Finite element simulation of the electro-chemo-mechanical behavior of articular cartilage

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Thesis to obtain the Master of Science Degree in

Biomedical Engineering

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November 2020
The work presented in this thesis was performed at Instituto Superior Técnico, during the period February-November 2020, under the supervision of Fernando Manuel Fernandes Simões and João Eurico Cabral da Fonseca.
Acknowledgments

I would like to thank my supervisors, Prof. Fernando Simões and Dr. João Eurico Fonseca, for providing guidance and support throughout this project and for sharing their knowledge with me. It is always a pleasure to work with such amazing professionals in their areas of expertise.

Secondly, I want to thank my parents for their friendship and for giving me the courage to always put all of me in everything I do. To all my friends and colleagues, I appreciate all the emotional support and all the shared adventures throughout the academic life.

It was a pleasure to experience the teaching provided by this amazing institution that is Instituto Superior Técnico. I leave this school, which today I call home, carrying in mind that nothing can be accomplished without effort.

Thank you all.
Declaration

I declare that this document is an original work of my own authorship and that it fulfills all the requirements of the Code of Conduct and Good Practices of the Universidade de Lisboa.
Abstract

Articular cartilage is a porous medium, reinforced by collagen fibers and saturated by an aqueous electrolyte. The presence of electrically charged macro-molecules, the proteoglycans, leads to electro-chemo-mechanical interactions in the tissue which enhance its adaptation to physiological actions. In the present work, (1) a constitutive law, and (2) a generalized diffusion model for articular cartilage, proposed by Loret et al. [1–3], are considered. In such model, the collagen fibers constitute the solid phase of the porous medium, whilst the fluid phase is composed by water, proteoglycans and dissolved inorganic salts. A finite element program is developed in MATLAB environment, whose formulation is based on the defined model, with the purpose of numerically simulate the response of an articular cartilage sample to a combination of chemical and mechanical actions.

A sample of articular cartilage, laterally confined, is immersed in a bath of variable chemical composition, always assuming the existence of electro-chemical equilibrium in the tissue-bath interface. Nonetheless, inside the tissue the equilibrium is not attained instantaneously. In fact, the time needed to establish a permanent regimen depends on the problem geometry and on some material properties, namely the percolation and diffusion times associated with Darcy's and Fick's laws, respectively. In the numerical simulations, spatial and temporal profiles are obtained, for several electrical, chemical and mechanical variables defined in the interior of the tissue, under the action of chemical and mechanical loads, which allow to characterize its behavior.

Keywords

Articular cartilage; Osteoarthritis; Electro-chemo-mechanical couplings; Finite element method
Resumo

A cartilagem articular é um meio poroso, reforçado por fibras de colagénio e saturado por um eletrólito aquoso. A presença de macromoléculas eletricamente carregadas, os proteoglicanos, origina a ocorrência de fenómenos de interação eletro-químio-mecânica que otimizam a adaptação do tecido às ações fisiológicas. No presente trabalho, (1) uma lei constitutiva e (2) um modelo de difusão generalizada para a cartilagem articular, desenvolvidos por Loret et al. [1–3], são considerados. Neste modelo, as fibras de colagénio constituem a fase sólida do meio poroso, enquanto que a fase fluida é composta por águas, proteoglicanos e sais inorgânicos dissolvidos. Um programa de elementos finitos formulado com base no modelo referido é desenvolvido em ambiente MATLAB com o objetivo de simular numericamente a resposta de um provete de cartilagem articular à combinação de ações químicas e mecânicas.

O provete de cartilagem articular, lateralmente confinado, está imerso num banho cuja composição química pode ser alterada, admitindo-se que existe sempre equilíbrio eletro-químico na interface entre o banho e o tecido. No entanto, o equilíbrio no interior do tecido não é atingido instantaneamente. De facto, o tempo necessário para se estabelecer o regime permanente depende da geometria do problema e de várias propriedades materiais como, por exemplo, o tempo de percolação e o tempo de difusão associados à lei de Darcy e à lei de Fick, respectivamente. Nas simulações numéricas obtém-se perfis espaciais e temporais de várias grandezas mecânicas, químicas e elétricas definidas no interior do tecido, devidos à ação isolada ou combinada de carregamentos químicos e mecânicos, que permitem caracterizar o seu comportamento.

