Solid- and fluid-like behaviour of biological tissues

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1 Introduction

The extracellular matrix (ECM) is an acellular polymer-like structure found around cells, composed primarily of collagen in animals and cellulose in plants [1, 2]. Examples of the ECM include the basement membrane of tissues, parts of bacterial biofilms and interstitial matrix in between cells. The ECM has a variety of functions such as structural support, intercellular signaling regulation and tissue separation. The matrix carries out these functions through chemical reactions, but also in virtue of its physical structure and mechanical properties.

Improving our understanding of the mechanics of the ECM, and specifically its response to stress, would determine great advances in fields such as tissue engineering, cancer and antimicrobial resistance. For example, it is thought that the plasticity of the ECM could be leveraged by cancer cells to invade tissues and that the speed of the turnover of the elements of the matrix has a great impact on wound repair. Moreover, bacteria enveloped by a thick biofilms are more resistant to antibiotics[3, 4].

The mechanics of the ECM are very difficult to measure because the matrix is part of a complex living organism. This generates complications on two different levels. Firstly, mechanical tests conducted on such a biological system *in vivo*, are unlikely to be able to extract the contribution of the ECM, because the accompanying cells may react to stress by either generating a chemical response or by simply growing or degrading the matrix to adjust to the deformation. Secondly, the matrix is physically constrained into its surroundings, and removing it from an organism may change its properties. The combination of the ECM being an evolving biological system and the strength of the cell-matrix interactions hinder experimental investigations of the ECM's mechanical properties.

Mathematical modelling is a helpful tool to capture the general characteristics of such a complex system, because it can provide the insight we are not able to obtain through experiments. This is the challenge we tried to address in this project, which is aimed at the creation of a versatile model able to describe and predict the mechanical properties of the ECM.

The model is motivated by observations of the ECM's mechanics, conducted on the wing disc of larvae of the fruit-fly *Drosophila*. Our experimental collaborators believe that, when subjected to a shearing force, the ECM of the fly exhibits both solid- and fluid-like behaviour. Solid-like behaviour occurs when a material deforms elastically when a force is applied on it, whereas fluid-like behaviour occurs when a material "flows" under the action of a shearing force. In the case of *Drosophila*'s tissues, it is thought that if a force was to be applied for short time periods, the matrix would deform elastically and then retain its original shape after the removal of the force. However, if a force was to be exerted for a longer period of time, the matrix would undergo irreversible deformations, "flowing" like a fluid.

One hypothesis for why the ECM has both solid- and fluid-like behaviour is that components of the matrix are continually replaced, a phenomenon we refer to as *turnover*. In fact, the ECM is mainly composed of collagen, which is purely elastic, and, if the material composition remains static, would be expected to have a purely elastic response to stress. However, collagen units are constantly added and removed from the matrix, as they degrade and replacements are produced by cells; this generates an effective flow of material, which may be responsible for the viscous nature of the ECM.

We wish to build a mathematical model that treats the matrix as a system of elastic elements (collagen) with replacement dynamics. Our goal is to test how this system reacts mechanically, and observe the emergence of the hypothesised solid- and fluid-like behaviour, otherwise known as viscoelasticity. Additionally, the model will be extended to include colour changing components in the ECM, for future comparison with *in vivo* fluorescent timer experiments.

