Stability bounds of a delay visco-elastic rheological model with substrate friction

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Abstract
Cells and tissues exhibit sustained oscillatory deformations during remodelling, migration or embryogenesis. Although it has been shown that these oscillations correlate with intracellular biochemical signalling, the role of these oscillations is as yet unclear, and whether they may trigger drastic cell reorganisation events or instabilities remains unknown. Here, we present a rheological model that incorporates elastic, viscous and frictional components, and that is able to generate oscillatory response through a delay adaptive process of the rest-length. We analyse its stability as a function of the model parameters and deduce analytical bounds of the stable domain. While increasing values of the delay and remodelling rate render the model unstable, we also show that increasing friction with the substrate destabilises the oscillatory response. This fact was unexpected and still needs to be verified experimentally. Furthermore, we numerically verify that the extension of the model with non-linear deformation measures is able to generate sustained oscillations converging towards a limit cycle. We interpret this sustained regime in terms of non-linear time varying stiffness parameters that alternate between stable and unstable regions of the linear model. We also note that this limit cycle is not present in the linear model. We study the phase diagram and the bifurcations of the non-linear model, based on our conclusions on the linear one. Such dynamic analysis of the delay visco-elastic model in the presence of friction is absent in the literature for both linear and non-linear rheologies. Our work also shows how

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increasing values of some parameters such as delay and friction decrease its stability, while other parameters such as stiffness stabilise the oscillatory response.

**Keywords** Oscillations · Delay differential equations · Visco-elasticity · Friction · Stability · Rheology · Cells

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1 Introduction

Oscillatory cell deformations are ubiquitous and have been quantified in vitro (Petrolli et al. 2019; Peyret et al. 2019) and in vivo, for instance in the segmented clock of mice (Yoshioka-Kobayashi et al. 2020), during *Drosophila* fly dorsal closure (Solon et al. 2009), cell intercalation in morphogenesis (Tao et al. 2019), or wound healing (Roldán et al. 2019). During apical constriction tissue oscillations have been associated with oscillatory calcium levels (Christodoulou and Skourides 2015; Suzuki et al. 2017), and in Kaouri et al. (2019) a mechanism of two-way coupling between these two types of oscillations was proposed. In other works, authors assume that the oscillatory response is due to signalling delays (Petrungaro et al. 2019) or myosin concentration fluctuations (Dierkes et al. 2014). In these references, it is shown that Ca$^{2+}$ and myosin precedes cellular strains in each oscillation. Here, we present a rheological model that without resorting to transport fields, explicitly incorporates the delay between the cell length adaptation and the current stretch.

Time delay has been included in numerous models in biology, with applications in biochemical negative feedback (Lapytsko and Schaber 2016), cell growth and division (Alarcón et al. 2014; Gyllenberg and Heijmans 1987), or cell maturation (Getto et al. 2019), but are less common in biomechanics. In our case the delay aims at mimicking the measured time-lag between the chemical signalling and the internal mechanical remodelling in the cell, as measured in different systems. These may include wound healing (Zulueta-Coarasa and Fernandez-Gonzalez 2018) and dorsal closure (Dierkes et al. 2014) in *Drosophila* fly, or other developmental processes (Christodoulou and Skourides 2015; Kaouri et al. 2019; Suzuki et al. 2017). Time delay in these cases may be from the order of seconds to a few minutes.

In our model, we introduce this delay in an evolution law of the cell or tissue rest-length. Such models with varying rest-length have been applied to stress relaxation (Khalilgharibi et al. 2019), morphogenesis (Clément et al. 2017), cortical mechanics (Doubrovinski et al. 2017), or endocytosis (Cavanaugh et al. 2020). They have the advantage of including a measurable quantity, the rest-length (Wyatt et al. 2020), and also furnishing the observed visco-elastic response. Here, we will adapt these models and include the delay response in conjunction with frictional or adhesive forces from the environment or substrate.

We focus on a generic system described by single values of length and rest-length at each time-step. Our model may be extended to multicellular systems where different lengths and sizes may oscillate asynchronously. Such multicellular extensions of one-
dimensional models have been presented in other works for other frictionless systems (Muñoz et al. 2018). Here, we will restrict our attention to the stability analysis of single cells, using linear and non-linear versions of our rheological model. We note that the latter has been motivated by the experimental observation of persistent oscillations. In our model, non-decaying stable oscillations are only achieved when a non-linear model is adopted.

Our visco-elastic model mimics the standard linear solid, but expressed in terms of delay rest-length changes, which provides the oscillatory character of the deformation. The stability of such system has been described in Muñoz et al. (2018) or in Borja et al. (2021) for planar frictionless dynamics of monolayers. Here, we extend such analysis to a frictional substrate, and deduce the stability conditions as a function of viscous, stiffness and friction parameters.