Palavras Chave

Cartilagem articular; Osteoartrose; Interacções electro-químio-mecânicas; Método dos elementos finitos
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Acronyms

ECM    extracellular matrix
FCD    fixed charge density
GAG    glycosaminoglycan
HA     hyaluronan
CS     chondroitin sulfate
KS     keratan sulfate
Abbreviations

EF  extrafibrillar
IF  intrafibrillar
PG  proteoglycan
Symbols

\( D_{kE} \)  \( k \)  coefficient of diffusion of the ionic species \( k \) in the EF phase

\( E_c \)  confined compression modulus

\( E_{sat} \)  confined compression modulus at the tissue’s saturation state

\( F \)  Faraday’s constant

\( K_h \)  hydraulic conductivity

\( M_{kE} \)  current mass of species \( k \) in the EF phase

\( R \)  gas constant

\( T \)  temperature

\( V_{kE} \)  current volume of species \( k \) in the EF phase

\( W \)  internal energy per unit of reference volume \( V_0 \)

\( \alpha_p \)  mechanical parameter

\( \alpha_w \)  mechanical parameter
\( N_{kE} \) molar content of species \( k \) in the EF phase

\( \mathcal{W} \) augmented internal energy

\( \mu_{kE}^{\text{ec}} \) electro-chemical potential of species \( k \) in the EF phase

\( \phi_E \) electrical potential in the EF phase

\( \pi_{\text{osm}} \) real bath osmotic pressure

\( \mathbf{\varepsilon} \) 4\textsuperscript{th} rank mechanical constitutive tensor

\( \sigma_e \) electrical conductivity of the tissue

\( \tau \) tortuosity factor

\( \mathbf{B}_u \) strain-displacement matrix

\( \mathbf{I}_e \) electrical current density

\( \mathbf{J}_k^d \) diffusive flux of the ionic species \( k \) with respect to the EF water velocity

\( \tilde{\pi}_{\text{osm}} \) fictitious bath osmotic pressure

\( \tilde{\epsilon}_{PG} \) fixed charge density

\( \tilde{p}_B \) fictitious bath pressure

\( \xi_k \) valence of the species \( k \)

\( g_{kE}^{\text{ec}} \) electro-chemical potential per unit of mole of species \( k \) in the EF phase
$k_e$  electro-osmotic coefficient

$k_{EE}$  permeability

$p_B$  real bath pressure

$p_E$  pressure in the EF phase

$u_{kE}^*$  effective ionic mobility in the EF phase

$N_{kE}$  mole number of species $k$ in the EF phase

$V$  current total volume of the porous medium

$V_0$  initial volume of the porous medium

$V_E$  EF volume

$\sigma$  total Cauchy stress tensor

$m_k$  molar mass of species $k$

$v_k$  molar volume of species $k$

$\rho^{kE}$  apparent density of species $k$ in the EF phase

$\rho_k$  intrinsic density of species $k$

$J_{kE}$  volume flux of species $k$ in the EF phase

$M_{kE}$  molar flux of species $k$ in the EF phase
\( \mathbf{v}_S \)  solid skeleton velocity

\( \mathbf{v}_{kE} \)  velocity of species \( k \) in the EF phase

\( c_{kE} \)  molar concentration of species \( k \) in the EF phase

\( m^{kE} \)  mass content of species \( k \) in the EF phase

\( n^{kE} \)  volume fraction of species \( k \) in the EF phase

\( v^{kE} \)  volume content of species \( k \) in the EF phase

\( x_{kE} \)  molar fraction of species \( k \) in the EF phase

\( \mathbf{E} \)  Green-Lagrange strain tensor

\( \mathbf{F} \)  gradient of deformation tensor

\( \mathbf{S} \)  2\(^{nd}\) Piola-Kirchhoff stress tensor
Introduction
Synovial joints (e.g. hip, shoulder, knee, elbow) are part of a specific group of joints presented in the human body, which allow the existence of some movements between bones, such as abduction, adduction, extension, flexion and rotation. A particular characteristic of synovial joints is the presence of a layer of articular cartilage in the extremities of the bones, being these bones connected by a fibrous capsule (synovial capsule) filled by a fluid (synovial fluid), which nourishes and lubricates the articular cartilage. In turn, the cartilage, being a soft tissue, allows for frictionless movements in the joint. The most common joint disease is osteoarthritis, which is characterized by a cellular and extracellular matrix disfunction, leading to secondary inflammation and disturbances in tissue biomechanics [4, 5].

In order to understand the influence that mechanical forces and changes in the biochemical composition of the synovial fluid will have on the natural bio-mechanical function of articulations and, in particular, on the damage of the cartilage covering the bone’s extremities, a suitable electro-chemical-mechanical model of the articular cartilage needs to be developed. Moreover, as a way to predict the evolution of degenerative cartilage diseases, as osteoarthritis, the time component also needs to be incorporated in such model.

1.1 Synovial Joints and Osteoarthritis

The connection between bones in the body is performed through an intermediary structure called joint. According to the level of movement that each joint allows, which is further dependent on the constitution and organization of its connective tissue, joints can be classified as: (a) synarthroses, if they are immovable, (b) amphiarthroses, if only a moderate movement is allowed, and (c) diarthroses, for the cases in which total free movement is possible [6].

