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OCCAM Preprint Number 12/64

Journal of Mathematical Biology manuscript No.
(will be inserted by the editor)

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Received: May 25, 2012 / Accepted: date

Abstract The mechanical behaviour of solid biological tissues has long been described using models based on classical continuum mechanics. However, the classical continuum theories of elasticity and viscoelasticity cannot easily capture the continual remodelling and associated structural changes of biological tissues. Furthermore, models drawn from plasticity theory are difficult to apply and interpret in this context, where there is no equivalent of a yield stress or flow rule. In this work, we describe a novel one-dimensional mathematical model of tissue remodelling based on the multiplicative decomposition of the deformation gradient. We express the mechanical effects of remodelling as an evolution equation for the 'effective strain', a measure of the difference between the current state and a hypothetical mechanically-relaxed state of the tissue. This morphoelastic model combines the simplicity and interpretability of classical viscoelastic models with the versatility of plasticity theory.

To demonstrate the utility of our approach, we derive and analyse a system of coupled partial differential equations that describes the deformation of fibroblast-populated collagen lattices. These lattices are rearranged by the fibroblast cells that inhabit them, and can subsequently contract to as little as 10% of their initial lateral (or vertical) extent. It has been observed that when this reorganisation is interrupted, the lattices re-expand slightly but do not return to their original size. We find that our morphoelastic model captures several important observed features of this process and that numerical values for the initial stiffness and viscosity of the collagen

This research was supported under Australian Research Council's Discovery Projects funding scheme (project number DP0878011). This publication was based on work supported in part by Award No. KUK-C1-013-04, made by King Abdullah University of Science and Technology (KAUST).

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gel, obtained by fitting our model to previously obtained data, compare well with the results of rheological experiments.

Keywords morphoelasticity · biomechanics · tissue plasticity · fibroblast-populated collagen lattices

Mathematics Subject Classification (2000) 74L15 · 74D99 · 74A05 · 74C99 · 92C10

1 Introduction

1.1 Growth, remodelling and morphoelasticity

The complex mechanical behaviour of biological materials has long been an active area of research. The importance of the mechanics of biological growth was first recognised by D'Arcy Thompson, whose classic tome *On Growth and Form* (Thompson, 1917), provided the basis for an analytical approach to the science of form (Gould, 1971). While this work remains influential, the scientific understanding of growth has advanced significantly over the last century. For instance, as discussed in Alberts et al (2008), the growth of soft tissues is now primarily understood as an increase in mass. The modelling of biological tissues remains an active area of research, and there has been much progress in recent years (a thorough review is provided by Wyn Jones and Chapman, 2012).

Like most materials, biological tissues appear to deform continuously when subjected to mechanical forces. Hence, it is often appropriate to model the physical behaviour of a tissue using classical continuum mechanics. However, living tissues are unusual in that they may contain cells that are capable of modifying the fundamental mechanical properties of their physical environment. There are a number of processes, most notably tissue growth, in which cells cooperatively alter the tissue structure, changing the relationship between stress and deformation (Chen and Hoger, 2000). Indeed, many tissues undergo a continual process of internal revision and mechanical restructuring, often referred to as 'remodelling' (Taber, 1995), in which physical properties of the material, including anisotropy and stiffness, evolve over time.

This active remodelling is thought to be significant in a wide range of biological processes. It is well known, for example, that fibroblast cells, which are found in the stroma of a wide range of tissues, actively remodel the surrounding extracellular matrix (ECM) by synthesising and reorganising collagen fibres, and that this remodelling is essential for tissue homeostasis and wound repair (Calvin, 1998; Grinnell, 2003; Majno and Joris, 2004). Moreover, the changes associated with biological remodelling can be very dramatic: for example, the stiffness of the nucleus of the human eye lens has been found to increase by a factor of 10^3–10^4 between the ages of thirty and fifty (Augusteyn, 2010).

Remodelling is also important because it affects the mechanical stresses experienced by cells in a tissue, which can subsequently modify aspects of cell behaviour. For instance, fibroblasts are known to change their morphology (Eastwood et al, 1996, 1998; Gabbiani, 2003; Tamariz and Grinnell, 2002; Tomasek et al, 2002) and phenotype (Amadeu et al, 2003; Gabbiani, 2003; Tomasek et al, 2002) in response to external mechanical cues. Most significantly, the mechanical stresses experienced by fibroblasts during the wound healing process stimulate them to differentiate into more contractile forms: protomyofibroblasts and myofibroblasts (Desmoulière et al, 2005; Gabbiani et al, 1972, 1978; Tomasek et al, 2002), which play a major rôle in the subsequent contraction of the wound. Although tissue contraction is less significant for successful wound healing in humans than in animals with an extensive *panniculus carnosus*, such as rats, where contraction results in 80% wound closure (Majno and Joris, 2004), excessive contraction is known to lead to wound healing pathologies in humans such as hypertrophic scars and contractures (Roseborough et al, 2004; Enoch and Leaper, 2005; Murphy et al, 2011). As well as being critically important in wound healing, the interplay between mechanical stress and active remodelling is very significant in a number of other biological situations such as embryo development (Steinberg, 1962) and morphogenesis (Lauffenburger and Griffith, 2001) (see Patwari and Lee, 2008, for a recent discussion).

Several theoretical frameworks have been proposed to capture the dynamics of remodelling. The first descriptions of the kinematics of biological growth, developed using continuum mechanics, were those by Hsu (1968), Cowin and Hegedus (1976), Hegedus and Cowin (1976) and Skalak and coworkers (Skalak, 1981; Skalak et al, 1982) (detailed reviews are provided by Taber, 1995, and Humphrey, 1995, 2003). A very significant advance was made in the mid 1990s, when Rodriguez et al (1994) and Cook (1995) independently developed the multiplicative decomposition of the deformation gradient as a mathematical framework for describing remodelling. This approach to remodelling is useful not only because it provides a clear and coherent way of understanding growth, but also because it leads to a natural way of describing residual stress (*i.e.* stress that persists even when all loads are removed). Although Fung (1967, 1973, 1990, 1993) had noted much earlier that some tissues (such as arteries) are structured so that it is impossible for the entire tissue to be free of residual stresses unless cuts are made, limited attempts had been made to describe these stresses mathematically.

The pioneering work of Rodriguez et al (1994) and Cook (1995) was later extended and expanded by Hoger and coworkers (see especially Chen and Hoger, 2000), Goriely and coworkers (Ben Amar and Goriely, 2005; Goriely and Ben Amar, 2007; Goriely et al, 2008), Ambrosi and coworkers (Ambrosi and Mollica, 2004; Ambrosi and Guana, 2007; Ambrosi and Guillou, 2007) and by Vandiver (2009). This biological work has developed alongside the continuing use of the multiplicative decomposition of the deformation gradient in thermoelasticity and plasticity, and the achievements made in thermoelasticity and plasticity have been used to inform biological models. This is exemplified by the cross-disciplinary work of Lubarda (2004) and Rajagopal and coworkers (see, for example, Rajagopal and Srinivasa, 2004). The multiplicative decomposition of the deformation gradient is now being used in models of biomechanical phenomena ranging from tissue growth (Ben Amar and Goriely, 2005) to the operation of the heart (Rausch et al, 2011), although it is important to note that this approach will only be valid when the tissue behaves elastically on the timescale of remodelling (Wyn Jones and Chapman, 2012), and that some authors have general reservations about the use of the multiplicative decomposition on theoretical grounds (Xiao et al, 2006).

Ambrosi et al (2011) have recently written an excellent review of current work on modelling growth and remodelling, in which they describe a number of applications for which the multiplicative decomposition of the deformation gradient has been used, ranging from the remodelling of heart muscle to morphogenesis. However, Ambrosi et al (2011) also note that there are problems and ambiguities to be resolved when developing appropriate laws to describe the evolution of the growth part of the deformation gradient in response to remodelling. As outlined in Sec. 2, many of these difficulties are avoided when we restrict our analysis to one-dimensional (1-D) Cartesian problems, but it is still necessary to ensure that the constitutive relation is appropriate for the type of remodelling under consideration.

While remodelling is important in a wide range of phenomena *in vivo*, surprisingly few *in vitro* experiments have been developed to explicitly investigate the macroscopic consequences of remodelling. A notable example of such an experiment is the contraction of fibroblast-populated collagen lattices (FPCLs): cultured fibroblasts embedded in (or placed on top of) three-dimensional (3-D) collagen matrices.

1.2 The permanent contraction of collagen lattices

FPCLs were developed by Elsdale and Bard (1972), who used them as a means of investigating fibroblast behaviour in a setting that closely resembles their natural environment. These lattices have since been used to study the traction forces exerted by fibroblasts in mechanically-relaxed (Bell et al, 1979; Steinberg et al, 1980; Bellows et al, 1981; Grinnell and Bennett, 1981; Ehrlich and Rajaratnam, 1990) and in mechanically-loaded environments (Grinnell and Lamke, 1984; Grinnell et al, 1999; Grinnell and Ho, 2002; Guidry and Grinnell, 1985, 1986; Hinz et al, 2001; Mudera et al, 2000). FPCLs have also been used to investigate the effects of various growth factors on fibroblasts (Grinnell et al, 1999; Schreiber et al, 2001) as well as the behaviour of indi-

vidual fibroblasts as they contract their environment while moving through the ECM (Roy et al, 1997, 1999). For further details of the range of experiments where FPCLs have been used, see the reviews by Dallon and Ehrlich (2008) and Grinnell (2003).

A scanning electron microscope image of a human fibroblast interacting with surrounding collagen fibrils, taken from Rhee and Grinnell (2007), is shown in Fig. 1. The activity seen in this figure results in a local increase in the density of the neighbouring fibrils and consequently a decrease in volume of the collagen lattice (Grinnell, 2003). An example of such behaviour, taken from an experiment by Kelynack (2009), is shown in Fig. 2.

