$, $m_2 = -1$, $C_3 = 1444$, $m_3 = 2$ |
| | $C_4 = -10108$, $m_4 = -2$, $C_5 = -458$, $m_5 = 3$, $C_6 = 1889$, $m_6 = -3$ |
| Ogden\textsubscript{7} (brain) | $C_1 = -187150$, $m_1 = 1$, $C_2 = -91970$, $m_2 = -1$, $C_3 = 109290$, $m_3 = 2$ |
| | $C_4 = 23200$, $m_4 = -2$, $C_5 = -33290$, $m_5 = 3$, $C_6 = -2290$, $m_6 = -3$ |
| | $C_7 = 4100$, $m_7 = 4$ |
| Ogden\textsubscript{8} (brain) | $C_1 = -639530$, $m_1 = 1$, $C_2 = -544840$, $m_2 = -1$, $C_3 = 322660$, $m_3 = 2$ |
| | $C_4 = 237040$, $m_4 = -2$, $C_5 = -88640$, $m_5 = 3$, $C_6 = -57830$, $m_6 = -3$ |
| | $C_7 = 10150$, $m_7 = 4$, $C_8 = 6080$, $m_8 = -4$ |
Table 4: The non-zero parameters for Ogden models fitted to shear modulus data for lean fat tissue at 3.5% shear superposed on up to 40% compression or tension.

| Material Model | Non-Zero Parameter Values |
|----------------|---------------------------|
| Ogden$_3$ (lean) | $C_1 = -3882$, $m_1 = 1$, $C_2 = -2113$, $m_2 = -1$  
 $C_3 = 931$, $m_3 = 2$ |
| Ogden$_4$ (lean) | $C_1 = 2342$, $m_1 = 1$, $C_2 = 4083$, $m_2 = -1$  
 $C_3 = -418$, $m_3 = 2$, $C_4 = -1337$, $m_4 = -2$ |
| Ogden$_5$ (lean) | $C_1 = 10608$, $m_1 = 1$, $C_2 = 8054$, $m_2 = -1$, $C_3 = -4281$, $m_3 = 2$  
 $C_4 = -2048$, $m_4 = -2$, $C_5 = 679$, $m_5 = 3$ |
| Ogden$_6$ (lean) | $C_1 = -25361$, $m_1 = 1$, $C_2 = -27961$, $m_2 = -1$, $C_3 = 8907$, $m_3 = 2$  
 $C_4 = 11175$, $m_4 = -2$, $C_5 = -1227$, $m_5 = 3$, $C_6 = -1914$, $m_6 = -3$ |
| Ogden$_7$ (lean) | $C_1 = -117600$, $m_1 = 1$, $C_2 = -81360$, $m_2 = -1$, $C_3 = 61650$, $m_3 = 2$  
 $C_4 = 27530$, $m_4 = -2$, $C_5 = -17260$, $m_5 = 3$, $C_6 = -3970$, $m_6 = -3$  
 $C_7 = 2000$, $m_7 = 4$ |
| Ogden$_8$ (lean) | $C_1 = -147280$, $m_1 = 1$, $C_2 = -111070$, $m_2 = -1$, $C_3 = 75640$, $m_3 = 2$  
 $C_4 = 41560$, $m_4 = -2$, $C_5 = -20890$, $m_5 = 3$, $C_6 = -7610$, $m_6 = -3$  
 $C_7 = 2390$, $m_7 = 4$, $C_8 = 400$, $m_8 = -4$ |
Table 5: The non-zero parameters for Ogden models fitted to shear modulus data for obese fat tissue at 3.5% shear superposed on up to 40% compression or tension.