![Figure 1.1: Illustration of an articular joint constituted by a cavity, surrounded by a fibrous capsule and filled with synovial liquid. The synovial membrane seals the fluid from the surrounding tissues. Covering the extremities of the bone, inside the joint, is a layer of articular cartilage [7].](image-url)
From the types of joints listed above, the diarthroses are the ones constituted by a fibrous capsule, which encloses the joint and is delimited by a synovial membrane. This capsule contains the synovial fluid, rich in nutrients, and within this cavity, the external layer of the bone (periosteum) is covered by articular or hyaline cartilage (see figure 1.1) [4,6].

As any other tissue of the body, during the natural aging process of life, the cartilage tissue of synovial joints may suffer modifications in the extracellular matrix (ECM), due to alterations in the normal function of the chondrocytes (cells presented in this tissue), that lose their full capacity to synthesize the ECM components [8,9]. Osteoarthritis is a disease characterized by the loss of articular cartilage in the joints (decrease of its thickness) due to an unbalance between synthesis and degradation of the cartilage components (promotion of the cells’ catabolic process over the anabolic one), culminating in altered biomechanics. Initially, the repair mechanisms are activated, in order to overcome the caused damage, but eventually the chondrocytes begin to fail to maintain the homeostatic state. In a later stage of this pathology, cartilage is almost absent and bones start to rub against each other, causing pain. Genetic factors, anatomic variants and mechanical overload of joints may be some of the causes for the cells disfunctionality, leading to osteoarthritis [5,9,10].

The understanding and knowledge of the tissue characteristics and its evolution through age is crucial in the improvement of prevention and treatment of the pathologies that may affect the cartilage tissue.

1.2 Structure and Composition of Articular Cartilage

Articular cartilage is a highly specialized connective tissue, lacking blood vessels and neurons, characterized as a saturated porous medium filled with a fluid, being composed by: water and dissolved inorganic salts, glycoproteins and lipids, which represents between 60% to 85% of the tissue volume, cells (chondrocytes), collagen fibers (mostly of type II) and proteoglycan (PG) molecules [4, 11–13]. The chondrocytes represent between 2% and 10% of the cartilage volume and are the specialized cells responsible for both the production and degradation of the ECM, being in this way in charge for its maintenance and repair [11,12]. Although not certain, it is believed that as a result of the fact that the cartilage tissue is avascular and absent of nervous cells, the chondrocytes have a very low capacity to replicate themselves, and therefore, when damaged, cartilage tissue also has a very low capability of regeneration [12,13].
According to the collagen fibers distribution across the tissue thickness, three main layers/zones may be distinguished: tangential, middle and deep. In the surface area of the cartilage, there is the tangential zone where the collagen fibers present a tangential orientation, with a high density of flattened chondrocytes and with the lower content of PGs among the 3 layers. This is the zone presenting contact with the synovial liquid and plays an important role in the protection and load transmission to the deeper layers. Subsequently, the middle zone can be found, where the density of chondrocytes, now with circular shapes, is more reduced and the PG molecules become more abundant. The collagen fibers are now randomly organized, being this the first layer contributing for the resistance to compressive forces. In the deeper zone, towards the external layer of the bone, parallel columns of fibers arise and the chondrocytes, structurally, follow the collagen fibers orientation, as one can see in figure 1.2. The thickness of the articular cartilage layer in joints may vary from joint to joint and may even vary within the same joint [6,13].

The aforementioned mechanical structure organization allows for a more uniform distribution of stresses along the joints' tissues and explains, in part, the reason for the anisotropic and inhomogeneous behavior of articular cartilage [11,13].

The collagen is a fundamental protein in the constitution of the ECM of the connective tissue, with the tropocollagen molecule as its basic unit. Each tropocollagen unit is composed by three polypeptide chains that coil around each other forming a triple helix. The subsequent polymerization of the tropocollagen molecules originate collagen fibrils that, when grouped together, create a collagen fiber (see figure 1.3). The triple helix configuration, in addition to the covalent cross links that can be formed between the fibrils, provide to the collagen its high resistance to tensile forces, which, in turn, provide the tissue with its tensile properties (stiffness and strength) [12].
Figure 1.3: Schematic of the collagen fibers’ synthesis process. Once the three alpha peptide chains are coiled together forming a procollagen molecule, the peptidase enzyme will remove the termini of the chains, originating the tropocollagen unit. Adapted from T. E. Kruger [15].

Proteoglycans are composed by a protein core attached to several glycosaminoglycan (GAG) chains, which may further form aggregations through a non-covalent protein linkage to a hyaluronan (HA) molecule (illustrated in figure 1.4). According to its glycosaminoglycan composition, different types of proteoglycans may be found among the tissue, being the most abundant one the aggrecan, which is gifted with the greatest capability to interact with the HA molecules through the link protein [11, 12]. The link protein provides stabilization to the PGs aggregation, which has a major importance in the normal function of articular cartilage, since this will contribute to the immobilization of PGs within the collagen network [11]. Apart the PGs that have the capability to form aggregations, there are also non-aggregating proteoglycans, which, in turn, have the ability to interact with the collagen fibrils [12].