The stability analysis is usually carried out through the inspection of the characteristic equation (Asl and Ulsoy 2003; Smith 2011), or semi-discretisation methods (Insperger and Stépán 2002; Sykora et al. 2019). We resort to the former method, and by analysing the associated Lambert function (Shinozaki and Mori 2006; Corless et al. 1996), we deduce strict and simple bounds of the stability region. We compare our analysis with some numerical solutions of the Delay Differential Equations (DDEs), and describe the oscillatory regimes and potential presence of bifurcation points for the linear and non-linear models. The deduction of such bounds, and the analysis of the stability of visco-elastic rheology with delay was absent in the literature, to the best of our knowledge.

The article is organised as follows. We describe the visco-elastic model in Sect. 2 together with the delay evolution law of the rest-length. In Sect. 3 the stability of a linear model is analysed, and some bounds as a function of the model parameters are given. A non-linear extension is presented in Sect. 4, which is solved numerically and is analysed with the help of the results obtained in the linearised model. Our findings are finally discussed in the Conclusions section.

2 Visco-elastic model with delay

We consider a material rheology that mimics the standard linear solid model: a purely elastic stress $\sigma^e$ in parallel with a visco-elastic stress $\sigma^v$. Figure 1 shows schematically the two branches. We assume a one-dimensional domain $D = [0, l(t)]$, with $l(t)$ a time dependent apparent (measurable) length of the domain.

The total stress in the solid $\sigma$ is given by the sum of elastic and visco-elastic contributions,

$$\sigma = \sigma^e + \sigma^v,$$

where each stress component is given by

$$\sigma^e = k_1 \varepsilon^e(l(t), l_0), \quad \sigma^v = k_2 \varepsilon^v(l(t), L(t))$$
Fig. 1 Schematic view of one-dimensional model, illustrating both elastic and visco-elastic branches with dissipative friction at the substrate.

with \( k_1 \) and \( k_2 \) the associated stiffness parameters. The deformation measures \( \varepsilon^e(l(t), l_0) \) and \( \varepsilon^v(l(t), L(t)) \) will be detailed in the next sections for the linear and non-linear models. As yet we mention that they depend, in addition to \( l(t) \), on the initial length \( l_0 = l(0) \) and the rest-length \( L(t) \) of the visco-elastic branch. This rest-length can be interpreted as an internal variable, whose evolution mimics the viscous response of Maxwell models (Muñoz and Albo 2013). In our model, the rest-length \( L(t) \) changes according to the following evolution law

\[
\dot{L}(t) = \gamma(l(t - \tau) - L(t - \tau)), \quad t > 0.
\]

where a superimposed dot denotes time derivatives, i.e. \( \dot{\bullet} = \frac{d\bullet}{dt} \). Parameter \( \gamma > 0 \) is the remodelling rate, which measures the rate at which the cell adapts its length to the difference \( l(t - \tau) - L(t - \tau) \). As pointed out in the introduction, this delay parameter \( \tau \geq 0 \) represents the retardation in the active response of cells (change in rest-length) due to changes in their sensed kinematics (deformations).

We also include in our model a viscous friction \( \sigma^\eta \) with the external substrate or environment, and given by an external force \( \sigma^\eta(t) = -\eta \dot{l}(t) \), with \( \eta \geq 0 \) a wet friction coefficient (see Fig. 1). In total, the balance law, \( \sigma^\eta = \sigma^e + \sigma^v \) reads in our case

\[
-\eta \dot{l}(t) = k_1 \varepsilon^e(l(t), l_0) + k_2 \varepsilon^v(l(t), L(t)), \quad t > 0.
\]

Due to the presence of the delay \( \tau \), initial conditions must be specified for \( t \in [-\tau, 0] \). For simplicity, we assume constant values

\[
l(t) = l_0, \quad t \in [-\tau, 0],
\]

\[
L(t) = L_0, \quad t \in [-\tau, 0],
\]

with \( l_0 \) and \( L_0 \) given constants.

Our problem is thus defined by a system of DDE given by the dynamic balance in (2), which should be solved together with the delay evolution law in (1) and initial conditions in (3)–(4). In the next sections we will analyse the stability and oscillatory regime of the system of DDE for linear and non-linear definitions of the general deformation measures \( \varepsilon^e \) and \( \varepsilon^v \) given in (2).
3 Stability analysis of linear model

3.1 Characteristic equations and analytical bounds

In order to simplify the stability analysis, we assume first linear definitions of the deformation measures as follows:

\[
\varepsilon^e(l(t), l_0) = l(t) - l_0, \\
\varepsilon^v(l(t), L(t)) = l(t) - L(t).
\]