| Material Model | Non-Zero Parameter Values |
|----------------|---------------------------|
| Ogden$_3$ (obese) | $C_1 = -12779$, $m_1 = 1$, $C_2 = -6634$, $m_2 = -1$ |
| | $C_3 = 3181$, $m_3 = 2$ |
| Ogden$_4$ (obese) | $C_1 = 6675$, $m_1 = 1$, $C_2 = 12733$, $m_2 = -1$ |
| | $C_3 = -1036$, $m_3 = 2$, $C_4 = -4180$, $m_4 = -2$ |
| Ogden$_5$ (obese) | $C_1 = 17032$, $m_1 = 1$, $C_2 = 17708$, $m_2 = -1$, $C_3 = -5876$, $m_3 = 2$ |
| | $C_4 = -5070$, $m_4 = -2$, $C_5 = 850$, $m_5 = 3$ |
| Ogden$_6$ (obese) | $C_1 = -17287$, $m_1 = 1$, $C_2 = -16654$, $m_2 = -1$, $C_3 = 6706$, $m_3 = 2$ |
| | $C_4 = 7546$, $m_4 = -2$, $C_5 = -968$, $m_5 = 3$, $C_6 = -1826$, $m_6 = -3$ |
| Ogden$_7$ (obese) | $C_1 = -294660$, $m_1 = 1$, $C_2 = -177230$, $m_2 = -1$, $C_3 = 165320$, $m_3 = 2$ |
| | $C_4 = 56730$, $m_4 = -2$, $C_5 = -49180$, $m_5 = 3$, $C_6 = -8000$, $m_6 = -3$ |
| | $C_7 = 6010$, $m_7 = 4$ |
| Ogden$_8$ (obese) | $C_1 = -169310$, $m_1 = 1$, $C_2 = -51570$, $m_2 = -1$, $C_3 = 106260$, $m_3 = 2$ |
| | $C_4 = -2630$, $m_4 = -2$, $C_5 = -33880$, $m_5 = 3$, $C_6 = 7420$, $m_6 = -3$ |
| | $C_7 = 4340$, $m_7 = 4$, $C_8 = -1690$, $m_8 = -4$ |
Figure 3: Brain data and models fit. Left: neo-Hookean, Mooney-Rivlin, Fung, and Gent models. Right: Ogden_4, Ogden_6, Ogden_8 models. (a) Shear modulus $\mu$ compared with experimental data for brain tissue at 2% shear superposed on up to 40% compression or tension; (b) the associated relative errors; and (c) the elastic modulus $E$ normalised to its value at 5% compression.
Figure 4: Fat data and models fit. Left: Lean fat tissue. Right: Obese fat tissue. (a) Shear modulus $\mu$ for Ogden$_4$, Ogden$_6$, Ogden$_8$ models compared with experimental data for fat tissue at 3.5% shear superposed on up to 40% compression or tension; (b) the associated relative errors; and (c) the elastic modulus $E$ normalised to its value at 5% compression.
Fung, and Gent models, all constant parameters were fitted. For the Ogden models, the non-zero coefficients $C_p$ were fitted while the corresponding exponents $m_p$ were fixed. For the Ogden models, the non-zero coefficients $C_p$ were fitted while the corresponding exponents $m_p$ were fixed. The fitting of the material parameters was performed using a nonlinear least squares procedure implemented in Matlab (`lsqnonlin.m`). By this procedure, the following (unconstrained) minimization problem was solved:

$$
\min_{c} \sum_{i=1}^{n} \left[ G(k_i, b_i; c) - \mu_i \right]^2,
$$

where $c = (c_1, c_2, \ldots, c_m)$ are the constant material parameters to be identified, $(b_i, \mu_i)$ are the pairs of data for the compressive or tensile strain and the shear modulus, respectively, and $G(k_i, b_i; c) = \mu(k_i, a_i)$ is the shear modulus defined by (2.6), such that $a_i = e^{b_i}$ is the stretch parameter, and the shear strain is constant and small, viz. 0.02 for brain and 0.035 for fat tissues, so we set $k_i = 0.02a_i$ and $k_i = 0.035a_i$, respectively, for all $i = 1, \cdots, n$.

In order to assess the accuracy with which the models capture the mechanical behaviour measured by the experiments, for each model, the relative error of the shear moduli to the given data was also computed, as follows:

$$
e_i = \frac{|\mu(k_i, a_i) - \mu_i|}{\mu_i}, \quad i = 1, \cdots, n. \quad (3.1)
$$

For the neo-Hookean, Mooney, Fung, and Gent models with constant parameters as indicated in Table 2, the shear moduli at 2% shear combined with up to 40% compression or tension, and their relative errors (3.1) are plotted in Figure 3 (a) and (b), respectively. Since the shear strain is small, the shear modulus $\mu_0$ defined by (2.7) is capable of predicting theoretically the corresponding mechanical behaviour of these models under the combined deformation. For these models, we further compute the elastic modulus $E$ defined by (2.3), and plot its values normalised to those at 5% compression in Figure 3 (c). Numerically:

- For the neo-Hookean material, the computed shear modulus $\mu$ defined by (2.6) is virtually constant, hence condition (ii) is valid, but (i) is not. For this material also, the relative values of the elastic modulus (2.10) plotted in Figure 3 (c) decrease when compression increases, hence condition (iii) is not valid. These results are all in agreement with the theoretical findings for the neo-Hookean model.