Figure 1.4: Illustration of an aggregation of several proteoglycans, being each PG molecule composed by a protein core and glycosaminoglycans, that further link to the hyaluronan molecule. The linkage between the proteoglycan and hyaluronan molecules is stabilized by a link protein.
The proteoglycans GAGs can be mainly distinguished in two groups: chondroitin sulfate (CS) and keratan sulfate (KS). The CS chain is composed, approximately, by 25 up to 30 disaccharide units, while the KS chain comprises around 13 units. The aggrecan type of PGs is constituted of about 150 GAG chains, that can be either CS or KS, randomly distributed throughout the chain. Moreover, with age, different types of aggrecans, with different GAGs composition, may be found in the cartilage tissue. In fact, aggrecans rich in CS are likely to be found throughout life, while aggrecans mostly composed by KS only start to be present during the adult stage of life [11].

At physiologic conditions, the GAG chains become negatively charged due to the presence of sulfate and carboxyl groups, thus generating a high number of fixed negative charges (fixed charge density (FCD)), which cause electrostatic repulsive forces between these molecules. The existence of this electrostatic repulsive forces plays an important role in the tissue compressive stiffness, since, when a compressive force is applied, the repulsion between the PG molecules will oppose to the movement, as outlined in figure 1.5, and, therefore, if the number of PGs increase in the cartilage tissue, the FCD will as well increase, thus increasing the compressive stiffness.

Figure 1.5: Representation of the repulsive forces between proteoglycans due to the FCD distribution. When applying a given compressive force, the PG molecules will be closer to each other, thus increasing the repulsive forces, which oppose to the compression. Adapted from V. Mow and C. Hung [11].

Depending on the joint, the deep zone may be the one with the higher amount of PGs and the lower concentration of water, which, in that case, makes this layer the one mostly responsible for the resistance to compressive stresses (see figure 1.6) [6, 12].

In order to maintain the electroneutrality of the tissue, counter-ions (e.g. Na+) will be attracted, according to Donnan’s osmotic effect, and these ions will form a cloud around the charged PGs, shielding the electrostatic repulsive forces [11]. Moreover, the system comprising the tissue and the surrounding environment will tend to evolve in order to achieve the chemical balance between the tissue and the synovial fluid, which means that, if the tissue structure and composition is maintained, but the chemical environment of the synovial fluid is changed, alterations in the articular cartilage behavior are caused. For instance, if the salt concentration (e.g. NaCl, CaCl2) in the synovial fluid increases (hypertonic medium), a higher amount of Na+ or Ca2+ cations are attracted inside the tissue, decreasing even more the electrostatic repulsions between PGs and, consequently, allowing for a higher deformation.
Figure 1.6: Variation of the FCD, and thus of the PGs density, along the cartilage tissue depth (from the tangential zone to the deep zone): sometimes is the middle zone the one presenting a higher content of PGs (as occurs in the femoral head), whilst other times is the deep zone. The tangential zone is always the one with the lower amount. The FCD units are here presented as milli-equivalent moles (mEq) per gram of wet tissue. Adapted from A. Maroudas [16].

of the tissue. On the other side, if a surrounding hypotonic medium is verified, less cations will also be present inside the tissue, leading to higher repulsive forces, higher compressive stiffness and, thus, lower deformations [17].

Moreover, the chemical composition of the medium surrounding the tissue has, additionally, an impact on its level of swelling and hydration. According to the osmotic effect, water tends to flow from a medium with lower concentration of ions to a medium with higher concentration. In this way, due to the fact that the PG molecule is negatively charged and counter-ions always exist inside the tissue, in the case of a hypotonic surrounding medium, an osmotic flow is generated leading to the migration of water from the hypotonic region (outside the tissue) towards the hypertonic region (inside), contributing for the swelling of the tissue [18]. However, when the surrounding medium becomes hypertonic (with higher concentration of salt), the tissue will lose water and will shrink (see figure 1.7) [17]. Since this is a system in constant change and subsequent evolution towards the equilibrium, with the migration of ions in and out of tissue, water will flow accordingly.

The pH of the environment and of the electrolyte inside the tissue itself, is another important factor defining the properties of a charged tissue, since it will affect the FCD. The collagen fibers, that at the neutral pH present no electric charge, at lower or higher pH, lose its neutrality, since the side chains of the amino acids composing these collagen fibers no longer have its internal charges balanced [3].

