A thermodynamically consistent poro-visco-elastic model of Extracellular Matrix

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Abstract.

1 Introduction

There are several studies supporting the central role of mechanical stimuli in tissue morphogenesis and homeostasis [5,40]. In tissues, cells are mainly surrounded by extracellular matrix (ECM), a soft porous media made up of networks of polymer chains and proteins. *In vitro* studies have shown that ECM rigidity and shear stresses can alone promote malignant phenotypes in a population of initially normal cells, impact on cell proliferation and differentiation [9]. Further experiments on solid tumour development have proven that this is often associated to a stiffening of the tissue compared to the surrounding healthy one [38], which results in the exposure of cells to higher compressive stresses as well as favouring the collapse of blood vessels and impeding the diffusion of substances in the extra-cellular environment ultimately decreasing the efficacy of numerous therapies [44]. Based on such evidence, it is now widely accepted that, unlike originally thought, biological process are not simply regulated by biochemical signals but by the complex interplay of mechanical and chemical stimuli.

Given the different physical nature and scale of phenomena involved, coupling micro-environment and cell behaviours is a problem of high complexity. This requires understanding processes occurring at different temporal and spatial scales and how they interplay to determine the macroscopic behaviour of a tissue, whether healthy or damaged. If we can learn to tune its properties, as cells already do, this could led to the development of novel therapies and completely change our approach to drug design. In order for this to be possible, alongside experiments, it is necessary to develop a theoretical framework able to capture both the biology and physics involved and which is consistent with the known universal laws of Nature [28].

With the development of new experimental techniques such as Atomic Force Microscopy (AFM), the local mechanical properties of a material can be measured with atomic precision [26]. When tested at this scale, soft tissues and the ECM in particular have been found to be visco-elastic [32]. Purely elastic solids only store energy when deformed, viscoelastic material instead exhibit a time-dependent response as part of the energy is dissipated in the deformation process. While a large amount of literature focuses on the elastic properties of

ECM, it remains unclear the role of viscosity in determining cell behaviour. However, the recent efforts to develop synthetic ECM, i.e. hydrogels, with tunable viscoelasticity, have now opened new research opportunities [12].

Despite the progress in experimental techniques, theoretical studies of viscoelastic soft materials remain limited. While experiments rapidly progress, most of the literature on mathematical modelling for soft matter has completely neglected viscous dissipation [10]. Whether this assumption might be valid for certain applications, the empirical studies previously mentioned highlight the need of including this component in the study of living tissues. Our works aims to develop a continuum mathematical model of the extracellular matrix which is consistent with the laws of thermodynamics, which accounts for its poro-visco-elastic properties and the coupling of mechanical, transport and electrical phenomena. At our present knowledge, there is no previous work in the literature capturing all these aspects. In [43,44] Xue et al. develop a nonlinear poroelastic theory for ECM, which couples all three physical phenomena but does not include viscous dissipation. In [20], the authors couple mechano-electrophysiological effects including the viscous dissipation but neglect transport; Caccavo et al. [10] propose a poro-viscoelastic model for neutral hydrogel, thus excluding electrical effects. Following these previous work, we will derive our model in the framework of linear non-equilibrium thermodynamics [28], multi-phase modelling and Biot's poroelastic theory of continuum [6].

Despite the large number of studies that have characterised the poro-elastic and visco-elastic properties of ECM independently, little is known about their combined effect. In the literature, two main constitutive models have been presented, but never rigorously compared. Instead of arbitrarily choosing one of the two, we here rely on both approaches, with the aim of identifying their differences and investigating experimental result which would allow us to experimentally test which one best describes the behaviour of soft tissues. From this point of view, our results are more widely applicable to the study of polyelectrolyte gels, which are largely applied as biomedical devices and as a synthetic equivalent of ECM.

Our work is organized as follows: in Section 2 we start with a brief overview of Classical Irreversible Thermodynamics. After presenting the composition of the ECM, Section 4 will be focusing on the derivation of the governing equation for the deformation and swelling of ECM. [... FOLLOWING SECTIONS TO UPDATE AS I WRITE.]