- For the Mooney-Rivlin material, the shear modulus $\mu$ increases as compression increases and decreases as tension increases, thus conditions (i) and (ii) are both satisfied. From the relative values of the elastic modulus plotted in Figure 3 (c), we also see that, for this material, the elastic modulus (2.11) increases under increasing compression, i.e. condition (iii) is satisfied as well. These results are again in agreement with the theoretical findings for the Mooney model. Unfortunately, the numerical values of the shear modulus attained by this model are much smaller than those required by the experimental results for brain tissue, as shown by the large relative error estimates, hence Mooney materials, which have proved excellent in describing elastomers and other materials with entropic elasticity, are inadequate for the modelling of this tissue.

- For the Fung and the Gent materials, the respective shear moduli $\mu$ increase as compression increases, i.e. condition (i) is satisfied, but since they also increase almost as fast in tension as in compression, condition (ii) is not satisfied. Moreover, the corresponding relative errors increase rapidly as either compression or tension increases, hence these materials do not capture the required physical behaviour in either of these deformations. For these models also, the monotonicity of the associated elastic modulus (2.12) and (2.13) changes, albeit slowly, so that the computed modulus remains almost constant before it increases as compression increases. Hence condition (iii) is in fact satisfied numerically.

As the neo-Hookean, Mooney, Fung, and Gent models fail to agree with the experimental results for brain tissue under combined stretch and shear, and similar results are shown to hold experimentally for adipose tissue, we illustrate numerically the behaviour of these material models in rapport to the brain data, but take these models no farther when modelling fat tissues.
Table 6: Relative errors of the shear modulus for hyperelastic models fitted to brain data.

| Compression or Tension (%) | neo-Hookean (brain) | Mooney (brain) | Fung (brain) | Gent (brain) |
|----------------------------|---------------------|----------------|--------------|-------------|
| -40.00                     | 80.05               | 70.25          | 60.61        | 50.18       |
| -30.00                     | 78.12               | 70.47          | 68.71        | 53.01       |
| -20.00                     | 69.50               | 62.75          | 64.51        | 51.97       |
| -10.00                     | 54.16               | 49.34          | 52.41        | 32.97       |
| 0.00                       | 1.00                | 1.00           | 1.05         | 0.05        |
| 10.00                      | 14.68               | 3.78           | 19.40        | 6.40        |
| 20.00                      | 36.15               | 11.49          | 62.31        | 7.56        |
| 30.00                      | 62.86               | 20.69          | 155.88       | 3.73        |
| 40.00                      | 123.73              | 50.03          | 474.16       | 51.08       |

Table 7: Relative errors of the shear modulus for Ogden models fitted to brain data.

