Mechanical pattern formation in biological tissue: Relax and go with the (viscous) flow

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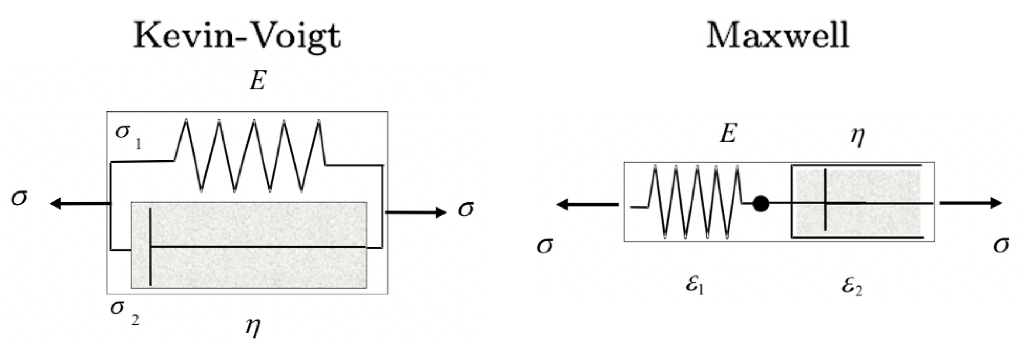
Models of linear viscoelasticity

Models of linear viscoelasticity can be represented by a combination of elastic springs and viscous dampers connected in parallel (*e.g.* Kelvin-Voigt model) and/or in series (*e.g.* Maxwell model).



Each model of viscoelasticity is characterised by a constitutive equation, relating the stress σ to the correspondent strain ε dictated by the way elastic and viscous components of the model are connected. Up to four components, the constitutive equation can be written as

$$\mathscr{L}_a[\sigma] = \mathscr{L}_b[\varepsilon] \tag{1}$$

where, for $y(t,\cdot) \in C^2(\mathbb{R}_+)$, the operators $\mathscr{L}_a[y]$ and $\mathscr{L}_b[y]$ are defined as

$$\mathscr{L}_a[y] = a_2\partial^2_{tt}y + a_1\partial_t y + a_0 y \tag{2}$$

$$\mathscr{L}_b[y] = b_2\partial^2_{tt}y + b_1\partial_t y + b_0 y \tag{3}$$

with parameters related to the elastic moduli (E_i) and viscosity coefficients (η_i) of the elastic and viscous components of the model:

Generic 4-parameters model	a_2	a_1	a_0	b_2	b_1	b_0
Linear elastic model	0	0	1	0	0	E
Linear viscous model	0	0	1	0	η	0
Kelvin-Voigt model	0	0	1	0	η	E
Maxwell model	0	$\frac{1}{E}$	$\frac{1}{\eta}$	0	1	0
SLS model	0	$\frac{1}{E_2}$	$\frac{1}{\eta}\left(1+\frac{E_1}{E_2}\right)$	0	1	$\frac{E_1}{\eta}$
Jeffrey model	0	$1+\frac{\eta_1}{\eta_2}$	$\frac{E}{\eta_2}$	η_1	E	0

Each model of viscoelasticity captures different properties of viscoelastic materials:

	Instantaneous elasticity	Delayed elasticity	Viscous flow	Instantaneous recovery	Delayed recovery	Permanent set	Stress relaxation
Linear elastic model	✓			✓			
Linear viscous model			✓			✓	N. A.
Kelvin-Voigt model		✓			✓		
Maxwell model	✓		✓	✓		✓	✓
SLS model	✓	✓		✓	✓		✓
Jeffrey model		✓	✓		✓	✓	✓

* Viscous flow: under constant stress, the strain increases linearly with time at a rate proportional to the stress and inversely proportional to viscosity.

Summary

Background: Mechanochemical models of pattern formation in biological tissue have helped us shed light on the role different mechanical cues have in cell aggregation phenomena, by considering the mechanical interaction between cells and the extracellular matrix (ECM). The cells and ECM are modelled as a linearly viscoelastic continuum, usually assumed to be a Kelvin-Voigt material, but this may not be the best model of viscoelasticity to use for biological tissue. In [1] we extend the theory of mechanochemical pattern formation to include a wider variety of models of linear viscoelasticity.

Results: Our results clearly indicate that models of linear viscoelasticity presenting viscous flow (linear viscous, Maxwell, Jeffrey model), which are better suited to represent soft tissue, have much higher pattern formation potential than those which do not (linear elastic, Kelvin-Voigt, standard linear solid model). This further highlights the need to consider experimentally determined rheological properties of the materials under study when formulating mechanochemical models of pattern formation.