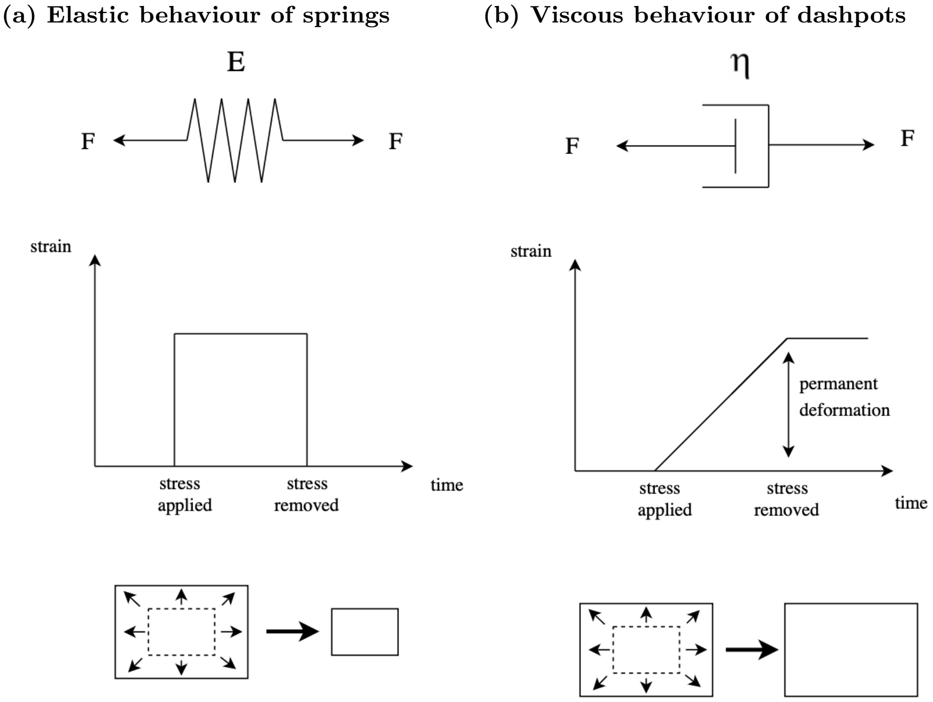

(a) Elastic behaviour of springs (b) Viscous behaviour of dashpots

Figure 1: Mechanical behaviour of (a) springs and (b) dashpots. Top: schematic drawing of a spring/dashpot. Middle: evolution of the strain under a fixed stress. Bottom: drawing of the observed changes when the stress is removed.

2 Basic models for viscoelasticity

Before building a model for the ECM, we investigate viscoelasticy, the combination of solid- and fluid-like behaviour, because it is hypothesised that the matrix behaves viscoelastically under the action of a force. The simplest models of viscoelasticity derive from the study of the mechanical properties of systems of springs and dashpots positioned in different arrangements.

Springs are the fundamental solid-like (or elastic) unit: they deform when a stress, which is a force per unit area, is applied on them, but they return to their original shape once the stress is removed, as shown in Fig. 1a. This results in a linear relation between the stress(σ) and the strain(ϵ), which is the relative deformation from the rest length.

$$\sigma_s = E\epsilon_s, \tag{1}$$

where the proportionality constant E is called the Young's modulus (or elastic stiffness) and is a property of each elastic material.

Dashpots are the fundamental fluid-like (or viscous) unit: forces are generated by viscous drag, and the resulting deformations due to an applied stress are permanent, as shown in Fig. 1b. In particular, the stress is proportional to the strain-rate

$$\sigma_d = \eta\dot{\epsilon}_d, \tag{2}$$

where η is the viscosity of the material, and the dot notation ($\dot{}$) denotes differentiation with respect to time (i.e. rate).

Systems combining springs and dashpots exhibit a combination of these characteristics, which we refer to as viscoelastic behaviour. The two simplest models of viscoelasticity are the Maxwell and the Kelvin-Voigt models [5]. Below, we introduce each of these models, summarise their stress-strain relations and find some resulting characteristic behaviours.

2.1 The Maxwell model

The Maxwell model is based on a spring and a dashpot positioned in series, as shown in Fig. 2a. In this system, the stress felt by the dashpot and the spring is the same

$$\sigma = \sigma_s = \sigma_d, \tag{3}$$

but the total strain (deformation) is given by the sum of the strain of the spring and that of the dashpot,

$$\epsilon = \epsilon_s + \epsilon_d. \tag{4}$$

Differentiating this with respect to time and using the spring and dashpot mechanical relations, Eqs. (1) & (2), gives the stress-strain relation for the Maxwell model

$$\dot{\epsilon} = \frac{\dot{\sigma}}{E} + \frac{\sigma}{\eta}. \tag{5}$$

The strain rate is consequently linear in both stress and stress rate.

2.1.1 Constant applied strain

If a given strain, $\epsilon = \epsilon_0$, is exerted on the system, then the initial stress is $\sigma_0 = E\epsilon_0$, and the stress evolves according to

$$\sigma(t) = E\epsilon_0 e^{\frac{-E}{\eta}t}. \tag{6}$$

The internal stress decays exponentially with time, as shown in Fig. 2b, a phenomenon known as stress relaxation.

2.1.2 Constant applied stress

If a constant stress, $\sigma = \sigma_0$, is exerted on the system then the strain rate is constant, meaning that the strain evolves linearly over time,

$$\epsilon = \frac{\sigma_0}{\eta}t. \tag{7}$$

This behaviour, which is the same as a Newtonian fluid under a constant applied stress, is shown in Fig. 2c.

2.2 The Kelvin-Voigt model

The Kelvin-Voigt model is based on a spring a dashpot positioned in parallel, as shown in Fig. 3a. In this system, the stress felt by the the system is the sum of the stress felt by the dashpot and that felt by the spring

$$\sigma = \sigma_s + \sigma_d. \tag{8}$$

However, the strain rate must be the same for both the spring and the dashpot

$$\epsilon = \epsilon_s = \epsilon_d. \tag{9}$$

Combining these gives the stress-strain relation

$$\sigma = E\epsilon + \eta\dot{\epsilon}. \tag{10}$$

The Kelvin-Voigt model therefore gives the stress as linear in both strain and strain-rate.

2.2.1 Constant applied strain

If a constant strain, $\epsilon = \epsilon_0$, is applied to the system, then the strain-rate is zero and so the stress is

$$\sigma = E\epsilon_0. \tag{11}$$

The material behaves purely elastically, which is shown in Fig. 3b, and there is no evidence of stress relaxation.