2 Non Equilibrium Thermodynamics.

While equilibrium thermodynamics can describe ideal processes, it does not apply to real processes which are irreversible. In this cases, the change in the entropy of a system $\mathrm{d}S$ results from both the reversible exchange of energy and matter with the external environment $\mathrm{d}_e S$ and the internal dissipation of energy during the process $\mathrm{d}_i S$ [28]:

$$\mathrm{d}S = \mathrm{d}_e S + \mathrm{d}_i S, \tag{1}$$

According to the second law of thermodynamics, which applies universally to any system or any of its sub-part $\mathrm{d}S_i \geq 0$. It is important to notice that the second law allows transformations in which total change in entropy dS of the system is negative. This occurs whenever $-\mathrm{d}_e S > \mathrm{d}_i S$ and it can lead to the spontaneous formation of complex and ordered structures such as living organisms. From this point of view, life has emerged as an efficient mechanism able to increase sufficiently the entropy of its environment [35].

In this study, we will focus on isothermal processes, i.e. $T = const.$ Under this assumption, as derived by Gurtin in [22], the second law of thermodynamics is equivalent to the following *energy imbalance inequality*:

$$\frac{\mathrm{d}}{\mathrm{d}t}\left\{\int_R \psi\right\} \leq W(R) + M(R) \tag{2}$$

where R is a arbitrary control volume of the system, ψ is the Helmholtz free energy, $W(R)$ is the rate at which the environment does work on R and $M(R)$ is the inflow of mass due to transport. It is important to note that, as long as the quantities involved are well defined, the energy inequality (2) holds for any isothermal process independently of the specific physical system considered. This imposes a constraint on the form of the function ψ and how this depends on the other thermodynamic variables, such as temperature or pressure, which are used to describe the system.

Non-equilibrium thermodynamics mainly focuses on defining the form of $\mathrm{d}_i S$, which, unlike the reversible entropy production $\mathrm{d}_e S$, is not a state variable but depends on the specific transformation applied to the system. Different theories have been proposed, [28], each with its assumptions and specific domain of applicability. In our study we will focus on "Classical Irreversible Thermodynamics" (CIT) which was pioneered by Onsager [37] and Prigogine [39] in the first half of the 20th century. One the most important assumptions of this theory is the *Local Equilibrium Hypothesis*, which guarantees thermodynamic variables, including entropy, are locally well-defined, [28]. Consequently, we can introduce the entropy density $s = s(\mathbf{x}, t)$ such that:

$$S = \int_R s \,\mathrm{d}V, \qquad \mathrm{d}s = \mathrm{d}_e s + \mathrm{d}_i s, \qquad \mathrm{d}_i s > 0, \tag{3}$$

and the local entropy production:

$$\sigma \equiv \frac{\mathrm{d}_i s}{\mathrm{d}t} \geq 0. \tag{4}$$

Another central aspect of the theory is the introduction of *thermodynamic forces* [1] F_m (causes) and *thermodynamic fluxes* J_m (effects) to describe the time evolution of the system during an irreversible transformation. These are related to σ as follows:

$$\sigma = \sum_m F_m J_m. \tag{5}$$

[1] Not to be intended in the mechanical sense

While the local equilibrium hypothesis is at the basis of most theories of non-equilibrium thermodynamics, the following two hypotheses uniquely identify CIT:

1. *Linear Relation between forces F and fluxes J*:

$$J_m = \sum_k L_{mk} F_k, \tag{6}$$

where the constant L_{mk} are referred to as **phenomenological coefficients**;
2. *Microscopic Reversibility*: time reversibility of processes at the micro-scale.

Starting from these two principles, in its seminal paper [37] Onsager derives the well-known *Onsager Reciprocal Relation*:

$$L_{mk} = L_{km}. \tag{7}$$

If we now consider an isothermal transformation in the framework of CIT, alongside with the energy imbalance inequality, we have that the following must hold:

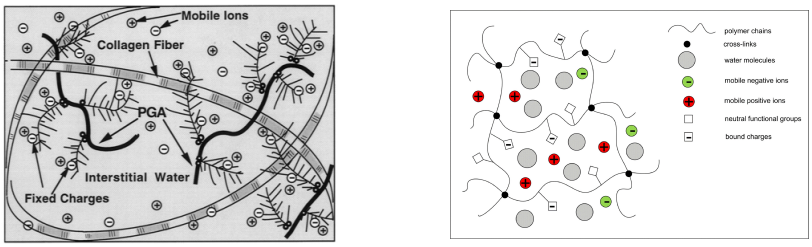
$$W(R) + M(R) - \frac{\mathrm{d}}{\mathrm{d}t}\left\{\int_R \psi\right\} = T \int_R \sigma \, \mathrm{d}V \tag{8}$$

In the past few decades, CIT has been applied successfully to the modelling of several physical phenomena of interest for engineers, physicists and applied mathematicians. However, its validity is limited to phenomena near-equilibrium, for which a linear approximation of the flux-force relation holds. The growing interest in more complex far-from-equilibrium phenomena has pushed toward the development of a more general framework for the study of a non-equilibrium phenomena. Since this goes beyond the purpose of our study, we will not discuss it further. We just want to mention the law of steepest entropy ascent, which, according to Beretta [3], seems to emerge as the fourth fundamental law of nature. In the linear regime, this principle can be used to prove Onsager's reciprocal relation [2], with no reference to the microscopic reversibility hypothesis, whose validity remains instead controversial [31].

3 Composition of Extracellular Matrix.

Despite the tissue-specific nature of Extracellular Matrix (ECM), as shown in Figure 1 (a), this is usually composed of a network of collagen fibrils entangled with proteoglycans (PGAs) which are covalently bonded to charged chains of glycosaminoglycans (GAGs). While collagen is mainly responsible for the mechanical behaviour of the tissue, GAGs can imbibe water, giving the extracellular matrix the ability to swell while maintaining its structural integrity. From this point of view, the ECM behaves as a polyelectrolyte gel [43,44]. As schematically illustrated in Figure 1(b), polyelectrolyte gels are 3D networks of cross-linked polymer chains that contain ionizable functional groups. When in solution the

gel swells, while the functional groups dissociate into fixed charges and mobile ions in the solution. Besides being largely present in the natural world, synthetic polyelectrolytes are currently employed for a wide range of applications, such as drug delivery, biomedical devices, scaffolds for tissue engineering and soft robotics [8,13,14,33]. Given their wide industrial application, there has been a growing effort in understanding their behaviour and translating it into mathematical models. In particular, research has been focusing on the phenomena of swelling, i.e. large deformation due to absorption of water, and the diffusion transport and release of solution [16,17,24,45]. However, only a small fraction of the study published accounts for the visco-elastic properties of the polymer network. As shown in Figure 1, the extracellular matrix falls into the definition



(a) (b)

Fig. 1: Analogy between ECM in soft tissue and polyelectrolytes hydrogels: (a) schematic diagram of the structure of the charged hydrated articular cartilage, reproduced from [41]; (b) an anionic polyelectrolyte gel modelled as a three-phase continuum, reproduced from [17].

of polyelectrolytes so that the knowledge acquired in the study of these materials can be transferred to soft tissues. For the purpose of this study, we will not explicitly distinguish between collagen, PGAs and GAGs. At the tissue level, this can be grouped into a single solid phase (the polymer networks), whose mechanical properties are treated as the average over the different components contribution. As common in multiphase models of tissue, we will assume that the matrix is isotropic and GAGs are evenly distributed on the network. While this is not a good approximation for tissue like cartilage, which are highly anisotropic, it does apply to the extracellular matrix found in other soft tissue like liver, brain and tumours. It is also important to point out that ECM has additional properties such as thermo-sensitivity and pH-sensitivity. However, both in living organisms and in experimental set-up temperature and pH are maintained fairly constant.

4 Model Development

4.1 Conservation Law.

As mentioned in the previous section, we here consider the ECM as a three-phase medium composed of a solid polymer network with fixed charges, a solvent (i.e. water molecules, interstitial fluid) and solutes (freely moving charges).