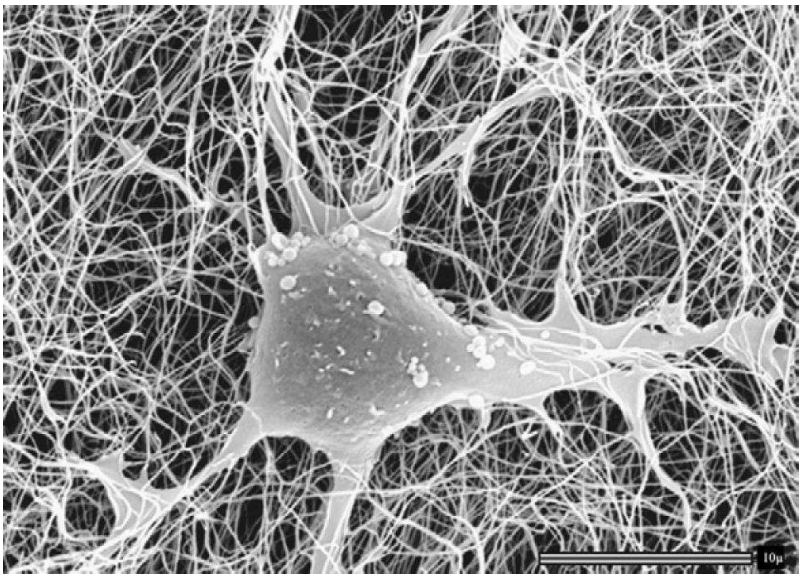

Fig. 1 Scanning electron microscope image of a human fibroblast interacting with 3D collagen matrices. Here, the fibroblast exhibits a dendritic structure, indicating that the environment is unstressed. The scale in the figure represents 10 microns. (Reprinted from *Advanced Drug Delivery Reviews* 59(13), Rhee S. and Grinnell F., *Fibroblast mechanics in 3D Collagen matrices*, pg 1299-1305, Copyright (2007) with permission from Elsevier).

While some degree of permanent contraction is always observed, it is believed that the mechanism of FPCL contraction depends on the mechanical environment in which the fibroblasts are cultured. As a result, it is useful to classify FPCLs by the mechanical set-up that is used. By this reckoning, there are three main types of FPCLs: free-floating, attached and stress-relaxed. The important features of these different lattices are described below.

Free-floating FPCLs were introduced by Bell et al (1979) and are prepared by polymerising a collagen gel with fibroblasts either in a bacteriological dish, to which the gel adheres poorly, or in a tissue culture dish, in which case the gel has to be detached after a certain time with a spatula. The lattice displayed in Fig. 2 is an example of a free-floating FPCL. In such lattices, the fibroblasts project a dendritic network of extensions and the tension is distributed isotropically (Grinnell et al, 2003; Rhee and Grinnell, 2007).

It has been observed that fibroblasts in free-floating lattices can generate significant traction forces (Majno and Joris, 2004; Grinnell, 2000), which reorganise the matrix and lead to contraction. While this reorganisation does not orient collagen fibrils in any particular direction, it can still cause these lattices to contract to as little as a tenth of their initial lateral (or vertical) extent (Bell et al, 1979; Steinberg et al, 1980; Grinnell and Lamke, 1984; Guidry and Grinnell, 1985), even in the absence of protomyofibroblast cells, which can exert greater forces. As this contraction gives rise to a mechanically relaxed tissue that resembles dermis, it has been proposed that such lattices can be used to describe the earliest stages of wound healing, before inflammation and tissue stress have activated the differentiation of fibroblasts (Grinnell, 1994). FPCLs are observed

to remain disk-shaped throughout the contraction process, which involves a reduction in thickness as well as diameter, although the edges of the disk are observed to eventually curl up (Bell et al, 1979).

Attached FPCLs are fibroblast-populated lattices that are polymerised in a tissue culture dish, to which the gel attaches firmly. A consequence of this experimental arrangement is that the lattices decrease in thickness but not in lateral area (Grinnell and Lamke, 1984; Guidry and Grinnell, 1985). The tension in such lattices is distributed anisotropically, while fibroblasts develop an elongated bipolar appearance, orienting themselves along the lines of tension (Stopak and Harris, 1982; Bellows et al, 1982; Grinnell, 1994; Tamariz and Grinnell, 2002). This reorganisation causes collagen fibrils to become oriented in the same plane as the substrate, which in turn gives rise to mechanical loading within the matrix. The contraction of such lattices, which involves a reduction in thickness alone, gives rise to a mechanically stressed tissue resembling granulation tissue, and it has therefore been proposed that such lattices can be used to model the early stage of wound healing when the granulation tissue begins to develop and exert stresses on its environment (Grinnell, 1994). Fibroblasts in such lattices organise a fibronectin matrix and develop prominent actin stress fibres (Farsi and Aubin, 1984; Mochitate et al, 1991; Halliday and Tomasek, 1995), which indicate the presence of protomyofibroblasts. The appearance of protomyofibroblasts in FPCLs is linked to the tensile state of the surrounding matrix. It has also been observed that fibroblasts in restrained matrices develop fibronexus junctions (Tomasek et al, 2002), which allow TGF-β, if present, to further stimulate the differentiation of protomyofibroblasts into myofibroblasts (Arora et al, 1999; Vaughan et al, 2000).

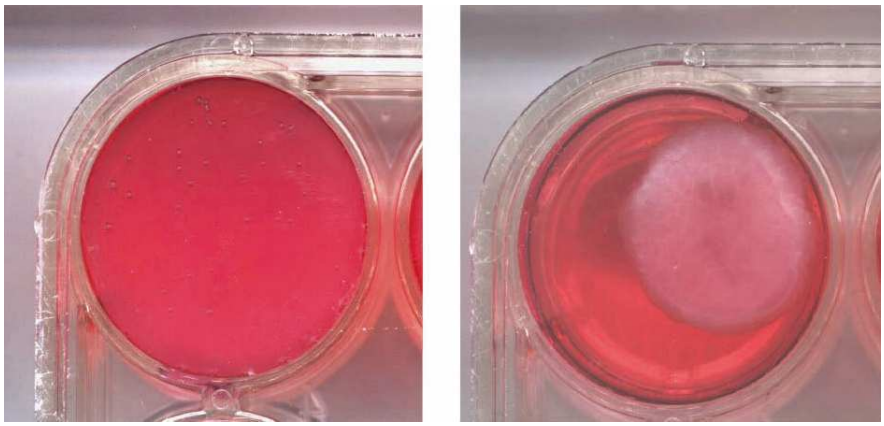

Fig. 2 Contraction of a solidified free-floating FPCL. The left image shows the initial configuration of a collagen gel, while the right image shows the configuration of the same gel after 48 hrs. (With kind permission from Springer Science+Business Media: *Methods in Molecular Biology: Kidney Research, Chapter 14. Cell-Populated Floating Collagen Lattices: An In Vitro Model of Parenchymal Contraction*, 466, 2009, 1-11, Kelynack, K. J., Figure 14.1).

Stress-relaxed FPCLs are prepared by polymerising a collagen lattice, allowing it to attach to a tissue culture dish for a set period and then detaching it (Tomasek et al, 1992). In such lattices, tensile stress develops while the matrix is anchored and these stresses are relieved via a sudden smooth muscle-like contraction when the matrix is released, as the cell extensions collapse and the stress fibres disappear (Mochitate et al, 1991; Tomasek et al, 1992; Lin et al, 1997). It has been proposed that stress-relaxed FPCLs can be used to model scar tissue, or the transition from granulation tissue to replacement dermis in wound healing or in tissue repair (Carlson and Longaker, 2004).

Experiments using radiolabelled collagen have been used to demonstrate that the degradation and replacement of collagen fibres is not a significant mechanism of contraction in attached lattices

(Guidry and Grinnell, 1985). Indeed, it seems plausible to assume in all cases that contraction is largely a result of the rearrangement of pre-existing collagen fibres by fibroblasts. Even still, the precise mechanism of lattice contraction is thought to vary, depending on the density and mechanical state of the lattice. The prime mechanism of stressed lattice contraction is believed to be *cell contraction*, which is associated with the protomyofibroblast and myofibroblast phenotypes that are prevalent in such environments (Dallon and Ehrlich, 2008). When these cells contract, they pull on the surrounding lattice, causing it to contract with them. It has been suggested that contraction in relaxed lattices of moderate cell density occurs through a *cell traction* mechanism (Dallon and Ehrlich, 2008), in which cell locomotion results in the compacting of collagen fibres by bundling thin fibrils (Harris et al, 1980; Ehrlich, 2003). As discussed in Dallon and Ehrlich (2008), the contraction of relaxed lattices of high cell density is believed to occur through a *cell elongation and spreading* mechanism, in which fibroblasts pull collagen fibrils towards them, thus compacting the gel. It was confirmed through the use of radiolabelled collagen that the concentration of proteins in the gel remained constant during this sort of the reorganisation process (Guidry and Grinnell, 1985). It is thus believed that degradation and replacement of collagen fibres is not a significant mechanism of lattice contraction.

In the experiments of Grinnell and coworkers (Grinnell and Lamke, 1984; Guidry and Grinnell, 1985, 1986), where different numbers of fibroblast cells were placed on top of, rather than embedded within, attached collagen lattices of varying concentration, it was observed that the rate and extent of contraction of the lattice is similar to experiments where fibroblasts are embedded within such lattices. However, most fibroblasts did not invade the lattice, and were instead found to spread over its surface while reorganising proximal collagen fibres in the direction of spreading. It was thus proposed that the reorganisation of the lattice away from the cells was chemically mediated by the secretion of cell-binding factors such as fibronectin and proteoglycans (Grinnell and Lamke, 1984). It was also observed that the addition of cytochalasin D, which suppresses gel reorganisation by inhibiting cell motility, resulted in a partial re-expansion of the gel (Guidry and Grinnell, 1985, 1986). The relative magnitude of the re-expansion was found to be smaller in gels that were contracted by fibroblasts for a greater period of time, which suggested that the collagen gels were first physically reorganised by fibroblasts and then stabilised by the continued presence of these cells.

The observation that the lattices only re-expand partially is very important, as it indicates that contraction is not simply the elastic response of the collagen lattice to traction forces applied by cells. Unlike other forms of remodelling, such as the hardening of the human eye lens described by Augusteyn (2010), which could be modelled using a time-dependent stress-strain relationship, FPCL contraction involves some form of cell-induced 'plastic' behaviour. That is, the active lattice remodelling by cells causes the unloaded state of the lattice to change over time in a manner analogous to classical plasticity. In order to describe this, we will need some description of the mechanical behaviour of the collagen lattice that takes into account the evolving unloaded state.

