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Coupling cellular phenotype and mechanics to understand extracellular matrix formation and homeostasis in osteoarthritis. ⋆

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Abstract: Osteoarthritis of the knee is a common degenerative disease during aging. It is typically caused by articular cartilage degeneration. Cartilage, which is located between bone surfaces, is a viscoelastic material aiming to absorb, redirect and transmit mechanical forces during movement. Without the cartilages' buffering capacity, bones come into direct contact inducing severe pain up to the stage where affected individuals loose mobility. The mechanisms of cartilage remodeling are poorly understood, and there is currently no effective method to reconstitute damaged cartilage. Cartilage consists of extracellular matrix (ECM) and a low density of cells (chondrocytes), which generate matrix proteins. The composition of the matrix gives the cartilage specific viscoelastic properties, which are sensed by chondrocytes feeding back on ECM remodeling. The aim of this study is to build a mathematical model that couples mechanical ECM properties with chondrocyte phenotype in the upkeep of cartilage homeostasis. We model the viscoelastic properties of the cartilage in terms of a linear Kelvin-Voigt model, where the dampening ratio feeds back on the phenotypic switching behaviour in chondrocytes. The chondrocytes, depending on their phenotypic state, may either produce proteoglycans or collagens or both, which alters the viscoelastic properties of the cartilage. We formulate a coupled system of equations integrating mechano-sensitive phenotypic switching behaviour of chondrocytes with respect to ECM remodelling. We define cartilage homeostasis as the fixed point of the derived systems of equations. Using this framework we can reproduce the long term changes in cartilage composition during aging.

Keywords: Extra Cellular Matrix, Attractors, Mechanical Systems, Switching Networks, Mathematical Models, Osteoarthritis.

1. INTRODUCTION

Osteoarthritis is a degenerative disease that affects the majority of individuals in the later stages of their life Lawrence et al. (2008). Osteoarthritis of the knee, hip and spine are particularly common. They induce severe pain and reduce mobility up to the stage where individuals cannot pursue their day-to-day duties. Currently, there is no effective treatment available. Joint replacement is thus the method of last resort to ensure patients' autonomy and life-quality. However, besides the risks, it poses an enormous financial burden for the health care systems, particularly in aging societies Buckwalter et al. (2004); Kim (2008).

Ostearthritis of the knee is typically characterized by cartilage degeneration. The cartilage is located between bone surfaces (see Figure 1). It is a avascular, viscoelastic tissue typically constituting extracellular matrix (ECM) and a low cell (chondrocytes) density. The cells constantly build- or degrade components of the ECM. The extracellular matrix consists mainly of water, cells and polymers. The polymers are matrix proteins belonging to the family of

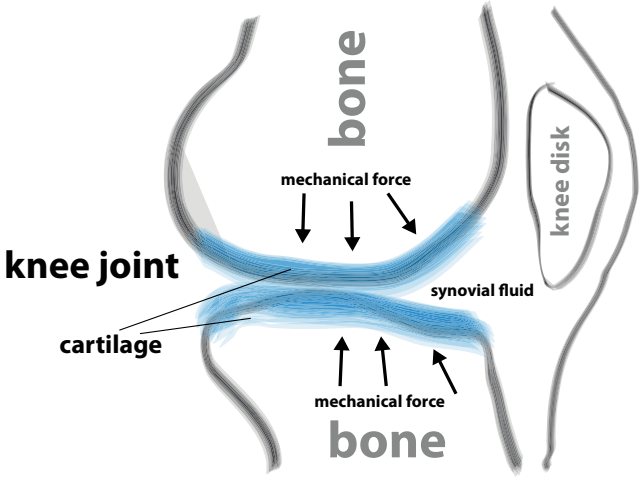

Fig. 1. Simplified depiction of the human knee with the cartilage highlighted in blue.

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collagens and proteoglycans, which determine both stiffness and elasticity of the tissue Humphrey et al. (2014); Mouw et al. (2014). The specific configuration and ratio of these constituents gives rise to mechanic properties, aiming to absorb, redirect and transmit mechanical forces that operate on the bone during movement. During osteoarthritis, these mechanical properties are lost and bones may come in direct contact provoking severe pain.