Inserting these expression into the balance equation (2), the set of DDE turn into the following form:

\[
-\eta \dot{l}(t) = k_1 (l(t) - l_0) + k_2 (l(t) - L(t)), \quad t > 0
\]

\[
\dot{L}(t) = \gamma (l(t) - l(t - \tau)) - L(t - \tau)), \quad t > 0
\]

with the initial conditions in (3)-(4). The coupled system of DDE can be written in a compact form as

\[
\dot{L}(t) + A L(t) + B L(t - \tau) + c = 0, \quad t > 0,
\]

with

\[
L(t) = \begin{bmatrix} l(t) \\ L(t) \end{bmatrix}; \quad A = \begin{bmatrix} k_1 + k_2 \eta & -k_2 \eta \\ 0 & 0 \end{bmatrix}; \quad B = \begin{bmatrix} -\gamma & 0 \\ 0 & \gamma \end{bmatrix}; \quad c = \begin{bmatrix} \frac{k_1 l_0}{\eta} \\ 0 \end{bmatrix}.
\]

Generally, the solution of the coupled system of DDE in (7) is characterized qualitatively (e.g. asymptotic, synchronous, oscillatory) by the exponents or the roots of the characteristic function (Erneux 2009; Smith 2011). In order to obtain this characteristic function, one might search for a solution in the form,

\[
L(t) = \sum_i e^{m_i t} L_i + L_0,
\]

where \( L_0 \) and \( L_i \) are constant vectors that depend on the chosen initial values, and \( m_i \in \mathbb{C} \) are the characteristic exponents. Clearly if all the exponent have negative real parts, i.e. \( Re(m_i) < 0 \), the solution is asymptotically stable with time. Substituting Eq. (8) into Eq. (7) gives for each term in the summation

\[
(m_i I + A + Be^{-m_i \tau}) L_i = 0.
\]

We remark that the above linear transformation must hold regardless of the initial conditions, that is to say, the determinant must always vanish. This allows us to express the characteristic function of the system as the determinant of the above matrix, which
gives
\[ f(m) := m^2 + \gamma me^{-m\tau} + \frac{k_1 + k_2}{\eta}m + \frac{\gamma k_1}{\eta}e^{-m\tau} = 0. \] (9)

We decompose the characteristic function to real and imaginary parts by substituting
\( m = \alpha + i \beta \) and then separating each part, leading to the following non-linear system
of equations,
\[
\begin{align*}
\text{Re } f(m) &= \alpha^2 - \beta^2 + \frac{k_1 + k_2}{\eta} \alpha + \gamma e^{-\alpha \tau} \left( \left( \alpha + \frac{k_1}{\eta} \right) \cos(\beta \tau) + \beta \sin(\beta \tau) \right), \\
\text{Im } f(m) &= 2\alpha \beta + \frac{k_1 + k_2}{\eta} \beta + \gamma e^{-\alpha \tau} \left( \beta \cos(\beta \tau) - \left( \alpha + \frac{k_1}{\eta} \right) \sin(\beta \tau) \right).
\end{align*}
\] (10)

The stability regions in the parameters space are determined by finding the boundaries where the number of unstable exponents changes, which means, at least one characteristic exponent crosses the imaginary axis from left to right. In such bifurcation events Eq. (10) will have at least one solution with positive \( \alpha \).

Here, we have constructed the phase diagram by solving the system in Eq. (10) numerically while monitoring the values of \( \alpha \) (see Fig. 2). If there is at least one root with a positive \( \alpha \) the solution was considered unstable.

With the aim of furnishing a practical bound for detecting stable solutions, we also give the following result:

**Proposition 1** The solution of the system of the DDE in Eq. (7) with initial conditions in Eq. (3) is stable as long as,

\[ k_1 + k_2 - \gamma \eta - k_1 \gamma \tau > 0. \] (11)

**Proof** Condition (11) is derived resorting to the results in Stépán (1989), and analysing the so-called \( D \)-curves defined as,

\[
\begin{align*}
R(\omega) := \text{Re } f(i\omega) &= -\omega^2 + \gamma \left( \frac{k_1}{\eta} \cos(\omega \tau) + \omega \sin(\omega \tau) \right), \\
S(\omega) := \text{Im } f(i\omega) &= \frac{k_1 + k_2}{\eta} \omega + \gamma \left( \omega \cos(\omega \tau) - \frac{k_1}{\eta} \sin(\omega \tau) \right),
\end{align*}
\] (12) (13)

with \( \omega \in [0, +\infty) \). The functions \( R(\omega) \) and \( S(\omega) \) provide infinite parametric curves that mark the region with constant number of unstable characteristic exponents. In particular, we resort to Theorem 2.19 in Stépán (1989), which indicates that the zeros of Eq. (9) have no real positive parts if and only if,

\[ S(\rho_k) \neq 0 \quad k = 1, \ldots, r, \] (14)