Recently, Goriely and Ben Amar (2007) coined the term *morphoelasticity* to describe the combination of elastic and 'plastic' changes that are the result of biological growth and remodelling. Despite some similarities, morphoelasticity is quite distinct from classical plasticity. For example, morphoelastic remodelling will generally occur throughout a tissue, not just in those regions where a yield stress is exceeded. Moreover, morphoelasticity can involve changes to the total mass of a tissue (in tissue growth, for example) and/or increases in internal energy, while plastic flow is always mass-conserving and dissipative.

A central aim of this paper is to develop a mathematical framework for FPCL contraction that captures key qualitative features of the contraction process, something that would be impossible to achieve with, for example, a Kelvin-Voigt viscoelastic constitutive law. We now briefly outline some of the previous mathematical approaches to modelling the behaviour of FPCLs.

1.3 Modelling the contraction of FPCLs

The earliest model of FPCL contraction was developed by Moon and Tranquillo (1993), who adapted the Tranquillo and Murray (1992) model of dermal wound healing to describe the contraction of a collagen microsphere. Barocas et al (1995) modified the Moon-Tranquillo model by replacing the Kelvin-Voigt constitutive law with a Maxwell constitutive law. Although this model is only valid for small displacement gradients, it can account for the permanence of matrix contraction, unlike the Moon-Tranquillo model. Barocas and coworkers also developed a biphasic model of collagen lattice contraction in which the interaction between the fibrous lattice and the permeating fluid medium is described using the theory of mixtures (Barocas et al, 1994; Barocas and Tranquillo, 1997). This model takes into account several important effects, including the partial expansion of collagen lattices after cell traction stresses are removed. Since the development of this model, Barocas and coworkers have used similar approaches to describe several experiments on collagen lattices (Chandran and Barocas, 2004, 2007; Girton et al, 2002; Knapp et al, 1999; Schreiber et al, 2003), using models that include fibroblast traction as an additive contribution to the total stress. Ferrenq et al (1997) developed a model of FPCL contraction that is similar to the Moon-Tranquillo model in that a linear Kelvin-Voigt constitutive law is used, but they restricted their focus to situations in which the displacement gradient is small and linear theory is valid.

Recent models of FPCL contraction include those by Ramtani and coworkers (Ramtani, 2004; Ramtani et al, 2002), who incorporate a repulsive interaction force between cells in order to account for the inhibition of gap junction formation at large cell densities, and Marquez, Zahalak and coworkers (Marquez et al, 2006, 2005a,b; Pryse et al, 2003; Zahalak et al, 2000), who considered individual cells and used Eshelby's solution to describe the local strain fields.

While these models have significantly advanced the understanding of this process, there have not yet been any models that explicitly take into account the continual mechanical restructuring of such lattices. In this work, we develop a mathematical description of the permanent contraction of FPCLs that incorporates the mechanical effects of remodelling.

To achieve this aim, we first require a systematic framework for modelling this morphoelasticity. In Sec. 2, we discuss the fundamental concepts that underlie the multiplicative decomposition of the deformation gradient and we use them to derive equations that are appropriate for describing the mechanical behaviour of a morphoelastic tissue like a contracting collagen lattice. In particular, we take advantage of the simplifications that can be made when the deformation of the lattice might be large, but the difference between the current state and the stress-free state is always small. Then, in Sec. 3, we construct an expression for the rate of morphoelastic contraction of an FPCL based on a plausible microscopic mechanism of cells rearranging the fibres of the lattice. This yields a model comprising of a set of partial differential equations, but these can be reduced further to a system of ordinary differential equations when cell motility is insignificant. We find that this simplified model replicates the qualitative features of previous experiments on contracting FPCLs. Moreover, as further justification of our approach, we fit our model to experimental data, and we find that the values we obtain for initial lattice stiffness and viscosity in our fitted model are consistent with the results from mechanical experiments on unpopulated collagen lattices.

2 Theoretical foundations: Effective strain and morphoelastic contraction

2.1 The multiplicative decomposition of the deformation gradient

In the 1960s, several researchers (most notably Lee, 1969) worked on developing mathematical methods for describing metal plasticity at large deformations. In Lee's approach, the observed deformation gradient tensor, $\boldsymbol{F}$, is expressed as the product of an elastic part and a plastic part. In this paper, we use the notation developed by Goriely and coworkers (Goriely and Ben Amar, 2007; Goriely et al, 2008; Vandiver and Goriely, 2009; Goriely and Moulton, 2011) so that $\boldsymbol{A}$ represents the elastic part of the deformation gradient and $\boldsymbol{G}$ represents the plastic/growth part of the

deformation gradient. In this form, Lee's decomposition is written as

$$\boldsymbol{F} = \boldsymbol{A}\,\boldsymbol{G}\,. \tag{1}$$

The physical interpretation of this decomposition is depicted in Figure 3: $\boldsymbol{G}$ is the deformation gradient tensor associated with a hypothetical deformation from the fixed reference state to a state where all internal stresses are relieved, while $\boldsymbol{A}$ represents the deformation from this 'zero stress state' to the current state. For a purely elastic material, the fixed reference state will also be the zero stress state, and we find that $\boldsymbol{G} \equiv \boldsymbol{I}$. However, plastic flow or morphoelastic remodelling enables the zero stress state, and hence $\boldsymbol{G}$, to evolve.

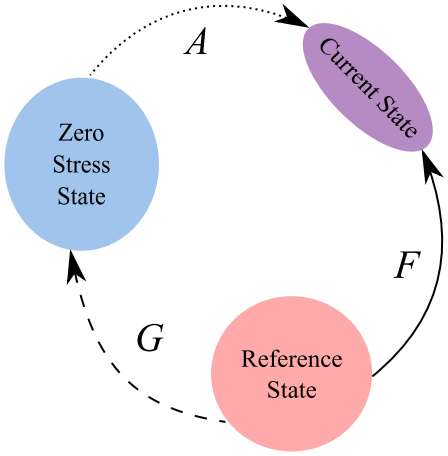

Fig. 3 The relationship between the reference state, the current state and the zero stress state. In our notation, $\boldsymbol{F}$ represents the overall deformation gradient from the reference state to the current state, while $\boldsymbol{G}$ represents the deformation from the reference state to the zero stress state and $\boldsymbol{A}$ represents the deformation from the zero stress state to the current state.

It is this use of the multiplicative decomposition of the deformation gradient to describe arbitrary changes to the zero stress state that makes it especially valuable in biomechanics. When the multiplicative decomposition of the deformation gradient is employed in finite plasticity, physical constraints can be used to make restrictions on the evolution of the zero stress state – for example, the volume of the zero stress state must be conserved in an incompressible material, and the rate of plastic energy dissipation must be positive. However, the framework provided by this decomposition is very general and we can use it to explore changes to the zero stress state that involve growth or that require the input of energy. In order to model an open system like a living tissue, in which cells are able to lay down new fibres and actively remodel their surroundings, this flexibility is essential.

An accessible introduction to the use of the multiplicative decomposition in biological applications can be found in Goriely and Moulton (2011), which begins with an analysis of a 1-D growing material that is relevant to the research presented here. One-dimensional Cartesian problems are considerably simpler to analyse than 3-D problems for a number of reasons. Firstly, a 1-D body can never be residually stressed: it is impossible to encounter the situation in which the zero stress state cannot be achieved without introducing cuts. Secondly, ensuring observer-independence of time derivatives is much simpler in 1-D than in two or three dimensions, since it is not necessary to consider the possibility of a rotating observer.

As we discuss later in Sec. 3.2, it is often appropriate to treat contracting FPCLs as 1-D bodies. Indeed, Ferrenq et al (1997) constructed a model of FPCL contraction in 1-D Cartesian coordinates and various authors have assumed radial symmetry to develop 1-D descriptions of FPCL contraction (Moon and Tranquillo, 1993; Ramtani et al, 2002; Ramtani, 2004). In the rest of

this section, we develop a simple mathematical framework for modelling the growth or contraction of a 1-D Cartesian morphoelastic body.

As described in standard continuum mechanics texts (for example, Gonzalez and Stuart, 2008), it is common to work in either of two different coordinate systems. One possibility is to use 'Lagrangian' or 'material' coordinates, in which each particle is labelled according to its position in the initial configuration of the body. Alternatively, it is possible to use 'Eulerian' or 'spatial' coordinates, in which each particle is labelled according to its current position. Holding the Lagrangian coordinate constant corresponds to observing a single particle, while holding the Eulerian coordinate constant corresponds to observing a single point in space. In one spatial dimension, we use X to represent the Lagrangian coordinate and x to represent the Eulerian coordinate. At any given time, there will be a one-to-one mapping from the initial configuration to the current configuration. Thus, we can always write $X = X(x, t)$ and $x = x(X, t)$; moreover, the fact that particles are not permitted to move through each other implies that $\partial x/\partial X > 0$.

Using this notation, the deformation gradient is given by the scalar function

$$F(X, t) = \frac{\partial x}{\partial X},$$

Following the 1-D version of equation (1) in Goriely and Moulton (2011), we express this as the product

$$F = \alpha\,\gamma, \tag{2}$$

where α is the local size ratio between the current state and the zero stress state (the elastic stretch), and γ is the local size ratio between the zero stress state and the initial state (the growth stretch).

In Goriely and Moulton (2011), the constitutive relation for 1-D growth is assumed to take the form

$$\frac{\partial \gamma}{\partial t} = g(x, t), \tag{3}$$

where $g(x, t)$ is representative of the rate of growth and can depend on position and time. While (3) is useful at small deformations (*i.e.* when $F \approx 1$), it leads to inconsistencies if the current state is significantly different from the initial state.

In order to obtain an equivalent of (3) for large deformations, we firstly note that $g(x, t)$ should satisfy

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_{X_A}^{X_B} \gamma(X, t)\,\mathrm{d}X = \int_{x(X_A,t)}^{x(X_B,t)} g(x, t)\,\mathrm{d}x. \tag{4}$$

That is, $g(x, t)$ should be defined with reference to the current configuration, but it should measure the rate of change of the zero stress state of any collection of material particles.