The fluid part of cartilage is therefore a vital component for this tissue, since it is responsible not only for the exchange of nutrients and waste products between the chondrocytes and the synovial fluid,
Figure 1.7: Illustrative representation of the swelling and shrinking behavior of the tissue depending on the chemical composition of the surrounding bath.

but also plays an important role in defining the cartilage behavior due to the presence of the dissolved inorganic free cations such as $Na^+$, $K^+$ and $Ca^{2+}$. Within the cartilage tissue, water may be found, besides inside the cells, in two different locations: (a) inside the collagen fibers, in the intrafibrillar (IF) space, or (b) outside the collagen fibers, in the extracellular (EF) space. In both spaces the water is free to move when some load (e.g. compressive force) is applied or due to the presence of an osmotic pressure [11,12,19].

Collagen and PGs are the main components of the articular cartilage responsible for the support of the internal stresses resulting from the external forces applied in the joints and, thus, these components, together with water and dissolved inorganic salts, will determine the biomechanical properties of the tissue.

Everyday the human body is subjected to a set of basic movements such as rising up from chairs or climb stairs, which will impose different types of forces in joints that can be several times higher than the body weight. When an external compressive force is applied in the cartilage tissue, an instantaneous deformation is perceived, resulting from its deformability. With the continuous application of the stress, at a certain point water will start to be expelled along time, thus decreasing the amount of water inside the tissue and the thickness of its matrix. Therefore, articular cartilage is sometimes described as a viscoelastic material [11,13,18]. Viscoelasticity is characterized as a mechanical property of materials that behave simultaneously as an elastic and as a viscous material. A material is designated as linearly viscous if its response to an external constant load (relation between the stress applied and the underwent deformation) varies linearly with time. On the other hand, an elastic material instantaneously deforms when a given stress is applied, maintaining the same deformation over time if the applied stress also remains constant, and, when the force is removed, the material immediately recovers its original configuration (see figure 1.8) [11]. In articular cartilage, the viscoelasticity is just apparent: it is not due to the connective tissue itself, but to the outflow of EF water during a compressive loading when the
stress overcomes the osmotic pressure [11].

Figure 1.8: Typical viscoelastic behavior, where, as a response to a constant applied stress (left), there is a time dependent deformation (right, full line). In the plot at the right, one can also see the deformation of purely viscous (dashed-dotted line) and elastic (dotted line) responses.

The mechanical properties of articular cartilage are a reflection of its constituents and mechanical structure, but, as previously highlighted, the chemical and electrical aspects, due to the presence of electrically charged species (*i.e.* proteoglycans) in the tissue, introduce electro-chemo-mechanical couplings that influence the behavior of articular cartilage.

### 1.3 Previous Models of the Behavior of Articular Cartilage

Over the past years, several studies regarding the understanding of the articular cartilage behavior were conducted. Due to the chemo-mechanical couplings present in articular cartilage, these studies are both of chemical or mechanical nature, progressing later to a mixed analysis, considering simultaneously the coupled behavior.

#### 1.3.1 Experimental Work of Eisenberg and Grodzinsky

One of the first experimental works conducted in the field of soft tissues had the authorship of Eisenberg and Grodzinsky [17], where a uniaxial confined compression was applied to a bovine articular cartilage sample, immersed in a bath subjected to changes in its ionic concentration. From this, the relationship between the stresses underwent by the tissue and the ionic strength of the bath was retrieved, with the results demonstrating the dependence of the material properties of the articular cartilage on the chemical content of the bath.

#### 1.3.2 The Biphasic and Triphasic Models of the Columbia University Group

In a work conducted by Mow et al. [20] the cartilage tissue was described as a combination of a fluid and a solid phase. In such model, the collagen matrix, along with the proteoglycans, compose the solid
phase of a matrix considered to be a porous, permeable medium. The fluid phase accounted for the interstitial fluid, being both phases formulated as incompressible.

The triphasic model, proposed by Lai et al. [21], is an extension of the first biphasic model, where the cartilage tissue is instead decomposed into three phases: one incompressible interstitial fluid phase, accounting for the presence of water, one ionic phase composed by the ionic species of NaCl (addition relatively to the biphasic model), and an incompressible solid phase, comprising the collagen and proteoglycans molecules of the porous-permeable ECM.

1.3.3 The Two Compartment Theory

According to the work developed by Maroudas and coworkers [19], the water inside the articular cartilage may be found in two distinct compartments, with such partition being significant for the mechanical aspects of the tissue behavior. The two compartments are particularized in the intrafibrillar phase, corresponding to the space within collagen fibers (between the collagen fibrils), and in the extrafibrillar phase, comprising the water that is outside the collagen fibers, covering the proteoglycan molecules. However, Maroudas et al. [19] did not attempt to model the mechanical behavior of the tissue.