| Compression or Tension (%) | Ogden3 (brain) | Ogden4 (brain) | Ogden5 (brain) | Ogden6 (brain) | Ogden7 (brain) | Ogden8 (brain) |
|----------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| -40.00                     | 7.03           | 3.93           | 0.67           | 0.12           | 0.07           | 0.03           |
| -30.00                     | 9.81           | 7.96           | 1.98           | 0.44           | 0.57           | 0.28           |
| -20.00                     | 6.67           | 2.49           | 1.74           | 0.42           | 2.45           | 1.49           |
| -10.00                     | 0.35           | 3.61           | 2.49           | 6.31           | 6.24           | 4.83           |
| 0.00                       | 47.87          | 47.44          | 20.59          | 20.67          | 13.99          | 14.00          |
| 10.00                      | 7.22           | 2.57           | 18.80          | 10.07          | 9.85           | 13.05          |
| 20.00                      | 19.13          | 34.92          | 11.50          | 6.76           | 4.27           | 7.75           |
| 30.00                      | 26.09          | 35.97          | 22.83          | 9.19           | 0.98           | 2.58           |
| 40.00                      | 19.20          | 44.63          | 9.27           | 3.14           | 0.10           | 0.42           |
For brain and fat tissues, we further determine six different Ogden-type models, with the associated constant parameters recorded in Tables 3, 4, and 5. In these tables, the Ogden$_N$ models have $N$ non-zero coefficients $C_p$, while the associated exponents $m_p$ are fixed. For these models, conditions (i) and (ii) are both valid. See also Figure 3 (a) and Figure 4 (a). The relative errors recorded in Table 7, 8, and 9 further suggest that Ogden$_7$ and Ogden$_8$ are the most successful in approximating the experimental data. Obviously, these last models contain a large number of parameters and are likely to over-fit the data. The purpose of including these models is to demonstrate that such a family of model is adequate to capture the mechanical responses of the biological tissues under investigation. See also Figure 3 (b) and Figure 4 (b). From the associated relative elastic modulus plotted in Figure 3 (c) and Figure 4 (c), we also see that this modulus increases under increasing compression, hence condition (iii) is valid as well. For all models, smaller relative values for the elastic modulus may be obtained when this modulus is defined by (2.4).

Table 8: Relative errors of the shear modulus for Ogden models fitted to lean fat data.

| Compression or Tension (%) | Ogden$_3$ (lean) | Ogden$_4$ (lean) | Ogden$_5$ (lean) | Ogden$_6$ (lean) | Ogden$_7$ (lean) | Ogden$_8$ (lean) |
|---------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| -40.00                    | 13.57           | 2.46            | 1.19            | 0.11            | 0.02            | 0.01            |
| -30.00                    | 24.42           | 11.75           | 7.29            | 0.97            | 0.31            | 0.26            |
| -20.00                    | 34.01           | 1.57            | 5.49            | 1.22            | 1.95            | 1.76            |
| -10.00                    | 9.86            | 24.70           | 18.93           | 6.31            | 6.20            | 5.90            |
| 0.00                      | 0.96            | 2.98            | 30.03           | 29.80           | 18.40           | 18.39           |
| 10.00                     | 87.37           | 2.44            | 12.90           | 15.87           | 15.55           | 16.23           |
| 20.00                     | 97.84           | 26.41           | 6.41            | 7.82            | 8.15            | 8.84            |
| 30.00                     | 34.75           | 13.39           | 17.74           | 7.46            | 1.65            | 1.85            |
| 40.00                     | 56.19           | 10.73           | 4.70            | 1.42            | 0.14            | 0.17            |

Table 9: Relative errors of the shear modulus for Ogden models fitted to obese fat data.

| Compression or Tension (%) | Ogden$_3$ (obese) | Ogden$_4$ (obese) | Ogden$_5$ (obese) | Ogden$_6$ (obese) | Ogden$_7$ (obese) | Ogden$_8$ (obese) |
|---------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| -40.00                    | 12.50             | 1.00              | 0.47              | 0.13              | 0.00              | 0.00              |
| -30.00                    | 17.25             | 4.82              | 3.07              | 1.18              | 0.03              | 0.10              |
| -20.00                    | 36.17             | 2.58              | 4.29              | 2.87              | 0.45              | 0.75              |
| -10.00                    | 37.45             | 11.62             | 8.34              | 2.87              | 2.72              | 3.30              |
| 0.00                      | 4.99              | 10.57             | 25.89             | 25.78             | 10.30             | 10.33             |
| 10.00                     | 102.75            | 5.77              | 1.25              | 8.78              | 8.43              | 7.35              |
| 20.00                     | 96.61             | 1.13              | 5.18              | 8.59              | 3.49              | 2.78              |
| 30.00                     | 29.33             | 10.34             | 0.05              | 6.39              | 0.82              | 0.61              |
| 40.00                     | 47.42             | 4.44              | 0.36              | 1.09              | 0.07              | 0.05              |