It follows from (4) that the relationship between $\gamma(X, t)$ and $g(x, t)$ is given by

$$\frac{\mathrm{D}\gamma}{\mathrm{D}t} = F\,g(x, t), \tag{5}$$

where D/Dt is the material derivative. While this reduces to (3) when $F \equiv 1$, the large deformations involved in FPCL contraction indicate that (5) will be the more appropriate equation in this case.

2.2 Strain evolution

Now, we expect that the stress at any point in the body will be related to the difference between the zero stress state and the current state. In Goriely and Moulton (2011), for example, two plausible constitutive laws that relate the stress, σ, to the elastic stretch, α, are given, namely:

$$\sigma = E\,(\alpha - 1), \tag{6}$$

$$\sigma = \frac{E}{3}\left(\alpha^2 - \alpha^{-1}\right), \tag{7}$$

where E is the Young's modulus, and μ is the elastic modulus. The first of these is analogous to Hooke's law for a linear elastic material, while the second describes a nonlinear neo-Hookean relationship between stress and deformation.

In cases where the current state is close to the zero stress state, and hence $\alpha \approx 1$, these two expressions for stress will give very similar results. Indeed, there are other constitutive laws relating σ to α that are effectively equivalent when $\alpha \approx 1$. One important example is

$$\sigma = E\left(1 - \alpha^{-1}\right). \tag{8}$$

Like (6), this is analogous to Hooke's law for a linear elastic material, but using an Eulerian measure of strain instead of a pseudo-Lagrangian measure of strain, since

$$\alpha - 1 = e^L = \lim_{\Delta x \to 0} \frac{\Delta x - \Delta z}{\Delta z}, \text{ while } 1 - \alpha^{-1} = e^E = \lim_{\Delta x \to 0} \frac{\Delta x - \Delta z}{\Delta x}.$$

We find that (8) has an interesting advantage over (6) and (7) when the current state is relatively close to the zero stress state: the evolution of Eulerian strain in response to growth can neatly be expressed as an advection equation with a source term that is independent of e^E.

In order to see this, we substitute (2) into (5) to obtain

$$F \frac{\mathrm{D}}{\mathrm{D}t} \alpha^{-1} + \alpha^{-1} \frac{\mathrm{D}F}{\mathrm{D}t} = F\, g(x,\, t)\,. \tag{9}$$

Since $F^{-1}\, DF/Dt = \partial v/\partial x$ where v is the velocity and where $\partial v/\partial x$ is the velocity gradient, it follows that α^{-1} satisfies the equation

$$\frac{\partial}{\partial t}\alpha^{-1} + \frac{\partial}{\partial x}\left(v\, \alpha^{-1}\right) = g(x,\, t)\,, \tag{10}$$

from which we find that

$$\frac{\partial e^E}{\partial t} + \frac{\partial}{\partial x}\left(e^E\, v\right) = \frac{\partial v}{\partial x} - g(x,\, t)\,. \tag{11}$$

While it is also possible to obtain an evolution equation for e^L, the result is considerably less elegant. Since the two are effectively equivalent when the difference between the current state and the zero stress state is small, we prefer to use the Eulerian strain, e^E. Similarly, it could be argued that a nonlinear model like (7) would be more accurate, but experimental observations indicate that most of the change in size of a contracting FPCL is due to the permanent rearrangement of fibres by fibroblasts (Guidry and Grinnell, 1985). Hence, it is appropriate to use (11) and assume a linear relationship between stress and strain.

Our mechanical model for a morphoelastic solid with small effective strain thus takes the form

$$\frac{\partial e^E}{\partial t} + \frac{\partial}{\partial x}\left(e^E\, v\right) = \frac{\partial v}{\partial x} - g(x,\, t),$$

$$\sigma = E\, e^E.$$

In the following section, we adapt this to develop a mechanical model that can be used to describe the contraction of a collagen lattice by fibroblasts. In particular, we introduce a form for the growth function, $g(x,\, t)$, based on a plausible mechanism by which fibroblasts contract the lattice. This ultimately leads to a full model of FPCL contraction, which we present in Sec. 3.2.

3 Biological application: The contraction of fibroblast-populated collagen lattices

3.1 A cell-based contraction model

The contraction of free-floating or attached collagen lattices is associated with both reversible elastic deformation and permanent changes to the lattice that result from remodelling. In the experiments performed by Guidry and Grinnell (1985), lattices were contracted by fibroblasts and then allowed to undergo a partial re-expansion after reorganisation is inhibited. While faster than the contraction process, this re-expansion was far from instantaneous. These results indicate that the time scale associated with the viscous relaxation of collagen lattices should not be ignored; it is preferable for us to use a Kelvin-Voigt viscoelastic constitutive law to relate stress and effective strain instead of the purely elastic law described in Sec. 2.2.

Additionally, the large deformations associated with lattice contraction may cause significant changes to the elastic properties of the collagen: We expect the collagen to become stiffer as it becomes denser. Following Ramtani et al (2002) and Ramtani (2004), we therefore propose that the elastic modulus of the collagen should be a function of collagen density. Incorporating viscoelasticity and the changing elastic modulus (but ignoring the activity of cells), this means that an appropriate constitutive law for a collagen lattice will take the form

$$\sigma = \mathcal{E}(\rho)\, e^E + \mu \frac{\partial v}{\partial x}, \tag{12}$$

where $\mathcal{E}(\rho)$ is the elastic modulus, ρ is the collagen density and μ is the collagen viscosity.

Next, we develop an expression for $g(x,\, t)$ that reflects the reduction in size of the zero stress state due to the active rearrangement of the lattice by cells. Importantly, this expression is based on the microscopic mechanism of cells applying traction and rearranging the fibres of the collagen lattice.

Our approach is to imagine the collagen lattice as a 1-D body containing evenly-spaced fibroblasts. Each fibroblast effectively acts as a force dipole, pulling on the collagen to either side of it and compressing the collagen directly under it. We assume that the mechanism of permanent lattice contraction is that each fibroblast rearranges the collagen directly under itself so that the lattice becomes permanently compressed. Thus, $g(x,\, t)$ will be negative and directly proportional to the compressive strain in the lattice under the cells.

In the analysis that follows, we assume that the arrangement of fibroblasts is perfectly periodic, corresponding to a situation where the fibroblast density is constant throughout. This analysis can easily extended to the case where the fibroblast density is slowly varying by defining the average strain using a representative volume element containing a small number of cells. For simplicity and brevity, however, we restrict our attention to the perfectly periodic case.

Specifically, we assume that the FPCL consists of a periodic array of identical units, each of which contains a single cell at its centre as shown in Figure 4. Within each unit, we construct a local coordinate system so that the unit extends from $-l_u$ to l_u and the cell extends from $-l_c$ to l_c. Thus, the cell density, n, is proportional to l_c/l_u. We also assume that the zero stress state is uniform across the unit (*i.e.* that γ is constant), so it is convenient for us to define l_z to be half the length that the unit would occupy if it were stress-free throughout.

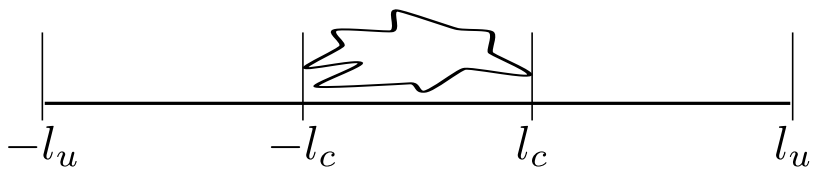

Fig. 4 A single cell within a periodic unit. The cell extends from $-l_c$ to l_c and the unit extends from $-l_u$ to l_u. The entire region has a uniform zero stress state and the length of the unit at zero stress is l_z.

In this situation, we find that the average effective strain throughout the unit is given by

$$e_{\text{avg}} = \frac{l_u - l_z}{l_u}. \tag{13}$$

This will be the strain measured in a representative volume element containing many cells and is therefore an appropriate measure of strain for us to use in the macroscopic model.

However, neither the stress nor the strain will be uniform on the scale of a single unit. As each cell pulls the lattice in towards itself, the collagen between $-l_u$ and $-l_c$ and the collagen between l_c and l_u will be under more tension (or less compression) than the collagen between $-l_c$ and l_c. More formally, each cell can be treated as a pair of body forces, both of magnitude τ_c; at $-l_c$ the cell pulls the collagen lattice to the right, while at l_c the cell pulls the lattice to the left. Neglecting inertial terms, the momentum balance equation within a single unit is then

$$\frac{\partial \sigma_u}{\partial x} = \tau_c \left(\delta(x - l_c) - \delta(x + l_c)\right),$$

where σ_u is the local stress and δ is the Dirac delta function. Integrating this equation with periodic boundary conditions, we find that

$$\sigma_u = \begin{cases} \sigma_{\text{out}}, & l_c < |x| < l_u, \\ \sigma_{\text{out}} - \tau_c, & |x| < l_c. \end{cases}$$

where σ_{out} represents the stress in the regions outside the cells.

While e_{avg} clearly represents the strain in a representative volume element, the appropriate formulation for the macroscopic stress is less obvious. It could be argued, for example, that a good measure of the macroscopic stress is the averaged stress,

$$\sigma_{\text{avg}} = \sigma_{\text{out}} - \frac{l_c\, \tau_c}{l_u},$$

since this is the weighted average value of $\sigma_u(x)$ throughout a representative volume element. However, this definition of macroscopic stress creates complications when applying macroscopic boundary conditions. Since each cell must apply a balanced pair of body forces to the lattice, it follows that either the boundary of the lattice occurs in a region where $\sigma = \sigma_{\text{out}}$, or there is an additional surface traction term that accounts for the effects of the end of the cell. In either case, we find that it is most convenient to express macroscopic boundary conditions in terms of σ_{out}: a free-floating lattice will have $\sigma_{\text{out}} = 0$ on the boundary, while a spring connected to the boundary (as in, for example, Marenzana et al, 2006) should be expressed as a relationship between σ_{out} and the displacement at the boundary.