1.3.4 Three Phase Model: two water compartments

Based on the two compartment structure formulated by Maroudas and coworkers, Loix et al. [22] proposed a three phase model with one solid and two fluid phases. In this model, the EF fluid phase included the EF water, the charged proteoglycans and dissolved ions, while the IF fluid phase was constituted by the IF water along with the dissolved salts. The collagen fibers were the components of the solid phase. The IF compartment only presented exchange of water and ions with the EF phase, being the latter the one that communicates with the environment exterior to the tissue. In order to model these exchanges of mass between the two fluid phases and between the EF compartment and the surrounding medium, the equations of mass transfer and generalized diffusion developed in Loret and Simões [2] were used. Moreover, the chemo-mechanical model presented by Loret and Simões [1, 23, 24] was implemented in the simulation of the mechanical response of the tissue using the finite element method.

Although very complete, this model requires the definition of several material parameters related to the characteristic transfer times between the IF and EF phases (the mass transfer between phases is not instantaneous) and to the difference of the pressure of water between these compartments, that can’t be obtained from the existing experimental data.

Comparing the model by Loix et al. [22] with the triphasic model by Lai et al. [21], some differences arise:

1. In the triphasic model the partition of the water in two compartments is not taken into account,
being the water considered in one single phase, and, therefore, the species concentrations and the FCD are computed with the total amount of water;

2. Both in the biphasic and in the triphasic model of the Columbia University group, the gathering of the tissue components into phases was conducted by the nature of the species themselves rather than based on mechanical or kinetic aspects. In this way, while in the triphasic model the water is allocated in a phase separated from the ionic species, in the two compartment model the fluid phase is composed by water as well as by ionic species, being the proteoglycans, in the former model, allocated in the solid phase. Therefore, the electroneutrality condition in the triphasic model comprises species from different phases, while in the model by Loix et al. [22] this condition is written for each one of the phases;

3. In the triphasic model the mechanical parameters depend on the ionic composition of the bath which is not a constitutive feature of the tissue, while in the model by Loix et al. [22] the notion of fictitious bath was, for the first time, introduced in order to overcome this issue.

1.4 Proposed Model

The approach here proposed follows the framework of the model presented by Loix et al. [22], where a three phase model is also considered, with one solid phase and two fluid phases, accounting for the presence of two water compartments (EF and IF phases). However, in the current model the contribution of the IF phase to the simulations is considered in a different and more simplified way, not requiring the definition of IF material parameters and functions. Exchange of mass (ions and water) between the EF phase and the environment surrounding the tissue (bath/synovial fluid) and diffusion of the ionic species within the EF phase are taken into account (see figure 1.9). Moreover, the constitutive law used here is different from the one used by Loix et al. [22].

Even though the exchange of ions between the two fluid phases is not included in this work, the exchange of water between the EF and IF phases will be, indirectly, accounted for. According to Basser et al. [25], during a compression test in a specimen extracted from the hip, the percentage of IF water varied from 23.32% to 27.80% of the total amount of water, in all the stages of the test. From this, a fixed value of 25% is considered in this work for the percentage of IF water with respect to the total amount of water, and consequently, the percentage attributed to the EF part is the remaining 75%. Exchange of ions between the two fluid phases, although existing, is not modelled and, therefore, there won’t be access to the values of the masses of the IF ionic species.

Only the presence of $Na^+$ and $Cl^-$ is considered in this model since NaCl is the most abundant salt in the tissue [11].
Figure 1.9: Representative scheme of the proposed model, in which the articular cartilage is taken as a partition of three phases: solid, EF fluid and IF fluid phases. In the EF phase, due to the presence of the negatively charged proteoglycans, there will always exist a fixed amount of $Na^+$ ions (immobile counter-ions), in order to maintain the electroneutrality of the phase. In addition, mobile ions (both $Na^+$ and $Cl^-$) are also present in the EF phase, which may diffuse inside this phase, and eventually be transferred to the IF phase or to the exterior through boundary membranes, guaranteeing the equilibrium between the exterior and interior of the tissue. Proteoglycans being macro-molecules, they won’t pass through the membranes, thus only existing in the EF phase. The different type of arrows between the IF and EF phases mean that IF/EF exchanges are, in this simpler model, indirectly considered accordingly to the observations of Basser et al. [25].

1.5 Thesis Overview

This thesis is structured in six chapters. In chapter 2 the details regarding the field and constitutive equations, that govern the behavior of the tissue, are given and the assumptions that were considered are also detailed. In chapter 3 the formulation of the finite element analysis is conducted and the description of the time integration algorithm is presented. In chapter 4 the proper values for the material parameters that enter in the constitutive model are defined from experimental results available in the literature. In chapter 5 the simulations conducted are outlined and the respective results are shown. For last, in chapter 6, the conclusions are presented and suggestions for future work are made.
Field and Constitutive Equations

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2.5 Osmotic Equilibrium (Fictitious Bath) ................................. 25
The cartilage sample described above is a multi-phase tissue, being as well a multi-species mixture, composed by water ($w$), sodium ($Na^+$), chloride ($Cl^-$), among others. In this work, two distinct phases will be directly modelled: the EF phase (fluid phase), $E = \{w, PG, Cl^-, Na^+\}$, and the solid phase (skeleton), composed by the cartilage fibers, $S = \{c\}$. The EF phase may be further divided in two distinct subsets: one composed by the mobile species, $E^{mo} = \{w, Cl^-, Na^+\}$, and one composed only by the ionic species, $E^{ions} = \{Cl^-, Na^+\}$.