and

\[ \sum_{k=1}^{r} (-1)^k S(\rho_k) = -1, \] (15)
Fig. 2 Phase diagrams for different pairs of material parameters. a Plane \((k_1, k_2)\), b plane \((k_1, \eta)\), c plane \((k_2, \eta)\) and d plane \((\tau, \gamma)\). The curves show stability boundaries for different values of the off-plane parameters. Continuous lines are obtained with the numerical solution of Eq. (10). Dashed lines represent the sufficient stability condition in Eq. (11). The regions which are labelled as stable are those with negative values for the real part of the root of the characteristic function \(\alpha\) and those labelled as unstable indicate the regions with at least a single positive value of \(\alpha\). In (a), the point indicated with the symbol \(*\) indicates experimental estimates of the values (see text in Section 3.2).

where \(\rho_1 \geq \ldots \geq \rho_r \geq 0\) are the non-negative roots of \(R(\omega)\), with \(r\) being an odd number. Moreover, we introduce a polynomial \(S^-(\omega)\) which defines a lower bound for the function \(S(\omega)\) such that,

\[
0 < S^-(\omega) \leq S(\omega) \quad \text{for} \quad \omega \in (0, +\infty).
\]  

(16)

In case that \(S(\omega)\) satisfies the stability conditions in Eq. (14) and (15), \(S^-(\omega)\) will also satisfy them by construction. An adequate choice for the polynomial \(S^-(\omega)\) can be obtained by exploiting the following inequalities,

\[
\cos(\omega \tau) \geq -1, \quad -\sin(\omega \tau) \geq -\omega \tau \quad \text{for} \quad \omega \in (0, +\infty)
\]

which lead to,

\[
S^-(\omega) = \left(\frac{k_1 + k_2}{\eta} - \gamma - \frac{k_1}{\eta} \gamma \tau\right)\omega.
\]
Since $\omega > 0$, the condition in Eq. (16) is satisfied as long as
\[ k_1 + k_2 - \gamma \eta - k_1 \gamma \tau > 0. \]
\[ \square \]

We point out that the main benefit of Proposition 1 is that it counts in the whole space of system parameters, giving the opportunity to cross check the stability taking into account the relative variations of system parameters. In the phase diagrams in the parametric space of Fig. 2, condition (11) is indicated with dashed lines. As it can be observed, it indicates stability regions that are smaller than those obtained by solving numerically Eq. (10). These plots emphasise the fact that although the bound in Eq. (16) does not provide a necessary condition, it provides a useful sufficient stability condition.

### 3.2 Preliminary discussion and experimental comparison

We remark two salient conclusions from the expression in the bound, which are also confirmed in the phase diagrams: increasing values of $\gamma \tau$ have an unstable effect in the lengths $l(t)$ and $L(t)$, as previously encountered in other models (Muñoz et al. 2018), while decreasing values of $\eta$ may render the oscillations stable. The latter is an unexpected result, since increasing viscosity has in general a stabilising or damping effect in mechanics. The destabilisation that increasing values of $\eta$ induces can be explained by noting that higher viscosity entails a retardation in the stress response (or lower rate $\dot{l}$), in our case given by $k_1 (l - l_0) + k_2 (l - L)$. Increasing the retardation in the stresses is similar to increasing the values of $\tau$, which also destabilises the lengths $l(t)$ and $L(t)$, due to a mismatch between the difference $l - L$ at time $t - \tau$ and the rate $\dot{L}$ at time $t$.

Although we are not aware of an experimental setup that may directly verify the bounds encountered, recent measurements of Drosophila condensation have correlated decaying deformation oscillations with a reduction in tissue viscosity (Karkali et al. 2021), confirming the relation between oscillatory regime and visco-elastic material properties.

In order to put into context the relevance of the deduced bound, we can use some values of the parameters reported in the literature for a similar rest-length based model. For instance, MDCK cells have a remodelling rate $\gamma \approx 0.02$, a characteristic time $t_c \approx 10s$ while $k_1 \approx 1kPa$ and $k_2 \approx 0.5kPa$ (Khalilgharibi et al. 2019), which imply that $\eta \approx t_c / (k_1^{-1} + k_2^{-1}) \approx 10^4 / 3$. Therefore, the inequality in (11) reads,
\[ \tau < \frac{1}{\gamma} + \frac{k_2}{\gamma k_1} - \frac{\eta}{k_1} \approx 70s. \]

The reported measured delay between myosin and deformations is of a similar order, from 2 minutes in wound healing (Zulueta-Coarasa and Fernandez-Gonzalez 2018) to 4 minutes in Drosophila dorsal closure (Dierkes et al. 2014), showing that is not far from the conservative stability bound of the linear problem. We will show in

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Section 4 that the stability limit of the linear model corresponds in fact to a limit of sustained oscillations in the non-linear model. It must be said though that the viscosity value that we have employed corresponding to the frictional contributions has not been directly measured, and that we have used an estimated value from the measured relaxation time.