Given that σ_{out} will be determined by the macroscopic force balance equation and e_{avg} will be governed by the strain evolution equation, we now wish to determine the strain in the cell region as a function of σ_{out} and e_{avg}. Assuming that viscous stresses are uniform (or negligible) in the neighbourhood of l_c and $-l_c$, we find that

$$\tau_c = \mathcal{E}(\rho)\,(e_{\text{out}} - e_{\text{cells}}), \tag{14}$$

where e_{out} is the strain outside the cell and e_{cells} is the strain within the region covered by the cell. We assume that the stress in the region outside the cell is governed by the constitutive law in (12), so that

$$\sigma_{\text{out}} = \mathcal{E}(\rho)\, e_{\text{out}} + \mu\, \frac{\partial v}{\partial x}\,. \tag{15}$$

Since the zero stress state is uniform throughout the unit, we find that

$$l_u - l_z = e_{\text{cells}}\, l_c + e_{\text{out}}\,(l_u - l_c)\,. \tag{16}$$

Thus, it follows that

$$e_{\text{cells}} = \frac{\sigma_{\text{out}} - \tau_c}{\mathcal{E}(\rho)}\,.$$

As e_{cells} represents the physical contraction experienced by the lattice directly under the cells, we assume that $g(x,\, t)$ is closely related to e_{cells}. Specifically, we assume that $g(x,\, t)$ is proportional to the amount that e_{cells} exceeds (*i.e.* is more negative than) a critical level of contraction, $-\hat{e}_{\text{crit}}$. Moreover, the rate of contraction of the zero stress will be proportional to the cell density, n, as this is representative of the proportion of the lattice that is accessible to the fibroblasts. Thus, we obtain the following constitutive law for $g(x,\, t)$:

$$g(x,\, t) = -\theta\, n \left(-\frac{\sigma_{\text{out}} - \tau_c}{\mathcal{E}(\rho)} - \hat{e}_{\text{crit}} \right)^{+}, \tag{17}$$

where θ is a constant of proportionality with dimensions of cell density^{-1} time^{-1} and $(\cdot)^{+}$ represents the positive part operator, so that $(X)^{+}$ is equal to zero when X is negative and X when X is positive. In the case where

$$-\frac{\sigma_{\text{out}} - \tau_c}{\mathcal{E}(\rho)} > \hat{e}_{\text{crit}}$$

throughout, it is possible to omit the positive part operator. Since this condition will almost always be fulfilled and the positive part operator can lead to numerical difficulties, we neglect the positive part operator in the rest of our analysis.

It should be noted that we have assumed that the zero stress state is always uniform within each cell and that this expression for $g(x,\, t)$ also gives a uniform rate of change to the zero stress state. However, it might be argued that the only region where the zero stress state is changing (due to the direct effect of fibroblast action) is the region where $-l_c < x < l_c$. Despite this, we expect that that cell motion (not included in this mechanical model) will mean that the contraction of the zero stress state is not confined to narrow regions. Moreover, experiments have been performed where cells were cultured on top of lattices instead of throughout lattices, and these still showed relatively uniform contraction (Grinnell and Lamke, 1984; Guidry and Grinnell, 1985, 1986). Hence, it is not unreasonable to assume that the changes to the zero stress state are evenly shared throughout each unit.

Now, it is also possible for us to rearrange (15) to give a constitutive relationship between σ_{out} and e_{avg}. Firstly, we note that a combination of (13) and (16) gives

$$e_{\text{avg}} = e_{\text{out}} + \frac{l_c}{l_u}\big(e_{\text{cells}} - e_{\text{out}}\big).$$

Using (14) and noting that l_c/l_u is proportional to the cell density, we find that

$$e_{\text{out}} = e_{\text{avg}} + \frac{n\,\sigma_c}{\mathcal{E}(\rho)},$$

where σ_c is defined as a rescaling of τ_c so that $n\,\sigma_c = l_c/l_u\,\tau_c$. Substituting into (15), this gives us our constitutive relationship between stress and strain:

$$\sigma_{\text{out}} = \mathcal{E}(\rho)\, e_{\text{avg}} + \mu\, \frac{\partial v}{\partial x} + n\,\sigma_c\,.$$

The $n\,\sigma_c$ term is analogous to the cell traction stress term found in other models of lattice contraction and dermal wound healing (Moon and Tranquillo, 1993; Tranquillo and Murray, 1992; Ferrenq et al, 1997; Tracqui et al, 1995). Indeed, by making σ_c a function of the lattice density and/or cell density (to incorporate the effects of crowding on traction stress, for example) we can recover identical expressions to those used in these earlier papers. However, we obtained the traction stress from the assumption that cells apply body forces to the collagen lattice rather than by asserting that the constitutive law should incorporate a traction stress. The consistency between these two treatments of cell traction gives us further confidence that both approaches are valid and useful.

Dropping the subscripts on e_{avg} and σ_{out}, we obtain the following set of equations to describe the mechanical behaviour of a contracting viscoelastic lattice:

$$\frac{\partial e}{\partial t} + \frac{\partial}{\partial x}(e\,v) = \frac{\partial v}{\partial x} + \theta\, n \left(-\frac{\sigma - n_l\,\sigma_c}{\mathcal{E}(\rho)} - \hat{e}_{\text{crit}} \right), \tag{18a}$$

$$\sigma = \mathcal{E}(\rho)\, e + \mu\, \frac{\partial v}{\partial x} + n\,\sigma_c\,, \tag{18b}$$

$$\frac{\partial \sigma}{\partial x} = 0\,, \tag{18c}$$

where $n_l = n\,l_u/l_c$ is the constant of proportionality that relates the cell density, n, to the cell length per unit length, l_c/l_u.

A full description of the mechanics of a contracting lattice will also require an initial condition on e and two boundary conditions, either on σ or v, that specify whether the ends of the lattice are tethered or stress-free. We now combine (18) with some assumptions about fibroblast motion and interactions in FPCLs to construct a full morphoelastic model of FPCL contraction.

3.2 The morphoelastic model of FPCL contraction

In the following we assume that the contraction of the lattice is due to the rearrangement of collagen fibrils by fibroblasts only, with the expectation that the results obtained using this assumption will be quantitatively similar to those obtained using a model that takes into account the rôle of protomyofibroblasts. Additionally, we assume that TGF-β is not present in the collagen lattice. As protomyofibroblasts require the presence of TGF-β in order to form differentiated myofibroblasts (Tomasek et al, 2002), we do not consider the activity of myofibroblast cells. While it has also been observed that fibroblasts in free-floating lattices become quiescent (Rosenfeldt and Grinnell, 2000) and a small fraction of these cells undergo apoptosis (cell death) (Fluck et al, 1998; Grinnell et al, 1999), we shall neglect these processes in our model.

Experimental data for the contraction of FPCLs are typically obtained by measuring the changing diameter (in the case of free-floating FPCLs) or thickness (in the case of attached FPCLs) of the lattice. The behaviour of such lattices can hence be modelled by considering one spatial dimension, which represents either the radius or thickness of the lattice. It should be noted that the mechanical model developed in Sec. 2 assumes one Cartesian spatial dimension and cannot be easily modified to obtain equations for the mechanics of radially symmetric lattice contraction. As a result, our model is best suited to attached, rather than free-floating, FPCLs. Nevertheless, as seen later in this section, our model is equally successful at fitting data obtained from free-floating as well as attached lattices. In the following derivation, we ignore the problems inherent in using a Cartesian model for free-floating FPCLs and assume that the same equations can be used to describe free-floating and attached FPCLs.

Following the conventions used in Sec.2.1, we use $x(X,\,t)$ to represent the position at time t of a particle initially located at X and $X(x,\,t)$ to represent the initial position of a particle at position x at time t. Since the lattice changes in size over time, the domain of interest can be expressed as $0 \le x \le l(t)$ or, equivalently, $0 \le X \le l_0$, where $l_0 = l(0)$. As illustrated in Fig. 5, the point $x = 0$ is taken to represent either the centre of a floating lattice or the fixed tethering point of an attached lattice. In either case, this point is fixed and we find that $x(0,\,t) = X(0,\,t) = 0$.

We define the Eulerian displacement, $u(x,\,t) = x - X(x,\,t)$, and the Eulerian displacement gradient, $w(x,\,t) = \partial u/\partial x$. Following the definitions of x and X, it follows that $u(x,\,0) = w(x,\,0) = 0$. Moreover, the fact that the centre or tethering point is fixed implies that $u(0,\,t) = 0$. Another important kinematic variable is the velocity, which is defined so that

$$v(x,\,t) = \frac{\mathrm{Du}}{\mathrm{Dt}} = \frac{\partial u}{\partial t} + v\,\frac{\partial u}{\partial x}\,.$$

Once again, the fixed centre/tethering point implies that $v(0,\,t) = 0$.

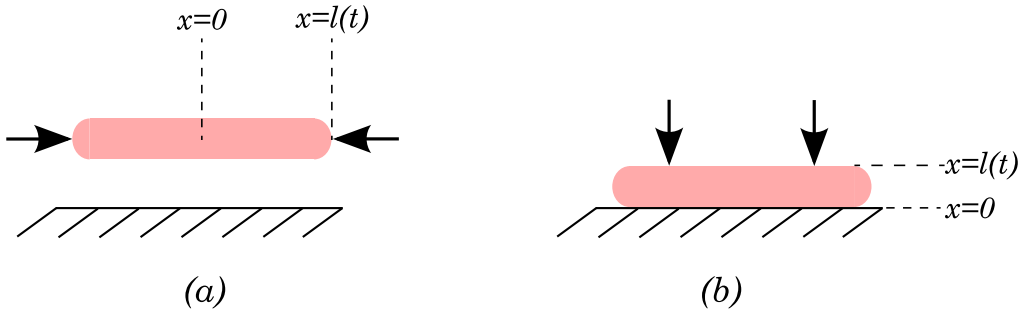

Fig. 5 Sketch of the different situations that can be described using our morphoelastic model. Here the dashed lines represent the substrate and the arrows represent the directions of contraction of the collagen lattice (pink). (a) In the case of a free-floating FPCL, we have symmetry about $x = 0$. (b) In the case of an attached FPCL, $x = 0$ represents the base of the lattice and $x = l(t)$ is the contracting edge. This situation can be thought of as the case of a lattice with a spring of infinite stiffness attached at $x = 0$.