In this way, two types of constitutive equations are required to described the tissue’s behavior: mechano-chemical equations, which account for the deformation, and generalized diffusion equations, describing the flux of the ionic species and water through the solid skeleton.

### 2.1 Mass and Volume Measures

During the development of the field and constitutive equations, that will be conducted further ahead, several mass and volume quantities in the EF phase will be used, which need therefore to be defined a priori.

The current volume and the current mass of the species in the EF phase will be denoted as $V_{kE}$ and $M_{kE}$, respectively. Considering $V_0$ the initial volume of the porous medium, and $V = V(t)$ and $V_F$ the current total and EF volumes, several other entities related to the species $k$ in this phase may be defined (see table 2.1).

<table>
<thead>
<tr>
<th>Table 2.1: Mass and volume measures</th>
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<tbody>
<tr>
<td><strong>Intrinsic Density</strong></td>
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<tr>
<td><strong>Molar Volume</strong></td>
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<tr>
<td><strong>Volume Fraction</strong></td>
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<tr>
<td><strong>Apparent Density</strong></td>
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<tr>
<td><strong>Volume Content</strong></td>
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<tr>
<td><strong>Mass Content</strong></td>
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<tr>
<td><strong>Molar Concentration</strong></td>
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<td><strong>Mole Number</strong></td>
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<tr>
<td><strong>Molar Fraction</strong></td>
</tr>
</tbody>
</table>

The density, molar mass and molar volume are intrinsic quantities of the species, that can be related by $\rho_k = \frac{M_{kE}}{V_{kE}} = \frac{\dot{m}_k}{\hat{m}_k}$. In the same way, the following relation may also be written: $v^{kE} = \frac{V_{kE}}{V_0} = \frac{m^{kE}}{\rho_k}$.

All the entities described above can be obtained for the EF phase as a whole summing all the contributions of the species: volume content $v^{E} = \sum_k v^{kE}$, volume fraction $n^E = \sum_k n^{kE}$ and total number of moles $N_E = \sum_k N_{kE}$.
2.2 Mass Balances

The mass balance equation of mobile EF species (water and ionic species) can be written as

\[
\frac{dm_{kE}^k}{dt} + \text{div} M_{kE} = 0, \quad k \in E^{mo}
\]  

(2.1)

where \( m_{kE}^k \) is the mass content of the species and \( M_{kE} \) is the mass flux of the species through the solid skeleton defined as

\[
\rho_k^{-1} M_{kE} = n_{kE} (v_{kE} - v_S)
\]  

(2.2)

where \( \rho_k, n_{kE} \) and \( v_{kE} \) are, respectively, the intrinsic density, the volume fraction and the velocity of species \( k \) and \( v_S \) is the solid skeleton velocity. Equation (2.1) reflects the fact that the change of mass of the fluid phase species is due to the mass exchange with the surroundings.

Dividing equation (2.1) by \( \rho_k \), one obtains

\[
\frac{dv_{kE}^k}{dt} + \text{div} J_{kE} = 0
\]  

(2.3)

where \( v_{kE}^k \) is the species volume content and \( J_{kE} \) is its volume flux through the solid skeleton

\[
J_{kE} = \rho_k^{-1} M_{kE} = n_{kE} (v_{kE} - v_S).
\]  

(2.4)

Assuming that the solid skeleton and all the EF species are incompressible, the change of volume of the tissue is symmetric to the change of the volume of the fluid phase due to diffusion, that is

\[
\text{div} v_S + \text{div} J_E = 0
\]  

(2.5)

where \( J_E = \sum_{k \in E} J_{kE} \), which is obtained summing up equation (2.4) for all the EF species and assuming that the velocity of the proteoglycans is equal to the solid phase velocity.

2.3 Momentum Balance

Neglecting body forces and dynamic effects, the balance of momentum equation is

\[
\text{div} \sigma = 0
\]  

(2.6)

where \( \sigma \) is the total Cauchy Stress Tensor.
2.4 The Global Structure of the Constitutive Equations

The global structure of the constitutive equations was previously developed, in a thermodynamic framework, in Loret and Simões (2005) [23, 24]. In such framework, the Clausius-Duhem inequality, neglecting thermal effects and considering the contribution of just one fluid phase (in this work the IF phase is indirectly taken into account), results in an expression that contains two terms of distinct natures and which, consequently, are required to be positive individually:

\[
\begin{align*}
\dot{D}_1 &= -\dot{W} + S : \dot{E} + \sum_{k \in E} g_{kE}^{ec} \dot{N}_{kE} \geq 0 \\
\dot{D}_2 &= -\sum_{k \in E} \nabla g_{kE}^{ec} \hat{v}_k \cdot \dot{J}_{kE} \geq 0
\end{align*}
\] (2.7)