In order to contextualise the values of the parameters in the phase diagrams in Fig. 2 with experimental measures, we first rewrite the equations in non-dimensional form,

\[
\dot{\tilde{l}} = \frac{t_c k_1}{\eta} (\tilde{l}(\tilde{t}) - \tilde{l}_0) + \frac{t_c k_2}{\eta} (\tilde{l}(\tilde{t}) - \tilde{L}(\tilde{t})) ,
\]

\[
\dot{\tilde{L}} = t_c \gamma (\tilde{l}(\tilde{t} - \tilde{\tau}) - \tilde{L}(\tilde{t} - \tilde{\tau})) ,
\]

with \( \tilde{l} = l/l_{ref} \), \( \tilde{L} = L/l_{ref} \), \( \tilde{\tau} = t/t_c \), the length \( l_{ref} \) a reference size, e.g. diameter of one cell (\( \sim 15\,\mu m \)), and the superimposed dot denoting derivatives with respect to non-dimensional time \( \tilde{t} \). The ranges of parameters used in Fig. 2 may be then regarded as non-dimensional parameters. In this case, our range of the delay in Fig. 2 (non-dimensional \( \tilde{\tau} \in [0, 10] \)) would correspond to dimensional values \( [0, 10t_c] = [0, 100s] \), which is of the order of the measured delays, \( \sim 2 \) minutes (Dierkes et al. 2014). Similarly, the non-dimensional stiffness parameters take the values \( \tilde{k}_1 = t_c k_1/\eta \sim 3 \) and \( \tilde{k}_2 = t_c k_2/\eta \sim 1.5 \), according to the experimental estimates in Khalilgharibi et al. (2019). This values are close to the stability boundary in the \((k_1, k_2)\) plane, and indicated with the symbol \(*\).

### 3.3 Numerical simulations

In order to verify the obtained stability limits, we have preformed some numerical tests considering the one-dimensional model presented in Fig. 1. The test mimics a previous compression state that is given by the following initial conditions,

\[
l(t) = L(t) = 1, \quad \tau < t \leq 0 \quad (17)
\]

\[
l(-\tau) = 0.9, \quad L(-\tau) = 1. \quad (18)
\]

In order to compare our results with previous values in the literature and with more general boundary conditions, we will also test different prescribed values of \( l(t) \) and additional external forces. Indeed, in the presence of a constant external force \( f \), the equilibrium equation in (2) reads,

\[
-\eta \dot{l}(t) + f = k_1 \left( l(t) - l_0 \right) + k_2 \left( l(t) - L(t) \right) , \quad (19)
\]

\[
\dot{L}(t) = \gamma \left( l(t - \tau) - L(t - \tau) \right) . \quad (20)
\]
Fig. 3 Time evolution of current length and rest-length for free unloaded conditions. a Parameters corresponding to a stable solution, although they do not satisfy the conservative bound in (11): \((k_1, k_2, \eta, \gamma, \tau) = (2, 3, 8, 0.5, 6)\). b Choice of parameters that lie outside of the stable domain: \((k_1, k_2, \eta, \gamma, \tau) = (3, 2, 8, 0.5, 6)\)

3.3.1 Unloaded free conditions

A backward Euler implicit time discretisation of equations in (19) yields the following set of equations, which are computed sequentially,

\[
\begin{align*}
L_{n+1} &= \Delta t \gamma (l_{n-\tau} - L_{n-\tau}), \\
l_{n+1} &= \frac{1}{\eta/\Delta t + k_1 + k_2} \left( \frac{\eta}{\Delta t} l_n + f_{n+1} + k_1 L_0 + k_2 L_{n+1} \right).
\end{align*}
\] (21)

Here, we consider the case \(f_n = 0, n = 0, 1, 2, \ldots, 200/\Delta t\) and \(\Delta t = 0.01\), which is found sufficiently accurate when being compared with smaller values. The resulting evolution of \(l_n\) and \(L_n\) is consistent with the stability analysis of the previous section. The presence of the delay \(\tau > 0\) produces oscillatory solutions for \(l\) and \(L\), as it can be seen in Fig. 3. The stability of these oscillations depends on the model parameters as indicated in the stability diagrams in Fig. 2. The first case in Fig. 3a corresponds to a stable solution, with parameters inside the stability domain, although they do not satisfy the more conservative bound in (11). We note that this condition is sufficient for stability, but not necessary. The second case in Fig. 3b yields unstable oscillations, with parameters that exceed the stability limits (and that consequently do not satisfy the inequality in (11)).