Next, we introduce expressions for the densities of the ECM, $\rho(x,\, t)$, and the fibroblast cells, $n(x,\, t)$. Since Guidry and Grinnell (1985) observed that collagen synthesis and degradation are insignificant in FPCLs, we propose that contraction proceeds only by rearrangement of the collagen lattice. In other words, we assume that the net creation of each species is zero during the timescale of the experiment. Furthermore, for this study, we assume that there is no migration of fibroblasts. As both species are subjected to passive advection, this assumption allows us to use simple continuity equations for each of the species, which can be solved explicitly (Clement, 1978) to give

$$n(x,\, t) = n_0\,(1 - w)\,, \tag{19}$$

$$\rho(x,\, t) = \rho_0\,(1 - w)\,, \tag{20}$$

where n_0 and ρ_0 are the (spatially uniform) initial densities of fibroblast cells and the ECM, respectively.

We assume that the lattice is initially at rest ($e(0) = 0$), and that lattice stiffness increases with density, adopting the simple linear form

$$\mathcal{E}(\rho) = \mathcal{E}_0 + k\,\frac{\rho - \rho_0}{\rho_0}\,,$$

where $\mathcal{E}_0$ is the elastic modulus when $\rho = \rho_0$ and k is a positive constant. It should be noted that other forms have been proposed to describe the dependence of the elastic modulus on density. For example, Ramtani and coworkers describe the relationship between elastic modulus and density as a power law (Ramtani et al, 2002; Ramtani, 2004). In the absence of further data, however, we use a simple, linear law.

The case of a free-floating FPCL (Fig. 5a) or an attached FPCL (Fig. 5b) can be described by using the stress-free boundary condition

$$\sigma(l(t), t) = 0\,, \tag{21}$$

and the displacement at $x = l(t)$ can be obtained by noting that

$$\int_0^{l(t)} w(\xi, t)\mathrm{d}\xi = u(l(t), t) = l(t) - l_0\,.$$

As we shall see, $w(x,\, t)$ is spatially homogeneous in the problem that we analyse. In this situation, it follows that

$$l(t) = \frac{l_0}{1 - w}\,. \tag{22}$$

Taking the material derivative of $w(x,\,t)$ and rearranging, we obtain the following evolution equation for $w(x,\,t)$:

$$\frac{\partial w}{\partial t} + \frac{\partial}{\partial x}\,(w\,v) = \frac{\partial v}{\partial x}\,. \tag{23}$$

In conjunction with the equations for the evolution of the effective strain (18a), the constitutive law for the total stress (18b) and the force balance equation (18c), equations (19)-(23) comprise an Eulerian model for the contraction of collagen by fibroblasts. This system can be non-dimensionalised by introducing the dimensionless variables

$$x^* = \frac{x}{l_0}\,, \qquad l^* = \frac{l}{l_0}\,, \qquad t^* = \frac{t}{h}\,, \qquad v^* = \frac{v\,h}{l_0}\,, \qquad w^* = w\,,$$
$$e^* = e\,, \qquad n^* = \frac{n}{n_0}\,, \qquad \rho^* = \frac{\rho}{\rho_0}\,, \qquad \sigma^* = \frac{\sigma}{\mathcal{E}_0}\,, \qquad \mathcal{E}^* = \frac{\mathcal{E}}{\mathcal{E}_0}\,,$$

and the dimensionless constants

$$\bar{\mu} = \frac{\mu}{\mathcal{E}_0\,h}\,, \qquad \bar{k} = \frac{k}{\mathcal{E}_0}\,, \qquad \bar{\tau} = \frac{\sigma_c\,n_0}{\mathcal{E}_0}\,, \qquad \bar{\theta} = h\,\theta\,n_l\,, \qquad \bar{e}_{\rm crit} = \frac{\hat{e}_{\rm crit}\,n_0}{n_l}\,, \tag{24}$$

where, for ease of comparison with experiment (see later), we choose $h = 1$ hr.

As this Eulerian model has a moving boundary at $x = l(t)$, we now adopt a Lagrangian coordinate system to obtain a model for which the right hand boundary is fixed. Conveniently, we find that transforming our equations to Lagrangian variables is equivalent to converting to characteristic variables: we ultimately obtain a system where the only differentiation is with respect to time. In the derivation that follows, it is important to distinguish between partial time derivatives with the Eulerian spatial coordinate held fixed and partial time derivatives with the Lagrangian spatial coordinate held fixed. Hence, we introduce the 'Lagrangian time variable', T, and we transform the entire problem from $(x,\,t)$ coordinates to $(X,\,T)$ coordinates.

Firstly, we define the Lagrangian displacement, $U(X,\,T) = x(X,\,T) - X$, and the Lagrangian velocity, $V(X,\,T) = \partial U/\partial T$. These are both identical to $u(x,\,t)$ and $v(x,\,t)$ with just a transformation of the independent variables. Now, we define the Lagrangian displacement gradient, $W(X,\,T) = \partial U/\partial X$, which is different from w since differentiation with respect to x is different from differentiation with respect to X. As described in Appendix A, however, the definitions of W and V lead to the identities

$$\frac{\partial}{\partial x} \equiv \frac{1}{1+W}\,\frac{\partial}{\partial X}\,, \tag{25}$$
$$\frac{\partial}{\partial t} \equiv \frac{\partial}{\partial T} - \frac{V}{1+W}\,\frac{\partial}{\partial X}\,, \tag{26}$$

and hence $w = W/(1+W)$. Based on these identities, it follows that

$$\frac{\partial \phi}{\partial t} + \frac{\partial}{\partial x}\,(\phi\,v) = \frac{1}{1+W}\,\frac{\partial \Phi}{\partial T}\,, \tag{27}$$

where $\Phi = \phi\,(1+W)$ and where ϕ is a general scalar quantity. This motivates the introduction of Lagrangian variables $N = n\,(1+W)$, $R = \rho\,(1+W)$, $S = \sigma\,(1+W)$ and $E = e\,(1+W)$, so that all of the advective time derivatives simply become partial time derivatives. From (19) and (20), we obtain the following exact expressions for the scaled densities N and R:

$$N(X,\,T) \equiv 1\,, \qquad R(X,\,T) \equiv 1\,,$$

while from (23), (18a), (18b) and (18c) we obtain the equations

$$\begin{aligned}
\frac{\partial W}{\partial T} &= \frac{\partial V}{\partial X}\,, \\
\frac{\partial E}{\partial T} &= \frac{\partial V}{\partial X} + N\,\bar{\theta}\left(-\frac{\frac{n_0}{n_l}\frac{S}{1+W} - \bar{\tau}}{\mathscr{E}(W)} - \bar{e}_{\mathrm{crit}}\right)\,, \\
S(X,\,T) &= \mathscr{E}(W)\,E + \bar{\mu}\,\frac{\partial V}{\partial X} + \bar{\tau}\,N\,, \\
\frac{\partial S}{\partial X} &= 0\,,
\end{aligned}$$

where $\mathscr{E}(W)$ is

$$\mathscr{E}(W) = 1 - \bar{k} + \frac{\bar{k}}{1+W}\,. \tag{28}$$

Using the stress-free boundary condition (21), it follows that

$$S(X,\,T) \equiv 0\,.$$

As W is independent of X, it follows that w is independent of x and hence (22) is appropriate. Moreover, the fact that W and E are both independent of X means that we can rewrite our system of PDEs as a pair of coupled ODEs for the displacement gradient and strain:

$$\frac{\mathrm{d}W}{\mathrm{d}T} = -\frac{1}{\bar{\mu}}\left(\mathscr{E}(W)\,E + \bar{\tau}\,N\right)\,, \tag{29}$$

$$\frac{\mathrm{d}E}{\mathrm{d}T} = \frac{\mathrm{d}W}{\mathrm{d}T} + N\,\bar{\theta}\left(\frac{\bar{\tau}}{\mathscr{E}(W)} - \bar{e}_{\mathrm{crit}}\right)\,. \tag{30}$$

This two-component model has five dimensionless free parameters: $\bar{\mu}$, $\bar{k}$, $\bar{\tau}$, $\bar{e}_{\mathrm{crit}}$ and $\bar{\theta}$.

In (29)-(30), the 'normal' contracting situation is described by setting $N(X,T) \equiv 1$, while the situation in which lattice reorganisation is inhibited by the addition of cytochalasin D at some time, T_{inh}, can be described by taking

$$N(X,T) = \begin{cases} 1\,, & T \le T_{\mathrm{inh}}\,, \\ 0\,, & T > T_{\mathrm{inh}}\,. \end{cases} \tag{31}$$

On non-dimensionalising (22) and converting to Lagrangian variables, we find

$$l(t) = 1 + W(T)\,. \tag{32}$$

Thus, our transformed ODE model gives easy access to the evolving length of the lattice, the physical variable variable most easily observed in experiments.

3.3 Comparison with experimental data

We now compare computational results for our model, obtained by numerically integrating (29)-(30), with previously obtained experimental data for contracting collagen lattices. We shall consider experiments by Bell et al (1979), Talas et al (1997) and Feng et al (2003), which were performed using free-floating FPCLs, as well as an experiment by Guidry and Grinnell (1985), which was performed using an attached FPCL and in which the lattice reorganisation was halted at various times.

We qualitatively describe the experimentally observed behaviour of the FPCL in each case by varying the parameter set $\left\{\bar{\mu}, \bar{\tau}, \bar{k}, \bar{e}_{\mathrm{crit}}, \bar{\theta}\right\}$ using the MATLAB subroutine `fminsearch`, such that we minimise the difference between the experimental values for the fraction of the original length (diameter or thickness) and the values of $l(t)$, given by (32) at the corresponding measurement times.

These parameter values can be used to infer the viscosity and initial stiffness of the gel in each experiment and this can be compared with results from rheological experiments. Firstly, we note that equation (18b) implies that the initial cell traction stress, σ_0, is given by

$$\sigma_0 = \sigma_c \, n_0.$$

Rearranging (24), we therefore see that the initial stiffness of the lattice is

$$\mathcal{E}_0 = \frac{\sigma_0}{\bar{\tau}}\,. \tag{33}$$

Now, various research groups have used cell-populated lattices attached to force monitors in order to determine the contraction forces that cells are capable of exerting (Eastwood et al, 1996; Kolodney and Wysolmerski, 1992; Wakatsuki et al, 2000). Their results can be used to determine the initial cell traction stress, since the total cell traction force will be the product of the contraction force per cell and the number of cells and force can be converted to stress by dividing by the cross-sectional area. Thus,

$$\sigma_0 = \frac{F_{\text{cell}}\, C}{A}, \tag{34}$$

where F_{cell} is the force applied per cell, C is the number of cells in the lattice, and A is the cross-sectional area of the lattice.