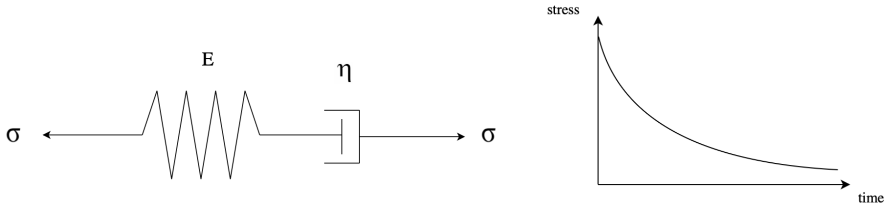
2.2.2 Constant applied stress

If a constant stress, $\sigma = \sigma_0$, is exerted on the system then the strain evolves according to

$$\epsilon = \frac{\sigma_0}{E}\left(1 - e^{\frac{-E}{\cdot}\eta t}\right) \tag{12}$$

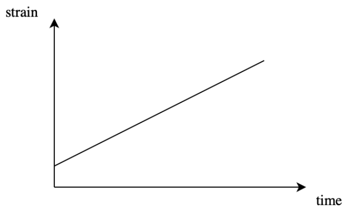
The strain of the viscoelastic material increases from zero and tends asymptotically to $\frac{\sigma_0}{E}$ at long times, as shown in Fig. 3c. This behaviour is known as viscoelastic creep: the time dependent deformation of a material subject to a constant stress.

Each model captures only one of these two typical viscoelastic materials' properties. This shows the simplicity of these models, that limits their applicability. However, they are a helpful tool to understand the general behaviour characteristics of viscoelasticity.



(a) Spring and dashpot in series

(b) Evolution of stress over time with a constant strain



(c) Evolution of strain over time with a constant stress

Figure 2: The Maxwell model of viscoelasticity. (a) A spring and a dashpot positioned in series, to model a viscoelastic material. (b) Under a fixed strain, the stress decays exponentially over time, a phenomenon know as stress relaxation. (c) A graph showing the linear relationship between strain and time, if a constant stress is applied. The gradient of the line is $\frac{\sigma_0}{\eta}$, initial stress over viscosity

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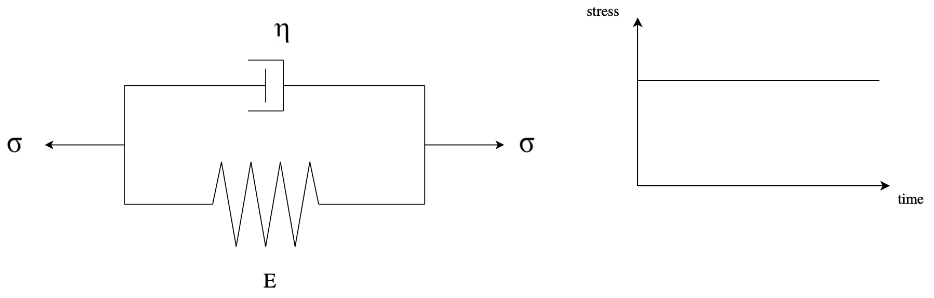
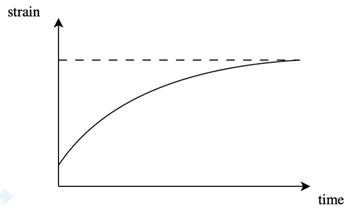


(a) Spring and dashpot in parallel

(b) Evolution of stress over time with a constant strain



(c) Evolution of strain over time with a constant stress

Figure 3: The Kelvin-Voigt model of viscoelasticity. (a) A spring and a dashpot positioned in parallel, to model a viscoelastic material. (b) The internal stress of a viscoelastic material remains constant over time when a constant strain is applied on the system. (c) Under the action of a constant stress, the strain tends asymptotically to a constant value (creep).

3 Spring turnover model

The main component of the ECM is collagen, which is purely elastic. Moreover, it is known that the ECM experiences a certain degree of *turnover* (or material replacement) of its components. The matrix's viscoelasticity can be hypothesised to be the result of this turnover. We explore this possibility using a mathematical model of the ECM, representing the collagen material as springs. Before introducing this model, we first analyse how springs behave mechanically in different arrangements.

3.1 Mechanical behaviour of different spring arrangements

Groups of springs can be positioned either in parallel or in series. These arrangements determine different relationships between the force, F, (or stress, σ) applied on the system, the elastic coefficients, k, of the springs, and the consequent deformation, $L_i - l_i$ (total length minus rest length), of the system. For full generality, we consider springs which may have different rest lengths, l_i, and different elastic coefficients, k_i. We wish to determine the properties (i.e. stiffness k and natural length l) of an equivalent spring that has the same behaviour as the arrangement of many springs.