We assume that the deformation of the ECM corresponds to the one of the solid network. As the tissue deform, the material element originally located at $\mathbf{X}$ in the initial configuration $\mathcal{B}_0$ is displaced to the point $\mathbf{x}$ in the current configuration $\mathcal{B}$. Such transformation is described by the deformation gradient tensor $\mathbb{F} = \partial\mathbf{x}/\partial\mathbf{X}$; the information about the change in ECM's volume due is encoded by $J = \det\mathbb{F}$. Since we assume the solid phase to be incompressible, any change in the volume can only be related to the migration of solvent and solutes molecules, whose nominal concentrations will be denoted by C_s and C_i respectively, $i = 1, \dots, N$ with N being the number of free ion species. This lead to the molecular incompressibility condition:

$$J = 1 + v_s C_s + \sum_{i=1}^{N} v_i C_i \tag{9}$$

where v_m are the characteristic molecular volume of each species in the solution. When considering the interstitial fluid, the contribution of ions to the volume can be neglected [43,44] so that Equation (9) reduces to:

$$J = 1 + v_s C_s. \tag{10}$$

Consequently, the volume fractions of fluid ϕ_f and solid ϕ_n phases in the gel are defined as:

$$\phi_f = \frac{v_s C_s}{1 + v_s C_s}, \qquad \phi_n = \frac{1}{1 + v_s C_s}. \tag{11}$$

where again we are neglecting the contribution of ions to the total volume. While C_m denote the number of each molecule per unit volume in the initial configuration for the m-th species in the solution, the actual concentration in the current state is denoted by $c_m = C_m/J$. Throughout the derivation of the model, we will be using the index $i = 1, \dots, N$ to denote the ionic species only, while $m \in \{s, 1, \dots, N\}$ to refer to all mobile species, i.e. both the solvent and solutes.

Mass conservation must apply to all mobile species and in the initial configuration this reads:

$$\dot{C}_m + \nabla_0 \cdot \mathbf{J}_m = 0, \tag{12}$$

where $\mathbf{J}_m$ is the nominal flux per unit area in the dry state and ∇_0 denote the gradient in the Lagrangian coordinates $\mathbf{X}$. Their counterparts in the actual configuration are denoted by $\mathbf{j}_m$ and ∇ and are defined according to the following rules:

$$\mathbf{J}_m = J\mathbb{F}^{-1}\mathbf{j}_m, \qquad \nabla_0(\cdot) = \mathbb{F}^T\nabla(\cdot). \tag{13}$$

When considering tissues or hydrogels, inertial and gravitational effect are commonly neglected, so that the conservation of momentum for the ECM reads:

$$\nabla_0 \cdot \mathbb{S} = 0 \tag{14}$$

$$\tag{15}$$

where $\mathbb{S}$ is the first Piola-Kirchoff tensor, which represents the stress state of the ECM in the initial configuration. The counterpart in the current configuration is the Cauchy stress tensor $\mathbb{T}$, which is related to $\mathbb{S}$ as follows:

$$\mathbb{T} = J^{-1}\mathbb{S}\mathbb{F}^T. \tag{16}$$

The presence of free moving ions generates and electric field which is denoted by $\mathbf{E}$ and $\mathbf{e}$ in the initial and current configuration respectively. Introducing the electrostatic potential Φ, we have that:

$$\mathbf{E} = -\nabla_0 \Phi, \qquad \mathbf{e} = -\nabla \Phi. \tag{17}$$

As in [24], we consider the matrix to be a dielectric material. Consequently, the presence of the electric field generates an electric displacement $\mathbf{H}$, which must obey Gauss law of electrostatics:

$$\nabla_0 \cdot \mathbf{H} = Q, \tag{18}$$

where Q is the local total charge, which accounts for both fixed and moving charges:

$$Q = e\left(\sum_i z_i C_i + z_f C_f\right), \tag{19}$$

where e is the elementary charge, C_f is the concentration of fix charges and z_m is the valence of the corresponding charged species. Note that C_f here corresponds to the concentration of GAGs, which is assumed to be a constant a fraction of C_s. As for above, we can move from nominal quantities to the corresponding value in the current configuration by applying the following rules:

$$\mathbf{H} = J\mathbf{h}\mathbb{F}^{-T}, \tag{20}$$

$$\mathbf{E} = \mathbb{F}^T\mathbf{e}, \tag{21}$$

where $\mathbf{h}$ is the electric displacement in the current configuration.

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