As explained above, for brain and fat tissues, it was observed experimentally that the shear modulus increases sharply under increasing compressive strain, but not under tensile strain, while the apparent elastic modulus increases or remains almost constant when compressive strain increases. The macroscopic, cm-scale, samples are heterogeneous on a smaller length scale since they are a mix of grey and white matter with boundaries between, but this heterogeneity does not
dominate the rheological response because grey and white matter do not differ strongly in stiffness, and the macroscopic viscoelastic response does not depend on precisely how the sample is cut or how large it is. Also a characteristic of these tissues is that they exhibit a predominantly isotropic incompressible behaviour. Here, we compare the behaviours of several nonlinear hyperelastic models, both theoretically and numerically, and test our results against available experimental data. Our analysis shows that neo-Hookean, Mooney-Rivlin, Fung, and Gent models, which have been successfully employed to date in the modelling of rubber and of other man-made or natural materials, are inadequate to model brain and fat tissues. Instead, for these tissues, Ogden models, with four, six, and eight coefficients, respectively, are found which are in excellent agreement with the experiments. The newly identified models can be easily implemented in finite element codes.

4 Conclusion

Biological tissues offer a great diversity of mechanical responses when subject to loads. Often, such behaviours appear counter-intuitive as our intuition has been forged by centuries of studies of engineering material often treated in the limit of small strains. It is then tempting to conclude that classical continuum mechanics is not suitable for modelling biological materials. However, aside from the very few classical models used indiscriminately for both rubbers and biological tissues, there is a vast pool of potential models that have yet to be explored, understood, and classified.

Our approach when confronted with a new constitutive phenomenon consists of two steps. First, based on experimental evidence, classify qualitative responses that a model ought to reproduce by an analytical study of relevant deformations. Second, for the models that pass the first sift, find suitable candidates in quantitative agreement with the data. As presented here, this approach was successful for the analysis of the response of brain and fat tissues, generating in the process models that are capable of predicting some of the key elastic properties underpinning the extraordinary mechanical performance of these tissues, and which can be integrated into large-scale computational framework. For claiming that the models presented here are universal models for brain and fat tissues, we demonstrate that a systematic approach in the framework of nonlinear elasticity based on experimental data provides phenomenological models that can be used to explore the large-scale response of tissues and organs. We have listed several models that fit the data increasingly well at the expense of an increase in the number of parameters. We leave it to the practitioners to decide, based on the problem and at hand and the range of deformation being studied, which model to use.

Our enquiry also suggests that the microscopic processes that generate macroscopic elastic response in these tissues are different than the ones found other soft-tissues or elastomers. Clearly, there is need for a better understanding of the mechanics of very soft tissues, particularly of brain, which is currently under intense study by researchers in both biophysics and computational mechanics, and adipose tissue, which is a growing area of investigation in clinical research.

Appendix A: Experimental Method

Brain and lean adipose tissues were harvested from adult male wild-type C57BL/6 mice and obese adipose tissue was collected from genetically obese ob/ob mice (The Jackson Laboratory, Bar Harbor, ME). Fresh tissues were stored in Dulbecco’s modified Eagle medium (DMEM, Gibco, Grand Island, NY) and tested within a maximum of three hours after sacrifice. Macroscopic rheometry using a Rheometrics fluids spectrometer III strain-controlled rheometer (Rheometrics, Piscataway, NY) fitted with 8 mm diameter parallel plates was used to measure the viscoelasticity of tissue samples using methods previously described in [22]. During testing, tissues were kept hydrated by surrounding the sample with phosphate buffered saline (PBS). Control experiments showed that the use of DMEM and PBS increased tissue weight only slightly - on average 4% for brain, 2% for fat.

Test samples were cut into disk-shaped samples using an 8 mm diameter stainless steel punch, maintaining the cerebral hemispheres, but removing the cerebellum, olfactory bulb, pons, and
medulla (Supplemental Figure 1). Note that an 8 mm diameter disk in the brain will necessarily contain a mixture of different tissues and structures. However, structures such as ventricles and vessels constitute a small percentage of the volume (2%) and are not arranged in a highly oriented manner. The bulk of the tissues consists of cells packed together and surrounded by soft matrices, which in the brain are flexible polysaccharides and so very likely to be close to isotropic (as found repeatedly in other experiments [8]). Since the length scale of the individual tissue components is much smaller than the length scale of the bulk tissue, the protocol provides an average mechanical response suitable for comparison with continuum models. If swelling occurs and we assuming that if deforms the sample equally in all directions, a typical 4% increase in volume yields 1% increase in height. A 1% change in height and the effect on G are relatively small compared to the deformations the samples are subjected to during measurement.