3.1.1 Springs in series

If n springs are arranged in series, such as Fig. 4a, the force on each spring must be equal,

$$F = k_1(L_1 - l_1) = k_2(L_2 - l_2) = \cdots = k_n(L_n - l_n), \tag{13}$$

where k_i is the elastic coefficient of spring i. Meanwhile, the resulting total chain length is the sum of each spring length, $L = \sum L_i$.

Substituting for each L_i, we find that our equivalent spring behaviour of the form $F = k(L - l)$ must have a natural length $l = \sum l_i$, and a stiffness obeying

$$\frac{1}{k} = \sum_{i=1}^{n} \frac{1}{i}, \tag{14}$$

i.e. it is the harmonic mean of the individual spring stiffnesses. As a consequence, if all springs are identical, the stiffness of the chain of springs is lower than the stiffness of the individual springs, by a factor $1/n$.

3.1.2 Springs in parallel

If n springs are arranged in parallel, as shown in Fig. 4b, then the total force is the sum of the force from each spring

$$F = \sum_{i=1}^{n} k_i(L_i - l_i). \tag{15}$$

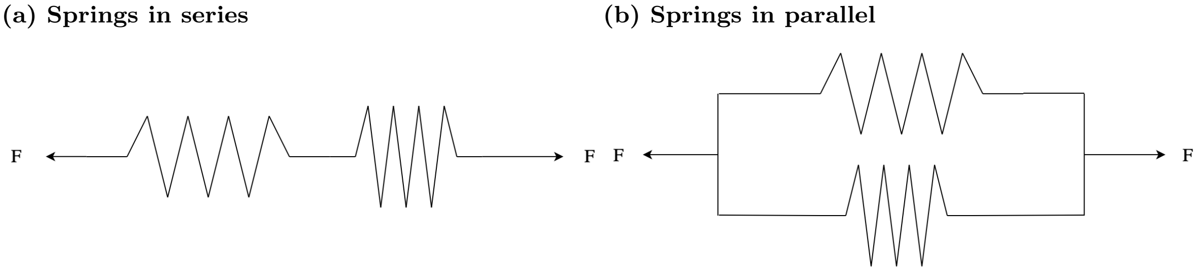
However, each spring has the same length L, and so we must have

$$k(L - l) = \sum k_i(L - l_i). \tag{16}$$

The equivalent stiffness of springs arranged in parallel is therefore

$$k = \sum_{i=1}^{n} k_i, \tag{17}$$

with natural length $l = \sum k_i l_i / k$. As a consequence, if all springs are identical, the stiffness of the chain of springs is greater than the stiffness of the individual, by a factor n.



(a) Springs in series **(b) Springs in parallel**

Figure 4: Arrangements of springs. (a) Two springs in series. (b) Two springs in parallel.

3.2 Modelling turnover

To create a model of the ECM, we consider a system of springs that represents the collagen networks observed in nature. The collagen units are represented by single springs, arranged in series to form a chain. We initially assume there is only one spring type, so that all springs are identical. These chains are positioned in parallel with each other to form a model of the ECM. The spring units can be added to or removed from spring chains, as shown in Fig. 5, and occur at given turnover rates.

The mechanical properties of the model are subsequently explored by applying either a constant stress or a constant strain on the system.

3.3 ODE solver

Knowledge of the proportion of spring chains with a given number of springs is essential to calculate the mechanical properties of the system. This value changes over time, because of the constant turnover of springs in and out of the system. We model its evolution by a set of ordinary differential equations (ODEs), given by

$$\frac{\mathrm{d}N_n}{\mathrm{d}t} = p_{n-1}N_{n-1} - (p_n + q_n)N_n + q_{n+1}N_{n+1}, \tag{18}$$

where

- N_n, the spring density, is the number of spring chains containing n number of springs,
- p_n is the rate at which a single spring is added to a chain with n springs,
- q_n is the rate at which a single spring is removed from a chain with n springs.

This equation, which gives the evolution of spring density over time, can be evolved numerically in time from a given initial condition using the Forward Euler method. The boundary conditions can be either a given applied stress or strain (on the walls), or a relation between the two. The relation between these mechanical boundary conditions and the spring density is governed by

$$F = \sum_{n=1}^{\infty} E\left(\frac{L}{ln} - 1\right) N_n \tag{19}$$

which is derived from the mechanical behaviour of springs arranged in series or in parallel.

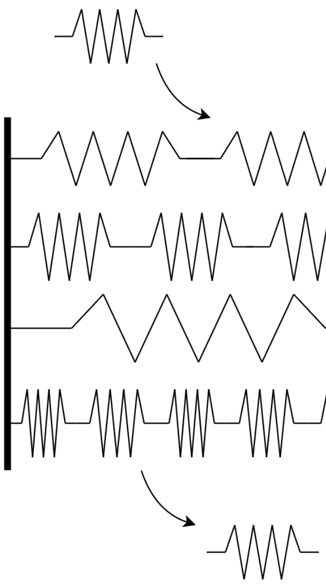


Figure 5: Springs turnover model: the ECM is modelled by a system of spring chains arranged in parallel. Each chain has a variable number of springs. Springs are added and removed from the system at certain rates.