The molecular mechanisms of cartilage formation, homeostasis and functional loss are not well understood. Several biochemical factors have been identified in association with ECM formation and -loss (see Wescoe et al. (2008) for an overview), however there is currently no causative and integrative framework that puts all factors in context. There has been a great interest in understanding cartilage growth, which motivated a number of modelling approaches: Some authors have modelled a feedback between cartilage formation and nutrient gradients Lutianov et al. (2011), with the aim of modelling cartilage re-growth after cell implantation into a defect region, while others focus on the effects of insulin-like growth factors (IGF) Zhang et al. (2009) or nutrients plus IGF Asfour et al. (2015) in cartilage explants. Notably, Kar et al. (2016) modelled cartilage degradation subject to interleukin-1 stimuli. None of these models takes the bio-mechanical properties of the tissue into account and how this may affect cartilage re-modelling. However, it has been shown that the presence- or absence of biochemical factors does not suffice to build a functional cartilage and several authors LeBaron and Athanasiou (2000); Ikenoue et al. (2003); Lee and Bader (1997) have shown that mechanical stimuli are essential to generate functional cartilage tissue *in vitro*. Modelling approaches by Catt et al. (2011) and Klisch et al. (2003, 2008) take the mechanical properties of growing cartilage explants into account, however the mechanosensitive behavior of chondrocytes and its feedback on ECM composition is not regarded. Thus, although the role of mechanics in cartilage remodeling is widely appreciated Wescoe et al. (2008); Ramage et al. (2009), there is currently no functional model integrating tissue mechanics with chondrocyte phenotypes. The aim of this project is to provide a first prototypical framework that allows integrating mechanical and phenotypic switching that give rise to cartilage formation and homeostasis. We will hereby focus on long-term behaviour and homeostasis in healthy cartilage.

2. CORE MODEL

The core idea of the presented work is that there exists a strong feedback between mechanical characteristics of the ECM and the phenotypic state of the chondrocytes that regulate ECM composition (see Fig. 2), which in turn alters the mechanical characteristics of the ECM. The specific feedback between loading, ECM composition and the phenotypic state of chondrocytes has been shown to be regulated by mechanosensitive receptors (mainly integrins and mechano-sensitive ion channels Mobasheri et al. (2002)) and it has been reported that chondrocytes respond to mechanical events locally around the cells Bachrach et al. (1995); Valhmu et al. (1998). In the present work we model and investigate the mechano-sensitive phenotypic switch in chondrocytes and its feedback on the ECM surrounding the cells.

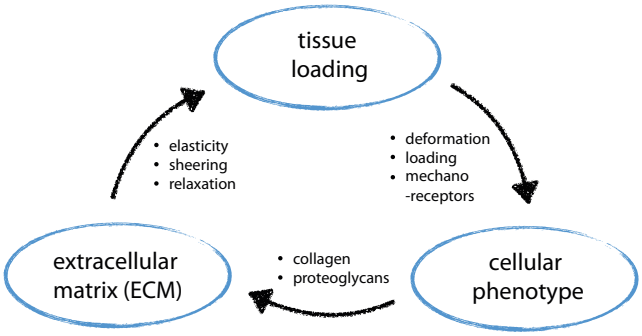

Fig. 2. Interplay between mechanics, metabolisms and tissue homeostasis.

2.1 Mechanical components

A viscoelastic material is modelled as a spring and a dashpot in parallel. The spring component provides the initial displacement as the cartilage experiences the impact, then after the impact is complete and the maximum deformation reached, the damper slowly reforms the cartilage back into its original shape using the stored energy of the initial impact. Biochemically, these properties can be explained by water displacement Mow (1989). Note that glycans can hold vast amounts of water due to their charged side chains. Viscoelastic materials can be modelled in different spring and damper configurations Li and Herzog (2004). We choose to model the cartilage as a linear Kelvin-Voigt model (the dashpot is a linear function of the velocity), since the non-linear dashpots considered elsewhere Edelsten et al. (2010) produce significant amounts of oscillations in the displacement of cartilage over time, which is biologically unrealistic. Furthermore, we omit the impact of velocities where the material will undergo an inelastic collision, which would be biologically unrealistic aswell.

Let $x(t)$ be the displacement in height of the cartilage at time t, then the equation of motion of the displacement through time is given by solving the following second order ordinary differential equation,

$$m\frac{d^2x(t)}{dt^2} + c_{damp}\frac{dx(t)}{dt} + c_{spring}x(t) = F_{external}, \quad (1)$$

where m is the mass of the cartilage, $c_{damp} > 0$ is the damping coefficient and $c_{spring} > 0$ is the elastic coefficient. In the absence of the damping term, the equation above would be the ODE of a simple harmonic oscillator. The damping controls how the tissue reforms back into its original shape. The term

$$\gamma := \frac{c_{damp}}{2 \times \sqrt{m \times c_{spring}}}, \quad (2)$$

is referred to as the *damping ratio*. If $\gamma < 1$, then the cartilage is *under damping*, that is, the damping is very small and the cartilage will keep oscillating. If $\gamma = 1$, then the cartilage is *critically damped*, meaning that the cartilage will come back to it original form in the shortest period of time. If $\gamma > 1$, then the cartilage is *over damped*, here the cartilage will take a larger period of time to get back to the original shape. In vivo studies of cartilage deformation have shown that articular cartilage is in the range of being critical to over damped Mauck et al. (2003b). In general loading scenarios, the cartilage reforms back into its original shape fairly quickly, being ready for the next loading