Mechanical model

- Let $t \in [0,\infty)$ indicate time and $x \in [0,1] \subset \mathbb{R}$ the spatial position in a 1D domain. Then $n(t,x)$, $\rho(t,x)$ and $u(t,x)$ indicate the cell density, ECM density and ECM displacement at time t and position x respectively. The ECM (small) strain is given by $\varepsilon(t,x) = \partial_x u(t,x)$, and the corresponding stress $\sigma(t,x)$ will be given by (1).
- The conservation equations for the cell density $n(t,x)$ and the ECM density $\rho(t,x)$, and the force-balance equation are given by the following PDEs

$$\partial_t n = \underbrace{D\partial^2_{xx}n}_{\text{diffusion}} - \underbrace{\alpha\partial_x(n\partial_x\rho)}_{\text{haptotaxis}} - \underbrace{\partial_x(n\partial_t u)}_{\text{advection}} + \underbrace{rn(1-n)}_{\text{logistic growth}} \tag{4}$$

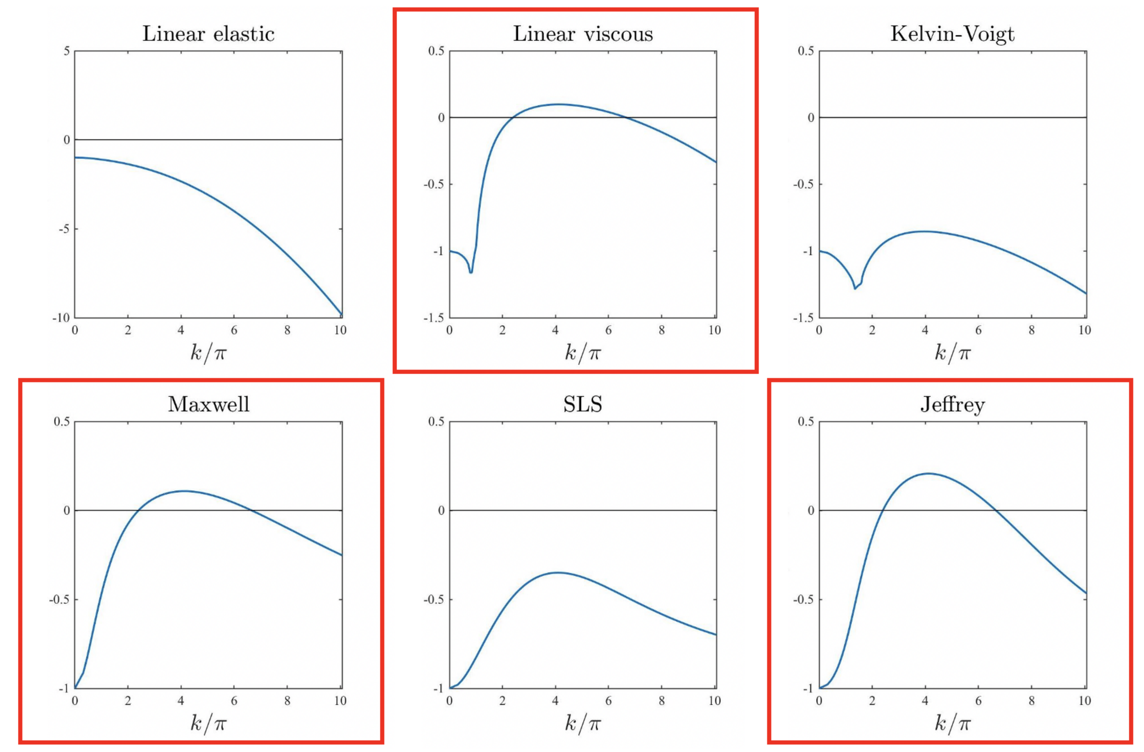
$$\partial_t \rho = -\underbrace{\partial_x(\rho\partial_t u)}_{\text{advection}} \tag{5}$$

$$\partial_x\left(\underbrace{\sigma}_{\substack{\text{ECM}\\ \text{stress}}} + \underbrace{\frac{\tau n}{1+\lambda n^2}(\rho + \beta\partial^2_{xx}\rho)}_{\substack{\text{stress due to}\\ \text{cell traction}}}\right) = \underbrace{s\rho u}_{\substack{\text{external forces}\\ \text{due to elastic}\\ \text{substratum}}} \tag{6}$$

complemented with periodic boundary conditions and initial conditions comprising small spatially inhomogeneous perturbations from the spatially homogeneous steady state $(n,\rho,u) = (1,1,0)$.
- Under the constitutive equation (1), equation (6) gives

$$\mathscr{L}_b\left[\partial^2_{xx}u\right] = \mathscr{L}_a\left[s\rho u - \partial_x\left(\frac{\tau n}{1+\lambda n^2}(\rho + \beta\partial^2_{xx}\rho)\right)\right]. \tag{7}$$