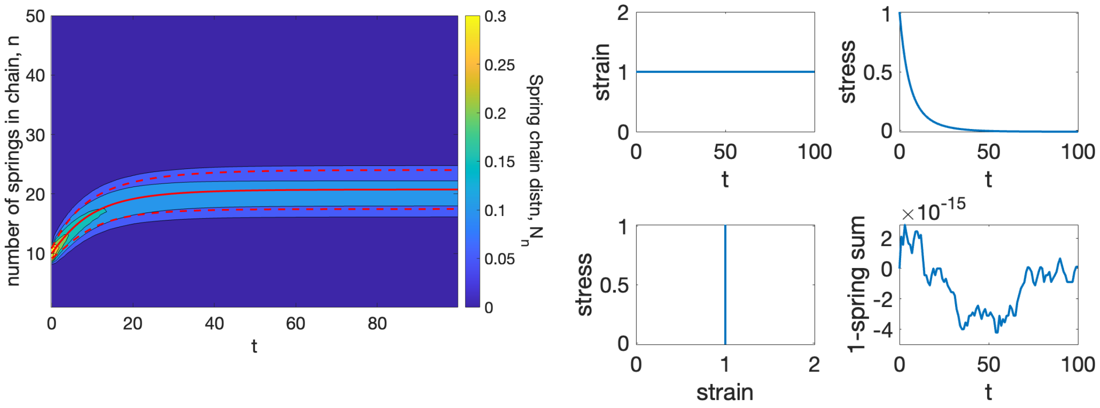
3.3.1 Parameters

The turnover rates p_n and q_n are, in general, arbitrary functions of spring number n, time t and the applied boundary conditions. We explore a physically-motivated choice for these parameters, where they are dependent on the energy required to insert or remove a spring from the chain.

There are two components that make up this energy: a binding or unbinding energy cost (that we assume constant) and the work done against elastic forces, which is a function of the number of springs in the chain. For example, removing a spring from a chain larger than the system size will be energetically more favourable than adding one to the same chain. Similarly, it will also be energetically more favourable than removing a spring from a chain with too few springs for the current system size. These energies are converted to rates via an Arrhenius relation, where the rates are proportional to exponentials of the required energy input.

3.3.2 Results

The ODE solver gave very promising results. When the mechanical properties of the system of spring chains were measured, some typical behaviours of viscoelastic materials emerged. In particular, when a fixed strain was applied on the system, stress relaxation was observed, as shown in Fig. 6. However, we did not observe evidence of viscoelastic creep under a constant applied stress. Another interesting result was the adjustment of the system towards a steady state distribution of springs in a chain.


(a) Spring density evolution

(b) Mechanical properties

Figure 6: (a) Evolution of the spring density per chain when a there is a constant strain of 1 applied on the system, by increasing the domain size from $L = 10l$ to $L = 20l$. (b) Mechanical properties of the model. Evolution of strain over time on the top-left figure, evolution of stress over time on the top-right figure, stress-strain relation on the bottom-left figure and sum of the total spring density on the bottom-right figure. On the stress-time graph the phenomenon of stress relaxation can be observed.

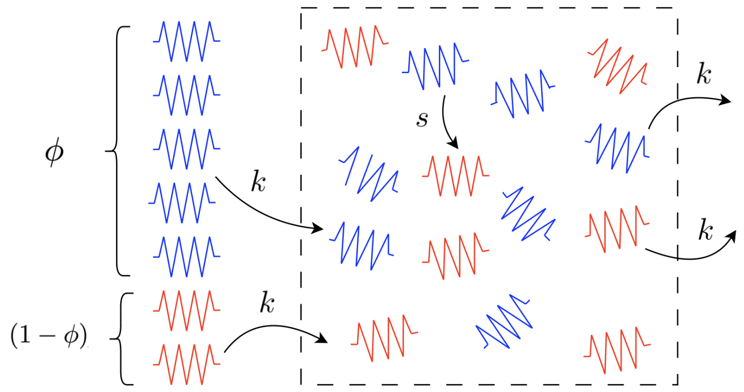


Figure 7: An illustration of our model of colour change of fluorescent components during turnover. Fluorescent springs are added to the system with proportion ϕ of blue and $1-\phi$ of red, at rate k. Once added, the springs change colour from blue to red at rate s. The springs are then removed from the system at rate k.

4 Addition of fluorescent timers

The spring turnover model outlined above illustrates that viscoelastic behaviour can be obtained from elastic components with turnover. However, the results are dependent on the choice of the parameters p and q. The values for these rates are not easy to determine, because of the complexity of measuring the turnover rate of collagen in the ECM.

Our experimental collaborators are using fluorescent-timer technology to improve the precision of the turnover rate measurement. This consists in genetically engineering the *Drosophila*, for it to produce collagen proteins with a molecular fluorescent marker attached to them, so that they are visible. Over time, these fluorescent timers transition from the colour blue to the colour red, allowing us to infer the age of the collagen.