However, a wide range of results for F_{cell} have been reported, ranging from from 0.1nN/cell (Eastwood et al, 1996) to 1000nN/cell (Wakatsuki et al, 2000). Here, we will use the result from Kolodney and Wysolmerski (1992), $F_{\text{cell}} = 500n$N/cell, which was obtained using fibroblast-populated matrices similar to those used in the experiments by Bell et al (1979), Talas et al (1997), Feng et al (2003) and Guidry and Grinnell (1985). Combining this value of F_{cell} with experimentally-reported values of C and A and the value of $\bar{\tau}$ obtained from model fitting, we can use (33) and (34) to recover values for the initial stiffness, $\mathcal{E}_0$. These are reported below in Table 1.

We also note from (24) that the viscosity of the lattice is given by

$$\mu = \bar{\mu}\, \mathcal{E}_0\, h\,. \tag{35}$$

Thus, for any (free-floating or attached) FPCL experiment in which the initial cross-sectional area and total number of fibroblast cells is known, we can find a parameter set for our model that yields the best fit to the experimental data and use it to estimate the stiffness and viscosity of the lattice from (33) and (35).

We begin by considering the experiments performed by Bell et al (1979), which yielded the first reported observation of FPCL contraction. In these experiments, different numbers of fibroblast cells were embedded in free-floating collagen lattices of varying ECM density, which contained fetal bovine serum. The fraction of the original length was then measured at various times over the course of several days. In the following, we consider their set of results that were obtained using 7.5×10^6 fibroblast cells embedded in a lattice of initial diameter 53mm. It was observed that this lattice subsequently contracted to around 10% of its original diameter in around 9 days. Using our model, we find that the best possible fit to the experimental data is obtained by using the parameter values $\bar{\mu} = 10.614$, $\bar{\tau} = 0.636$, $\bar{k} = 6.87 \times 10^{-2}$, $\bar{e}_{\text{crit}} = 0.339$ and $\bar{\theta} = 1.71 \times 10^{-2}$ (see Fig. 6a). The predicted values for the initial stiffness of the lattice and the predicted viscosity for this case (and for the subsequent fits) are shown in Table 1, and a comparison of these values with previously obtained experimental values is presented later.

We next consider the experiments of Talas et al (1997), in which the difference between the effects of normal and recessive dystrophic epidermolysis bullosa fibroblasts were investigated. For the case of normal fibroblasts, 2.5×10^5 cells were embedded in a lattice with a diameter of approximately 2.18cm. It was observed that the lattice contracted to around 37% of its original area in around 7 days. We find that the best possible fit to the experimental data is obtained by using the parameter values $\bar{\mu} = 6.47$, $\bar{\tau} = 0.224$, $\bar{k} = 9.56 \times 10^{-2}$, $\bar{e}_{\text{crit}} = 0.173$ and $\bar{\theta} = 2.71 \times 10^{-2}$ (see Fig. 6b).

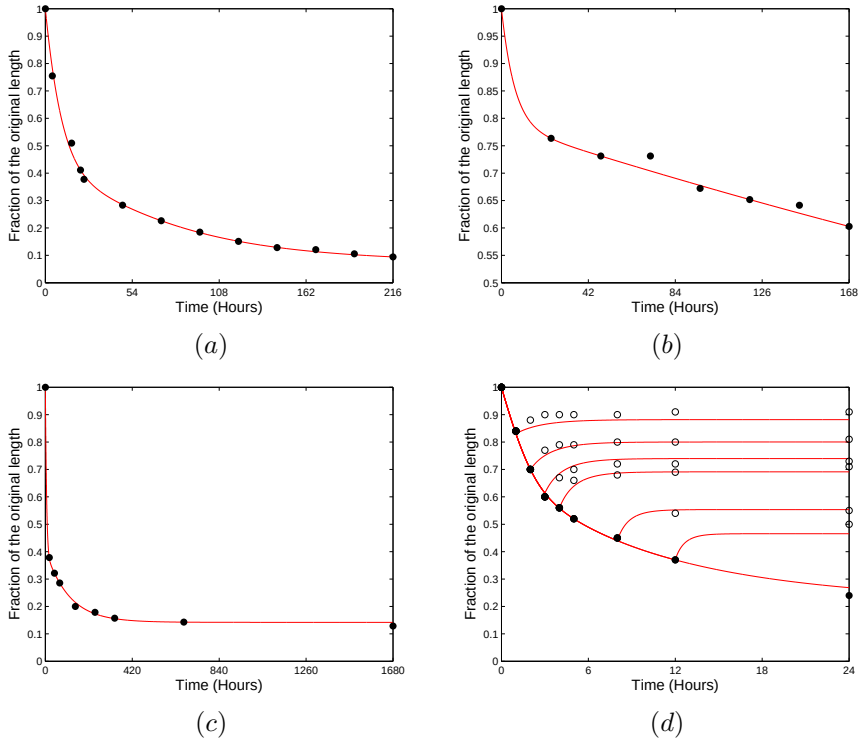

Fig. 6 Numerical results for $l(t)$ (32) obtained by running simulations of the system (29)-(30) with various parameter values (denoted by red solid lines) superimposed with data for the fraction of the original length (diameter or thickness) from different experiments (denoted by dark circles). (a) Results obtained with parameter values $\bar{\mu} = 10.614$, $\bar{\tau} = 0.636$, $\bar{k} = 6.87 \times 10^{-2}$, $\bar{e}_{\text{crit}} = 0.339$ and $\bar{\theta} = 1.71 \times 10^{-2}$ superimposed with data from Bell et al (1979). (b) Results obtained with parameter values $\bar{\mu} = 6.47$, $\bar{\tau} = 0.224$, $\bar{k} = 9.56 \times 10^{-2}$, $\bar{e}_{\text{crit}} = 0.173$ and $\bar{\theta} = 2.71 \times 10^{-2}$ superimposed with data from Talas et al (1997). (c) Results obtained with parameter values $\bar{\mu} = 7.57$, $\bar{\tau} = 0.719$, $\bar{k} = 0.139$, $\bar{e}_{\text{crit}} = 0.389$ and $\bar{\theta} = 1.4 \times 10^{-2}$ superimposed with data from Feng et al (2003). (d) Results obtained with parameter values $\bar{\mu} = 2.44$, $\bar{\tau} = 0.445$, $\bar{k} = 1.939$, $\bar{e}_{\text{crit}} = 5.49 \times 10^{-2}$ and $\bar{\theta} = 0.366$ superimposed with data from Guidry and Grinnell (1985).

Next, we consider the experiments of Feng et al (2003), in which the mechanical properties of contracted collagen gels were investigated. Here, 2.5×10^6 fibroblast cells were embedded within a lattice of initial diameter 100mm. It was observed that the lattice contracted to around 13% of its original diameter by the end of the experiment, with most of the contraction occurring within the first few days. In this case, the best possible fit to the experimental data is obtained by using the parameter values $\bar{\mu} = 7.57$, $\bar{\tau} = 0.719$, $\bar{k} = 0.139$, $\bar{e}_{\text{crit}} = 0.389$ and $\bar{\theta} = 1.4 \times 10^{-2}$ (see Fig. 6c).

Finally, we consider the results of Guidry and Grinnell (1985), obtained when 10^5 fibroblasts were placed on an attached lattice of diameter 12mm. It was observed that this lattice contracted to about 24% of its original thickness in around 1 day. As the presence of protomyofibroblasts was not reported in these experiments, it is likely that the observed contraction is primarily due to the activity of fibroblasts and hence our model can be used to approximate this behaviour. We simulate the effect of adding cytochalasin D by allowing $N(X, T)$ to take the form (31). Results obtained using a set of parameters that gave an optimally close fit to the experimental data are shown in Fig. 6d. We find that in addition to the contraction of this gel, our model can capture the observed partial re-expansion. This can be seen by taking the parameters $\bar{\mu} = 2.44$, $\bar{\tau} = 0.445$, $\bar{k} = 1.939$, $\bar{e}_{\text{crit}} = 5.49 \times 10^{-2}$ and $\bar{\theta} = 0.366$ (see Fig. 6d).

Experiment	Number of cells	Initial gel diameter (cm)	Predicted $\mathcal{E}_0$ (Pa)	Predicted μ (Pa sec)
Bell et al (1979)	7.5×10^6	5.3	2.67×10^3	1.02×10^8
Talas et al (1997)	2.5×10^5	2.18	1.49×10^3	3.47×10^7
Feng et al (2003)	2.5×10^6	10	2.21×10^2	6.03×10^6
Guidry and Grinnell (1985)	1.0×10^5	1.2	9.93×10^2	8.74×10^6

Table 1 Summary of the experimental values for the number of fibroblast cells in the collagen gel and the initial gel diameter, as well as the predicted values for the initial stiffness and viscosity of the gel.

In Table 1, we present a set of estimates for the initial stiffness and viscosity of the lattice for each of the four experiments considered above. We see that the predicted values for the initial stiffness for the gel range from 2.21×10^2–2.67×10^3Pa. This is in agreement with the experimental results of Knapp et al (1997), who estimated the shear modulus of a collagen gel to be 1.185×10^3Pa. We note that there is a large range of experimental values for the stiffness of a collagen gel. For instance, in the experiment by Chapuis and Agache (1992), the stiffness modulus of a collagen lattice was measured to be in the range 6×10^4–10^6Pa. The reasons for this include the fact that the gels in these experiments were seeded with fibroblasts, which reorganise the lattices and can thus cause their stiffness to change rapidly, prior to measurement. We also see from Table 1 that the predicted values for the viscosities of the gel range from 6.03×10^6–1.02×10^8Pa sec. This is once again in agreement with the experimental results of Knapp et al (1997), where the shear viscosity of a collagen gel was found to be 1.24×10^7Pa sec. We therefore find that our model provides reasonable estimates of the initial stiffness and the viscosity of the gel in each case.