3.3.2 Prescribed deformation

Here, we choose a constant value of the apparent length \(l(t)\), with an initial discontinuity:

\[
\begin{align*}
L(t) &= L_0 = 1, \quad -\tau \leq t \leq 0, \\
l(-\tau) &= 0.9, \quad l = l_0 = 1, \quad -\tau < t.
\end{align*}
\]
Fig. 4  The evolution of the rest-length with fixed values for the apparent length \( l(t) \). The stability is in this case identical to the friction-less models (Muñoz et al. 2018). \( \textbf{a} \) Stable oscillatory solution when \( \gamma = 0.35, \tau = 4 \), i.e. \( \frac{1}{2} < \gamma \tau < \frac{\pi}{2} \). \( \textbf{b} \) Unstable solution for \( \gamma = 0.35 \) and \( \tau = 4.6 \), i.e. \( \gamma \tau > \frac{\pi}{2} \).

In this case, \( \dot{L}(t) = 0, t > 0 \), so the first differential gives us a reaction force term equal to \( k_2(l_0 - L(t)) \), while the DDE reads

\[ \dot{L} = \gamma(l_0 - L(t - \tau)). \]

This DDE (or equivalent forms) has been extensively studied (Smith 2011; Muñoz et al. 2018), and is known to yield oscillatory values of rest-length \( L(t) \) whenever \( \gamma \tau > \frac{1}{\epsilon} \), and unstable oscillations whenever \( \gamma \tau > \frac{\pi}{2} \). This has been confirmed by the numerical simulations in Fig. 4.

### 3.3.3 Prescribed forces

We now impose and external force \( f = 0.2 \). Since this value only affects the value of the vector \( c \) in Equation (7), the stability is consequently unaffected by the value of \( f \). The plots in Fig. 5 confirm this fact. These plots show the apparent length as a function of time, while the rest-length is shown as the contourplot on the varying domain \( x \in [0, l(t)] \).

### 4 Extension to non-linear model: strain–based rheology

Instead of the deformation measure based on the displacements \( l(t) - l_0 \) and \( l(t) - L(t) \), we now rewrite the equilibrium equations in terms of the relative displacement (strain) measures \( (l(t) - l_0)/l_0 \) and \( (l(t) - L(t))/L(t) \),

\[ \varepsilon^e(l(t), l_0) = \frac{l(t) - l_0}{l_0}, \]
\[ \varepsilon^v(l(t), L(t)) = \frac{l(t) - L(t)}{L(t)}. \]
Fig. 5 Kymograph of evolution of current length and rest-length (colour map) with prescribed compression forces \( f (x = 0) = -f (x = 1) = 0.2 \). (a) Solution with parameters inside stability domain: \((k_1, k_2, \eta, \gamma, \tau) = (1, 1, 1, 0.5, 6)\). (b) Time evolution when the stability boundary is exceeded: \((k_1, k_2, \eta, \gamma, \tau) = (1, 1, 3, 0.6, 6)\).

While this is a more common deformation measure, with non-dimensional values, these expressions, when inserted into the equilibrium equations in (2) yield a set of non-linear DDE:

\[
- \eta \dot{l}(t) = k_1 \left( \frac{l(t) - l_0}{l_0} \right) + k_2 \left( \frac{l(t) - L(t)}{L(t)} \right),
\]

\[
\dot{L}(t) = \gamma \left( l(t - \tau) - L(t - \tau) \right).
\]

4.1 Bifurcations and limit cycles

We aim at studying the oscillatory character and stability of these equations. However, due to their non-linearity, we cannot directly retrieve a characteristic equation from an assumed solution with the form in (8). We will instead analyse the linearised system around a periodic solution \( l(t) = l^* (t) \) and \( L(t) = L^* (t) \). In this case, the linearised DDE reads:

\[
- \eta \delta l = k_1 \left( \frac{L^*}{l^*} \right) \delta l + k_2 \left( \frac{L^*}{L^*} \delta L \right),
\]

\[
\delta L = \gamma \left( \delta l - \delta L \right).
\]

Note that the second DDE was already linear, and thus remains unchanged. After pointing out that the non-linear DDE in (22) has the fixed point solution \( l^* = L^* = l_0 \), and that the linearisation around this solution yields the same linear system in (5)-(6), but with \( \eta \) replaced by \( \eta l_0 \). Consequently, the stability limits of the linear analysis correspond to a Hopf bifurcation of the non-linear system, where periodic solution arises since the root of the characteristic function of the linearised solution crosses the imaginary axis. We have verified this conclusion numerically and with the package DDE-BIFTool (Engelborghs et al. 2002), which furnished us the same limits shown in Fig. 2 for the bifurcation points on the different parameter planes when using \( l_0 = 1 \).
Fig. 6a Oscillatory regime of the non-linear model on the $L$-$l$ space for $(k_1, k_2, \gamma, \tau, \eta, l_0) = (1, 0.8, 1.2, 3.5, 1.2)$ and initial conditions $(L(0), l(0)) = (2, 1.5)$ for $-\tau \leq t \leq 0$. Nullclines $\dot{l}(t) = 0$ and $\dot{L}(t + \tau) = 0$ are shown in thick continuous and dashed lines, respectively. The intersection of the trajectories with the latter nullcline are shown with $\times$ symbol, while the $+$ symbol is plotted on the same trajectory but $\tau$ time after the intersection, corresponding to a vertical tangent of the trajectory ($\dot{L} = 0$).

b Stability diagram on the $(\tau, \gamma)$ parameter space with parameters $(k_1, k_2, \eta) = (1, 1, 2)$.