We may therefore expect that, if the turnover is slow compared to the colour transition, then the matrix would be seen to contain mostly red collagen, because the collagen remains in the matrix for a long time. Conversely, if the turnover is fast compared to the colour change, then the main observed colour would be blue, since the collagen is constantly renewed. Tracking the colour change of the collagen in the ECM allows to infer the speed of the collagen turnover.

It is important to note that the collagen proteins are not produced adjacent to the ECM and have to travel some distance within the fly before they reach the matrix. Consequently, some collagen may have already changed colour to red before entering the ECM. This has been taken into account in the model, where both blue and red springs can be added to the system.

Given the efficacy of tracking the turnover rate using fluorescent timer technology, we decided to extend the spring turnover model to include the colour change element.

4.1 Mechanics-free colour change

Initially, we incorporated the colour change element in a model system that does not take into account the mechanics of the springs to illustrate that observing fluorescence allows us to determine turnover rate. This system is governed by a turnover rate k, and a colour change rate s, both of which we assume constant. We illustrate this system in Fig. 7.

Given that the total number of springs in the system is N_{tot}, the ODEs that describe the evolution of the number of springs of each colour in the system are composed of:

- The number of springs entering the system from the surrounding bath of springs. This depends on the turnover parameter, k, and on the proportion of springs of a certain colour

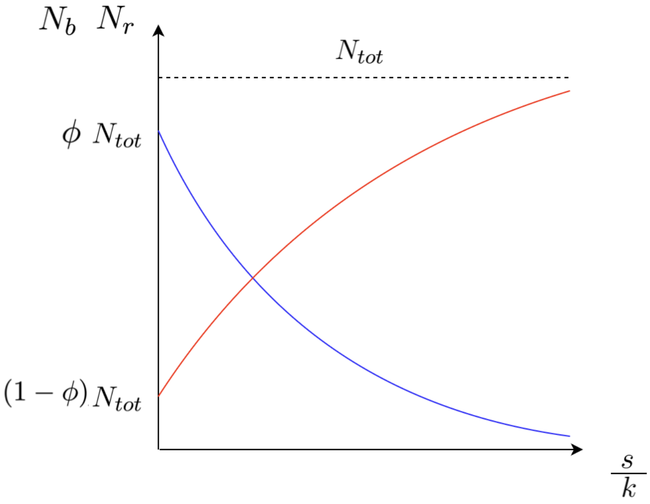


Figure 8: The steady state number of blue and red springs, N_b and N_r, vary with the ratio of the colour change rate s and the turnover rate k, where N_{tot} is the total number of springs. As the colour change rate increases, or equivalently the turnover rate decreases, more red springs and fewer blue springs will be observed.

present in the bath from which springs are drawn. The proportion of blue springs in the bath is ϕ, and that of the red springs is $1-\phi$.

- The number of springs leaving the system, which depends on the turnover parameter, k, and on the current number of springs of each colour in the system (N_b and N_r).
- The number of springs that change colour from blue to red, sN_b, where s is the colour change parameter.

The governing evolution equations for this system can then be written as

$$\frac{\mathrm{d}N_b}{\mathrm{d}t} = \phi k N_{tot} - sN_b - kN_b, \tag{20}$$

$$\frac{\mathrm{d}N_r}{\mathrm{d}t} = (1-\phi)kN_{tot} + sN_b - kN_r. \tag{21}$$

We consider steady state solutions of these ODEs, which obey

$$N_b = \frac{\phi k N_{tot}}{s+k}, \tag{22}$$

$$N_r = (1-\phi)N_{tot} + \frac{sN_b}{k}. \tag{23}$$

From these solutions, shown in Fig. 8, the turnover rate can be inferred from a given colour change rate s by measuring the proportions of red and blue springs in the system, since this uniquely determines s/k.

We see that, in the limit of fast and slow turnover, the solutions have the following properties:

- If $k \gg s$ (fast turnover, or slow colour change)

$$N_b = \phi N_{tot}, \tag{24}$$

$$N_r = (1-\phi)N_{tot}. \tag{25}$$

The proportion of red and blue springs only depends on the ratio ϕ of how many blue or red springs are added.