4 Discussion

In this work, we develop a 1-D theory of morphoelasticity, which takes into account the continual changes to the zero stress state of a material in response to a prescribed rate of growth. By making certain assumptions about the dependence of growth on other physical parameters, a changing zero stress state can be used to model a range of biological processes that involve internal remodelling of a tissue's mechanical structure. In order to demonstrate the flexibility and versatility of this theory, we present a biological application: the contraction of FPCLs. While some mathematical models of this process have been developed, they cannot be used to explain the permanent contraction that persists even if reorganisation is inhibited by killing the fibroblasts or by otherwise preventing them from altering the lattice. However, this phenomenon can easily be explained and investigated using our morphoelastic model.

Our model describes the evolution of the length of an attached or free-floating collagen lattice as it is contracted by fibroblasts. Comparisons between numerical solutions of the model and previously obtained experimental data indicate that our model closely approximates the observed behaviour of FPCLs. Using the parameter values that provide the best fit to the data, we were also able to predict values for the stiffness and viscosity of the gel in each case. We find that our predictions are consistent with previously measured values from rheological tests. We note that this approach may provide a guideline for devising new experiments for the study of FPCLs.

There are a number of features of the morphoelastic model developed in Sec. 2 and its application to contracting FPCLs that are worthy of further consideration. Firstly, while it is more conventional to use Lagrangian coordinates in solid mechanics (see, for example, Roberts, 1994, and Gonzalez and Stuart, 2008), in this work we develop an *Eulerian* framework for stress and strain. In describing situations in which the zero stress state does not evolve, the use of Lagrangian coordinates will lead to equations with fixed boundaries and a useful variational structure. However, as described in Yavari (2010), the introduction of a changing zero stress state leads to new terms that need to be incorporated into the energy balance equation, and these can only be obtained by careful attention to the geometry of the full problem. Thus, Lagrangian coordinates are

not obviously the best choice in morphoelastic problems. Moreover, Eulerian coordinates have a distinct advantage in the case where the zero stress state is close to the current state, but might be quite different from the initial state. In this case, using Eulerian coordinates makes it possible to apply aspects of small deformation theory, such as the linear stress-strain relationship. The use of Lagrangian coordinates would make it far more difficult to exploit such linear approximations, and would furthermore require us to carefully consider the difference between the true Eulerian (Cauchy) stress, and the Lagrangian (Piola-Kirchoff) stress.

Although we develop our model in Eulerian coordinates, we ultimately revert to Lagrangian coordinates in order to avoid the problems inherent in a system with a moving boundary. The lack of diffusion in our simplified model allows us to exploit the fact that a conversion to Lagrangian coordinates corresponds to a conversion to characteristic variables, and we are thus able to simplify our model to a system of ordinary differential equations. In a more general problem, it would be more appropriate to retain the Eulerian framework and rescale the moving boundary with $l(t)$ to convert it to a fixed boundary problem (Crank, 1957).

Indeed, there are several obvious ways of extending the model presented here that would require this sort of approach. For example, we could consider a case where the initial cell density profile, $n(x, 0)$ is nonuniform, and/or the case where cells undergo random motion as well as advection with the contracting lattice. While more complicated models like these would be more faithful to the true physical mechanisms of lattice contraction, the fact that the simple model presented in this paper yields a good fit with experimental data indicates that additional complexity may not be needed.

An interesting variation to the FPCL experiment involves attaching force measurement devices to the collagen lattice (Kolodney and Wysolmerski, 1992; Brown et al, 1996; Marenzana et al, 2006) in order to measure the total contractile force exerted by the cells. In each case, the force measurement device provides a finite resistance to the contraction of the lattice, and so the contraction process can be described using a caricature model of an FPCL with springs attached to the contracting edge. Mathematically, the relevant change to our model would be achieved by replacing the stress-free boundary condition in (21) with a boundary condition that relates the stress at $x = l(t)$ to the displacement at that boundary.

A further complication in modelling the attachment of force measurement devices is that the increased elastic tension in this case could lead fibroblasts to modulate into protomyofibroblasts (Tomasek et al, 2002), and it may also be necessary to make the cell-associated stress, σ_c, a function of elastic stress in order to deal with the increased stress from these cells. This modulation of fibroblasts into protomyofibroblasts can also occur in stress-relaxed FPCLs (Tomasek et al, 1992), which causes the lattice to contract rapidly when released. In the additional presence of TGF-β, protomyofibroblasts will further modulate into myofibroblasts (Tomasek et al, 2002; Gabbiani, 2003; Desmoulière et al, 2005, 1993). In order to capture the effect of these highly contractile cells, our model could be modified via the addition of a new species for protomyofibroblasts (or myofibroblasts), a new chemical species, TGF-β, and including a conversion term in the equation for the fibroblasts. Such a model could potentially be used to describe all commonly used types of FPCLs.

The morphoelastic approach detailed in this paper, where an evolution law is developed for the effective strain but a conventional stress-strain relationship is used, could potentially be applied to several other biological processes including soft tissue growth, arterial remodelling, aneurysm development, morphogenesis, initiation of stretch marks and solid tumour growth. Another important potential application of this theory is the development of a mechanochemical model of dermal wound healing. Most previous models of wound healing applied the assumption that human skin can behave as a viscoelastic material (Silver et al, 2003), and incorporated a viscoelastic constitutive law. However, as the time scale of viscous relaxation in the skin is much shorter than the time scale of wound healing, it is doubtful that this effect is responsible for the apparent 'flow' associated with wound healing. Indeed, the permanent contraction observed in some pathological scars instead suggests that morphoelastic changes to the underlying extracellular matrix are particularly significant during the wound healing process. Furthermore, it can be shown that the use of a viscoelastic constitutive law can lead to unphysical results such as oscillations in displacement

(Hall, 2008). A compartmental model of wound healing that considers the complementary rôles of transforming growth factor-β and tissue tension, and which incorporates morphoelasticity rather than viscoelasticity, was developed by Murphy et al (2011).

Although our morphoelastic model closely captures the important features of the permanent contraction of FPCLs, the approach used here can only truly be justified in 1-D Cartesian coordinates. Hence, our model is most appropriate for attached lattices, but it cannot provide a complete description of cylindrical, free-floating lattices. While cylindrical and spherical symmetries can be incorporated into reaction-diffusion equations with only minor adjustments, the changes to elasticity theory are more significant. For example, a cylindrical formulation of floating FPCL contraction would need to distinguish between hoop stresses and radial stresses, and we would need to take into account the possibility of residual stresses associated with the morphoelastic changes.

Unfortunately, there remains a lot of ambiguity surrounding the precise specification of 3D laws for the evolution of the zero stress state. As noted in Ambrosi et al (2011), there has been little success in using thermodynamic arguments to develop general frameworks for morphoelasticity. Additionally, there are uniqueness issues surrounding the multiplicative decomposition of the deformation gradient and it is difficult to ensure that any phenomenological evolution law is appropriately observer-independent. Although some effort has gone into resolving these problems (especially in the engineering literature – see, for example, Lubarda, 2001 and Xiao et al, 2006), the resulting models are often densely expressed and difficult to apply to biological morphoelasticity. As noted in Hall (2008), some progress can be made by considering possible three-dimensional generalisations of (4), but there is a need for further work in this area.

Despite these challenges, the morphoelastic framework presented here has significant advantages over other approaches to describing biological remodelling. In particular, phenomena like the permanent contraction of a collagen lattice, which our model can describe, are inaccessible to classical Kelvin-Voigt models and are very different from the stress-induced contraction observed in Maxwell models. By explicitly considering the evolving zero stress state and defining strain in terms of the difference between the current state and the zero stress state, we find that we do not need to make large changes to our model in order to incorporate morphoelasticity. Indeed, we can even use conventional constitutive laws to relate the stress to the strain. The 1-D morphoelastic framework described in this paper provides us with a simple and meaningful technique to the describe some of the intricacies of FPCL contraction and biological remodelling, and it has the potential to be used in a wide range of other areas.

A Derivation of the spatial and temporal transformations between coordinate systems

The Eulerian displacement gradient is the derivative of $u(x,\, t)$, and can be thus written as

$$w = \frac{\partial}{\partial x}\,(x - X) = 1 - \frac{\partial X}{\partial x}\,.$$

Similarly, the Lagrangian displacement gradient can be written as

$$W(X,\, T) = \frac{\partial}{\partial X}\,(x - X) = \frac{1}{1-w} - 1\,.$$

We thus have the relation

$$1 + W = \frac{1}{1-w}\,. \tag{36}$$

Using the chain rule, the Eulerian spatial derivative is

$$\frac{\partial}{\partial x} \equiv \frac{\partial X}{\partial x}\frac{\partial}{\partial X} + \frac{\partial T}{\partial x}\frac{\partial}{\partial T}\,.$$

The derivative $\partial T/\partial x$ is equal to zero, and we can expand X using

$$X = x - \int_0^x w(\xi, t)\mathrm{d}\xi\,.$$

This, in conjunction with (36), gives us the following transformation for the spatial derivative

$$\frac{\partial}{\partial x} \equiv \frac{1}{1+W}\frac{\partial}{\partial X}\,. \tag{37}$$

We similarly use the chain rule for the temporal derivative,

$$\frac{\partial}{\partial t} \equiv \frac{\partial X}{\partial t}\frac{\partial}{\partial X} + \frac{\partial T}{\partial t}\frac{\partial}{\partial T}\,.$$

The derivative $\partial T/\partial t$ is equal to one, and so we have

$$\frac{\partial}{\partial t} \equiv \frac{\partial}{\partial t}\left(\int_0^x 1 - w(\xi,t)\,\mathrm{d}\xi\right)\frac{\partial}{\partial X} + \frac{\partial}{\partial T}\,.$$

Using (23), we have

$$\frac{\partial}{\partial t} \equiv \int_0^x \frac{\partial}{\partial \xi}\left(w(\xi,t)\,v(\xi,t) - v(\xi,t)\right)\,\mathrm{d}\xi\frac{\partial}{\partial X} + \frac{\partial}{\partial T}\,,$$

which, on using (36) and the fact that $V \equiv v$, gives us the following transformation for the temporal derivative

$$\frac{\partial}{\partial t} \equiv \frac{\partial}{\partial T} - \frac{V}{1+W}\frac{\partial}{\partial X}\,. \tag{38}$$

Equations (37) and (38) can be combined with (23) to obtain the following relation between the Lagrangian displacement gradient and velocity:

$$\frac{\partial W}{\partial T} = \frac{\partial V}{\partial X}\,. \tag{39}$$

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