Supplemental Figure 1: Typical samples of brain, obese, and lean fat tissues are cut using an 8 mm diameter stainless steel punch. Major brain structures, such as cerebellum and olfactory bulb, are removed. The samples did not exhibit any anisotropic characteristics.

To avoid sample slippage during shear deformation and to perform uniaxial extension, fibrin gel was used to glue the sample to the rheometer plate. Fibrin gel was prepared by mixing equal volumes of 28 mg/ml salmon fibrinogen solution with 125 U/ml of thrombin (Sea Run Holdings, Freeport, ME) directly on the lower rheometer plate, and the sample was immediately positioned. Subsequently, a thin layer of fibrin gel was pipetted onto the upper surface of the tissue, and the top plate was lowered until a positive normal force (1 g) was measured by a force transducer. Control experiments showed that addition of fibrin glue did not affect the viscoelastic properties of the tissue samples.

The dynamic shear storage modulus $G'$ was measured as a function of time (brain: 2% oscillatory shear strain, 2 rad/s frequency; fat: 3.5% shear strain, 2.5 rad/s frequency) and increasing tensile/compressive strain (0% to 40%, Supplemental Figure 1). For both brain [22] and lean fat, recoverable deformation was observed when the compressed sample was returned to its initial height and the shear modulus $G'$ returned to its uncompressed value (Supplemental Figure 2). Obese fat largely recovers, but residual stresses appear to remain after 40% compression. This may be indicative of tissue damage at higher levels of compression, but does not negate the compression-stiffening phenomenon observed. During each incremental compression, $G'$ demonstrated a relaxation response. Therefore, for the purposes of model fitting, $G'$ values after 100 seconds of relaxation were used. In tension, the following correction was applied to account for the decrease in cross-sectional area during testing under the assumption that volume is conserved, $G'_{\text{actual}} = G'_{\text{measured}}(1 + \lambda)^2$, where $G'$ is the storage modulus and $\lambda$ is the axial strain. To determine the linear viscoelastic region for each tissue, the shear moduli $G'$ of brain and lean fat were measured with respect to increasing shear strain up to 10% ($n = 3$ each, Supplemental Figure 3). The experimentally measurable linear viscoelastic region for brain and fat were determined to be 0.15-2.5% and 0.15-4% strain, respectively.
Supplemental Figure 2: A. Experimental data for brain. Shear modulus was measured over time and with increasing tension/compression (0% to 40%). $G'$ relaxes to equilibrium after 100 seconds. Recoverable deformation was observed when the compressed sample was returned to its initial height and the shear modulus $G'$ returned to its uncompressed value. B. Experimental data for lean and obese fat. Shear modulus was measured over time and with increasing tension/compression (0% to 40%). $G'$ does not relax completely to equilibrium after 100 seconds, particularly for compression levels of 30% and above. For lean fat, recoverable deformation was observed when the compressed sample was returned to its initial height and the shear modulus $G'$ returned to its uncompressed value. Obese fat largely recovers, but residual stresses appear to remain after 40% compression.

Supplemental Figure 3: A. Shear modulus of brain with increasing shear strains. The linear viscoelastic region was determined to be approximately 0.15-2.5% strain. B. Shear modulus of lean fat with increasing shear strains. The linear viscoelastic region was determined to be 0.15-4% strain.
Authors’ Contributions

AG and PAJ conceived of and designed the study; LAM and AG carried out the hyperelastic analysis and drafted the manuscript; LKC and PAJ carried out the experimental work and helped draft the manuscript. All authors gave final approval for publication.

Acknowledgements

We would like to thank the hospitality of the NSF-Mathematical Biosciences Institute in Ohio for the workshop where the ideas presented here were first discussed, as well as key discussions with Prof. Ellen Kuhl of Stanford University.

Funding

AG is a Wolfson/Royal Society Merit Award Holder and acknowledges support by the Marie Curie European Reintegration Grant BKRVRG0. The support for LAM by the Engineering and Physical Sciences Research Council of Great Britain under research grant EP/M011992/1 is gratefully acknowledged.

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