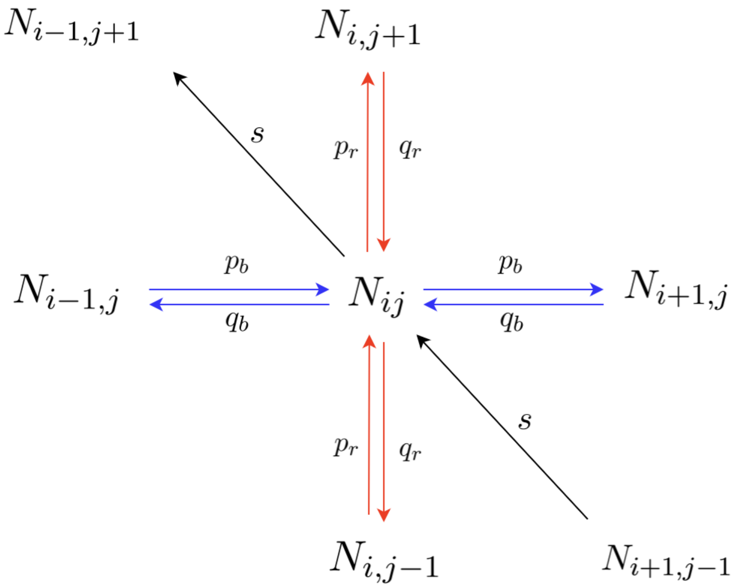


Figure 9: Graph showing the parameters that influence the spring density N_{ij} and the proportion of red and blue springs in the system. On the horizontal axis, the parameters p_b and q_b show how blue springs are added or removed from the system. On the vertical axis, the parameters p_r and q_r show how red springs are added or removed from the system. On the diagonal axis, the parameter s determines the rate at which blue springs change colour to red.

- If $k \ll s$ (slow turnover, or fast colour change)

$$N_b = \frac{\phi k N_{tot}}{s} \to 0, \tag{26}$$

$$N_r = (1-\phi)N_{tot} + \frac{sN_b}{k} = (1-\phi)N_{tot} + \phi N_{tot} \to N_{tot}. \tag{27}$$

  The rate at which the springs change colour is much faster than the turnover rate, and so all the springs in the system change colour to be red.

4.2 Spring turnover model with colour change

The model system above gave a general impression of how springs of different colour can be incorporated into the system to provide more precise measurement of the spring turnover. However, it was lacking the mechanical elements of the model outlined in §3. In this section, we explain how we updated the model in §3 for it to include the distinction between blue and red springs and the colour change parameter. The previous model was governed by the ODE measuring the density of springs in a chain:

$$\frac{\mathrm{d}N_n}{\mathrm{d}t} = p_{n-1}N_{n-1} - (p_n + q_n)N_n + q_{n+1}N_{n+1}. \tag{28}$$

In this new scenario, the density of springs in a chain N_n has to take into account the colour distinction. We therefore split the springs into colours and now denote the density by N_{ij}, where i and j are the number of blue and red springs in a chain respectively. Although we consider blue and red springs separately, we assume that they have the same mechanical properties.

The new model needs to include distinct rates for adding and removing springs of different colours, as they might differ in reality. These updated parameters are:

- p_b and p_r, which are the rates at which blue and red springs are added to a spring chain, respectively. We assume they depend on the ratio ϕ of blue and red springs present in the bath from which springs flow in the system, and are drawn proportionally:

$$p_b(i,j) = \phi p(i+j), \tag{29}$$

$$p_r(i,j) = (1-\phi)p(i+j), \tag{30}$$

where p is the rate used in the previous spring turnover model of §3.

- q_b and q_r, which are the rates at which blue and red springs are removed from a spring chain, respectively. We assume that they depend on the proportion of red and blue springs present in the system, considering that each spring has the same chance of being removed

$$q_b(i,j) = \frac{i}{i+j}q(i+j), \tag{31}$$

$$q_r(i,j) = \frac{j}{i+j}q(i+j). \tag{32}$$

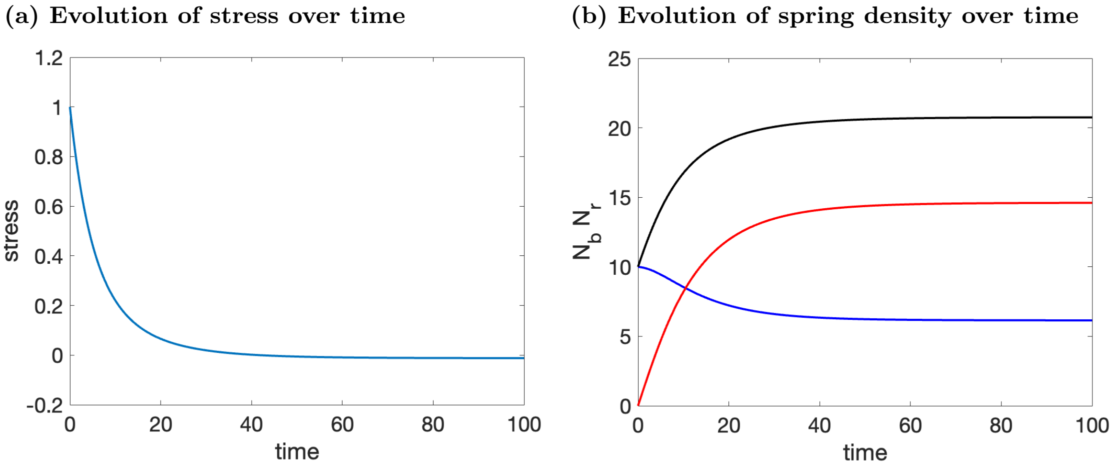
Finally, the rate at which springs change colour from blue to red needs to be taken into account in the model, which we assume is a constant rate s. These modifications result in the following system of ODEs, describing the evolution of the density of blue and red springs in a chain:

$$\begin{aligned}\frac{\mathrm{d}N_{ij}}{\mathrm{d}t} &= p_b(i-1,j)N_{i-1,j} - p_b(i,j)N_{ij} + p_r(i,j-1)N_{i,j-1} - p_r(i,j)N_{ij} \\ &\quad + q_b(i+1,j)N_{i+1,j} - q_b(i,j)N_{ij} + q_r(i,j+1)N_{i,j+1} - q_r(i,j)N_{ij} \\ &\quad + sN_{i+1,j-1} - sN_{ij}.\end{aligned} \tag{33}$$

Fig. 9 is a helpful tool to visualise what the ODE represents.

The ODE is solved numerically using the Forward Euler method in MATLAB. We show an example solution in Fig. 10. Here, the initial condition is that all the springs are blue, the springs that enter the system from the bath are assumed to be all blue ($\phi = 1$) and the colour change parameter is set as $s = 0.1$. A fixed strain is applied on the system, exactly as in Fig. 6.

Over time, as shown in Fig. 10a, we observe an exponential decrease in stress (stress relaxation), the same behaviour observed in the model without the colour change element (Fig. 6). Regarding the distribution of chains of with different numbers of springs, the MATLAB solver shows an increase in the average number of springs per chain, as already seen in the first model. Moreover, we register an increase in the spring density of red springs and a reduction in the density of the blue springs.


(a) Evolution of stress over time

(b) Evolution of spring density over time

Figure 10: Numerical solution of the ODE that describes the spring turnover model with colour change. Here, parameters are the same as in Fig. 6. (a) Evolution of stress over time in the springs turnover model with colour change. The stress decays exponentially over time, a phenomenon known as stress relaxation. (b) Evolution of the proportion of red and blue springs (per chain) in the system over time. The initial condition has all springs being blue, with only blue springs added. The average springs per chain in the system increases until it reaches a steady state (black line). Meanwhile, the number of blue springs per chain decreases and the red springs per chain increases (red and blue lines)

5 Conclusions

The goal of the project was the realisation of a model capturing the mechanical characteristics of the ECM. The outcome is a model containing springs arranged in chains of different lengths, to represent the collagen units in the ECM that undergo turnover, as observed in the matrix.

Our experimental collaborators expected the ECM to behave as a viscoelastic material over long enough timescales, due to the effects of turnover. To explore the mechanics of the ECM, we studied the behaviour of springs, the basic unit of our model, when positioned in parallel or in series, with addition and subtraction of units at given rates. In particular, we focused on their responses to a fixed strain or a fixed stress. Our results show that having elastic components with a mechanism for replacement can give rise to viscoelastic effects.

We also analysed the basic models of viscoelasticity, the Maxwell and the Kelvin-Voigt model, that could be used to describe similar systems. These models show different phenomenological behaviour. In comparison, our model only exhibited certain characteristics of viscoelastic materials, such as stress relaxation.

These investigations on viscoelastic behaviour and on spring mechanics allowed us to better understand and improve the model of the ECM, described by an ODE and solved numerically on MATLAB.

Furthermore, we expanded this model to include fluorescent timers, an experimental technology that attaches coloured markers to collagen. Over time these markers change from blue to red at a given rate, allowing the age of the collagen to be measured, with the idea that this can help determine the rate of turnover of the matrix.

We used a simplified model lacking the mechanical elements of our previous spring model to explore the interaction of turnover and colour change. At steady state, it showed that measuring the proportion of each colour determines the turnover rate, emphasising the utility of this experimental method.

To incorporate this development into our mechanical model, we divided our springs into different colours, blue and red, with an added colour change parameter that determines the rate of change between these colours. This specified a model of springs with turnover and colour change, including the mechanical elements, ruled by an ODE with multiple colour-specific parameters.

Given the short time frame of this project, we were not able to fully analyse how the system behaves under different initial conditions, such as varying strain and stress. A more thorough exploration will help us understand the interactions of turnover, mechanics and colour change. In addition, calibration of the turnover parameters alongside our experimental collaborators may be needed to restrict ourselves to more realistic values. Nevertheless, our work provides an excellent starting point to explore the mechanical behaviour of a system as complex as the ECM.

Notably, mathematical modelling of biology is a very challenging subject, because it involves the abstraction and simplification of extremely complex living systems. However, mathematics offers valuable insights and predictive capabilities for the behaviour of such systems, particularly when they that are so complex that robust and reliable experimental investigations are difficult.

This project uses mathematical modelling to understand the behaviour of the ECM. We hope further research will build on this work to investigate the extracellular matrix's role in contexts such as antibiotic resistance, cancer propagation and wound repair.

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