However, the non-linear model is far richer than the linear one. Unlike the linear model, it exhibits sustained oscillations beyond the bifurcation points, that converge towards a limit cycle. Fig. 6a shows an example of a trajectory on the $(L, l)$ plane for a solution converging to a limit cycle. The condition $\dot{l} = 0$, i.e. $l = l_0(k_1 + k_2)/l_0/L$, is also shown in the same Figure as a curved nullcline, corresponding to trajectories with a horizontal tangent when intersecting this nullcline, while the condition $l(t) = L(t)$ corresponds to a vertical tangent, but delayed by $\tau$, consistently with the DDE in (23). In the figure, the intersection with nullcline $\dot{L} = 0$ is indicated with the symbol $\times$, e.g. at time $\tilde{t}$, while the time instant $\tilde{t} + \tau$ is indicated with symbol $+$. Additionally, we have also analysed the stability of the periodic solutions by looking on the modulus of the Floquet multipliers (eigenvalues of the linearised solution) (Guckenheimer and Holmes 1983), also with the help of software DDE-BIFTool, which computes them numerically. Figure 6b shows their approximate distribution around the bifurcation limit on the $(\tau, \gamma)$ plane. It can be observed a region beyond the bifurcation limit with sustained oscillations (limit cycles), in which the largest modulus of the Floquet multipliers is less than one.

The dependence of the stability limits on some of the model parameters is illustrated in Fig. 7, which shows the bifurcation diagrams and Hopf bifurcation points of the rest-length $L(t)$ as a function of friction $\eta$ and stiffness $k_2$. It can be observed that bifurcation points separate periodic and steady-state solutions given by $L(t) = l(t) = l_0$, and that the stability of the periodic solution is not guaranteed far from the bifurcation point. This is detected by the largest Floquet multiplier, which becomes larger than 1 for a given value of $\eta$. We also point out that the domain of stability of $k_2$ is reduced when $\eta$ increases, blueas shown in Fig. 2a. Furthermore, the oscillations of $L(t)$ and $l(t)$ in the presence of a limit cycle are not necessary around the fix point $L(t) = l(t) = l_0$, which corresponds to the intersection of the nullclines (thick black lines) in Fig. 6a.
4.2 Stability analysis in terms of modified stiffness

The stability analysis in the two-parameter plane \((k_1, k_2)\) of the linear DDE can be also exploited in the non-linear model. The solution of the perturbed problem \(\delta l = l - l^*\) and \(\delta L = L - L^*\) close to the solution \((L^*, l^*)\) in (24) can be written very similarly to the linear DDE,

\[-\eta \dot{\delta l}(t) = \hat{k}_1 \delta l + \hat{k}_2 \delta L(t), \tag{26}\]
\[\delta \dot{L}(t) = \gamma (l(t - \tau) - L(t - \tau)). \tag{27}\]

but with modified varying stiffness parameters defined as,

\[\hat{k}_1 = \frac{k_1}{l^*} + \frac{k_2}{L^*} \left( 1 - \frac{l^*}{L^*} \right), \tag{28}\]
\[\hat{k}_2 = \frac{k_2 l^*}{L^*^2}. \tag{29}\]

For a time varying periodic solution \((L^*, l^*)\), the modified stiffness \(\hat{k}_1\) and \(\hat{k}_2\) may either i) be fully located on the stable region of the linear model in (5)-(6), ii) be solely located on the unstable regions, or iii) reach values on the two regions. In the first case, from the analysis of the linearised form, we can conclude that the solution will be stable and with decaying oscillations, while in the second case unstable oscillations will be most likely obtained, before a very small value of \(L\) or negative value of \(l\) is reached. In the third case, there is no guarantee that it will be stable, but the modified stiffness \(\hat{k}_1\) and \(\hat{k}_2\) may eventually oscillate between stable and unstable regions, with a corresponding limit cycles on the \((L(t), l(t))\) and \((\hat{k}_1, \hat{k}_2)\) planes.