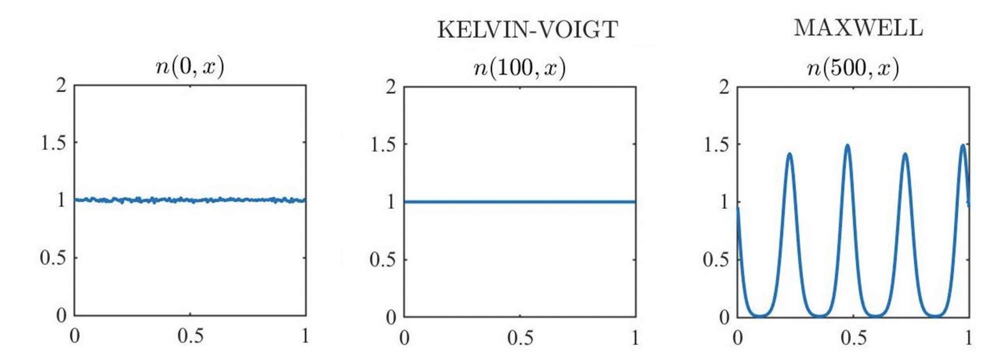
Linear stability analysis results



Perturbing the spatially homogeneous steady state $(n,\rho,u) = (1,1,0)$ with small spatially inhomogeneous perturbations proportional to $\exp[\psi t + ikx]$, under the same parameter set P_0, we obtain the dispersion relations $\mathrm{Re}(\psi(k^2))$ plotted on the left for the different models of viscoelasticity. We expect perturbations to grow in time for models of viscoelasticity presenting viscous flow (in red) and to disappear for the others. $P_0 = \{D = 0.01,\ \alpha = 0.05,\ s = 10,\ \lambda = 0.5,\ \tau = 0.2,\ \beta = 0.005,\ r = E = \eta = 1,\ E_1 = E_2 = 0.5E,\ \eta_1 = \eta_2 = 0.5\eta\}$.

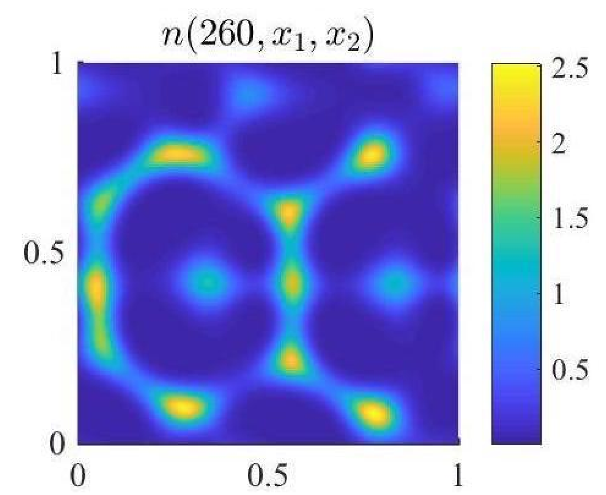
Numerical simulations

1D simulations for the Kelvin-Voigt and the Maxwell model



Starting from small random initial perturbations of the steady state $(n,\rho,u) = (1,1,0)$ (left) we observe that, under the same parameter set P_0, the perturbations quickly disappear using the Kelvin-Voigt model (centre), while patterns arise with the Maxwell model (right). This is in agreement with the dispersion relations obtained under P_0 (*cf.* top right for Kelvin-Voigt, bottom left for Maxwell).

Quick look into the extension to 2D



Example of pattern that may arise in 2D for Maxwell model from random initial perturbations of the steady state $(n,\rho,\mathbf{u}) = (1,1,\mathbf{0})$, which resulted to be stable under the same perturbation for Kelvin-Voigt model (omitted) under the same parameter set. This was obtained under simplifying assumptions on the parameters, as the extension to 2D of the constitutive equations for models of viscoelasticity (other than Kelvin-Voigt) requires an explicit distinction between elastic and viscous contributions to the matrix displacement.

Numerical method

Numerical solutions are constructed using the Method of Lines. Finite difference and finite volume approximations of the spatial derivatives are used, together with first order upwinding for the flux terms, to obtain a system of ODEs, solved implicitly with the MATLAB solver ode15i [2].

References

[1] C. Villa, M.A.J. Chaplain, A. Gerisch, T. Lorenzi, Mechanical models of pattern and form in biological tissues: the role of stress-strain constitutive equations, Bulletin of Mathematical Biology, 83:80, 2021

[2] Matlab code available on GitLab (https://git-ce.rwth-aachen.de/alf.gerisch/VillaEtAl2021BullMathBiol); numerical scheme detailed in Supplementary Material 7 of [1]