We illustrate the different situations and evolution of the modified stiffness \(\hat{k}_1\) and \(\hat{k}_2\) in Figs. 8, 9 and 10, where different numerical solutions of Eqs. (22) and (23) are computed. Figure 8a shows the time evolution of \(l(t)\) and \(L(t)\) in the case of
sustained oscillations, that is, with amplitudes that converge asymptotically towards a limit cycle. We also plot in Fig. 8b the modified parameters \( \hat{k}_1 \) and \( \hat{k}_2 \), together with the stable and unstable domains in the \((k_1, k_2)\) plane. These domains have been computed finding the roots of the characteristic equations, in the same manner that the curves in Figure 2 have been obtained. It can be observed that although the initial values are located in the unstable region, \((\hat{k}_1, \hat{k}_2)\) oscillate between the unstable and stable regions, reaching a limit cycle that alternates between the two domains. This corresponds to situation iii) described above.

We have also tested other parameter settings, with an initial location of \((\hat{k}_1, \hat{k}_2)\) in the parametric space farther from the stability boundary (see Fig. 9). Although the values of \( \hat{k}_1 \) and \( \hat{k}_2 \) eventually cross the stable domain, they exhibit oscillations that reach the singular value \( L(t) = 0 \) for some \( t > 0 \), which renders the DDEs in (22) ill-posed. Instead, when using values that are farther inside the stability region, as it is the case in Fig. 10, the oscillations stabilise before reaching this singular value. This is the case described in case i) above. Although we are not able to furnish bounds for non-linear stability, we can interpret the presence of stable, sustained, or unstable (or singular) oscillations according to the distance of the initial value of \((\hat{k}_1, \hat{k}_2)\) to the stability boundary of the linear case.

5 Conclusions

Motivated by the presence of delays between myosin signalling and deformation (Dierkes et al. 2014), and visco-elastic response of embryonic tissues (Clément et al. 2017), we have presented a rheological model that includes elastic, viscous and frictional contributions, and which is able to exhibit oscillations, as observed in various experiments (Christodoulou and Skourides 2015; Kaouri et al. 2019; Suzuki et al. 2017).
We have analysed the stability of the model when using a linear deformation measure and as a function of the model parameters. We have recovered previous qualitative results, which show that increasing values of the delay $\tau$ and the remodelling rate $\gamma$ (a quantity that is inversely proportional to tissue viscosity), render the oscillations unstable. Remarkably, increasing values of the viscous friction of the domain with respect to external boundary also destabilise the system.

By studying the characteristic function of the DDE we have provided sufficient conditions of stability in the parameter space and bounds to the stability region. This analysis have also allowed us to explain the presence of sustained oscillations in a non-linear version of the model, which correspond to limit cycles. This persistent oscillations in the tissue deformations are frequently observed (Petrolli et al. 2019; Peyret et al. 2019), and are only achieved in our study when a non-linear strain measure
is employed. We have detected numerically the bifurcation points separating stable spirals, limit cycles and instabilities. We have also interpreted such transitions in terms of modified dynamic stiffnesses, which may take values in the stable or unstable domains of the stiffness parameter in the linear model.

We note that despite that visco-elastic models based on rest-length changes are increasingly common (Cavanaugh et al. 2020; Clément et al. 2017; Khalilgharibi et al. 2019), their stability in the presence of delayed response has not been studied. Here, we have provided such an analysis, which may also help to explain the observed sudden deformations in embryo development and morphogenesis. Some prominent examples are fluctuations apical constriction (Christodoulou and Skourides 2015; Suzuki et al. 2017), which may for instance become pulsatile prior to Drosophila invagination process (Martin et al. 2009).

The implication of these pulsations during morphogenesis needs further study, but the ubiquitous presence of these oscillations in morphogenetic events may be no coincidence, and may in fact trigger growth processes in (visco)elastic domains, similarly to so-called morphoelasticity (Goriely 2017). In our case though, the material would incorporate a viscous component and a delay in the growth process, as our equivalent Equation (1) does. This evolution law can be interpreted as a strain-driven adaptation (Erlich et al. 2020), in contrast to other stress dependent growth processes (Muñoz et al. 2010; Taber 2008), with eventual changes in the target stress. Our choice for the former is motivated by the possibility of directly measuring rest-lengths experimentally (Wyatt et al. 2020), in contrast to stresses or forces.

We have restricted our analysis to one-dimensional homogeneous elements. However, since the kinematics is written in terms of elemental lengths, it is applicable for instance to two- and three-dimensional vertex models, where the segments can adopt the rest-length rheology, as it has been already employed for instance in wound healing simulations (Mosaffa et al. 2020), in the absence of delay though. The extension to two and three-dimensional continuum models would require substantial changes, upon considering more sophisticated energy functionals such as Neo-Hookean materials or with specific stiffening-softening. This venue demands further model linearisation and bifurcation analysis, and importantly, the definition of the resting configuration for analysing its stability. We leave such extensions for future work.

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