2.4.1 Mechanical Equation: Deformation

Regarding the fact that articular cartilage is considered to be a hyperelastic material, the first term \(\dot{D}_1\) in equation (2.7) is considered to exactly vanish, that is

\[
\dot{W} = S : \dot{E} + \sum_{k \in E} g_{kE}^{ec} \dot{N}_{kE}, \quad k \in E
\] (2.8)

where (\(\dot{\cdot}\)) denotes a time derivative, \(W = W(E, N_{kE})\) is the internal energy per unit of reference or initial volume \(V_0\), \(S\) is the 2\(^{nd}\) Piola-Kirchhoff stress tensor, \(E\) is the Green-Lagrange strain tensor (\(E = \frac{1}{2}(F^T F - I)\), where \(F\) is the gradient of deformation tensor), \(g_{kE}^{ec}\) is the electro-chemical potential per unit of mole of species \(k\) and \(N_{kE}\) is the molar content of species \(k\) (\(N_{kE} = \frac{N_{kE, E}}{V_0}\), where \(N_{kE}\) is the number of moles of species \(k\)).

Additionally, for the formulation of the equations that govern the behavior of the tissue’s deformation, two constraints need to be included: the electroneutrality and incompressibility conditions. The electroneutrality condition introduces a constraint in the constitutive equation, that incrementally can be written as:

\[
\dot{I}_{el} = F \sum_{k} \xi_k \dot{N}_{kE} = 0, \quad k \in E
\] (2.9)

where \(F\) is Faraday’s constant and \(\xi_k\) is the valence of the species \(k\). The incompressibility of all the tissue constituents introduces a second constraint in the constitutive equations, that incrementally can be written as:

\[
\dot{I}_{inc} = j = \sum_{k} \hat{v}_k \dot{N}_{kE} = 0, \quad k \in E
\] (2.10)
where $J = \frac{V}{V_0} = \det \mathbf{F}$ and $\hat{v}_k$ is the molar volume of the species ($\hat{v}_k = \frac{\hat{V}_k}{N_{kE}}$). Since $\dot{J} = J\mathbf{F}^{-\top} : \dot{\mathbf{F}}$, this constraint can also be written as:

$$\dot{I}_{inc} = \det \mathbf{F} \mathbf{F}^{-\top} : \dot{\mathbf{F}} - \sum_k \hat{v}_k \dot{N}_{kE} = 0, \quad k \in E. \quad (2.11)$$

In order to satisfy the two aforementioned constraints, an augmented internal energy $\mathcal{W}$ needs to be defined, that results from the introduction of the Lagrange multipliers $\phi_E$ and $p_E$, interpreted, respectively, as the electrical potential and the pressure in the fluid phase

$$\mathcal{W} = W(\mathbf{E}, N_{kE}) - \phi_E I_{el} + p_E I_{inc} \quad (2.12)$$

from which results

$$\dot{\mathcal{W}} = \mathbf{S} : \dot{\mathbf{E}} + \sum_k g_{kE}^{ce} \dot{N}_{kE} - \phi_E F \sum_k \xi_k \dot{N}_{kE} + p_E (\det \mathbf{F} \mathbf{F}^{-\top} : \dot{\mathbf{F}} - \sum_k \hat{v}_k \dot{N}_{kE})$$

$$= \mathbf{S} : \dot{\mathbf{E}} + \sum_k g_{kE}^{ce} \dot{N}_{kE}, \quad k \in E \quad (2.13)$$

where $\mathbf{S} = \mathbf{S} + p_E \det \mathbf{F} \mathbf{F}^{-1} \mathbf{F}^{-\top}$ and $g_{kE}^{ce} = g_{kE}^{ce} - \hat{v}_k p_E - F\phi_E \xi_k$ are the effective 2nd Piola-Kirchhoff stress tensor and the effective electro-chemical potential, respectively.

Since $\dot{\mathcal{W}}$ is also defined as:

$$\dot{\mathcal{W}} = \frac{\partial \mathcal{W}}{\partial \mathbf{E}} : \dot{\mathbf{E}} + \sum_k \frac{\partial \mathcal{W}}{\partial N_{kE}} \dot{N}_{kE}, \quad k \in E, \quad (2.14)$$

the coupled chemo-hyperelastic constitutive equations are obtained from $\mathbf{S} = \frac{\partial \mathcal{W}}{\partial \mathbf{E}}$ and $g_{kE}^{ce} = \frac{\partial \mathcal{W}}{\partial N_{kE}}$, subjected to the constraints $I_{inc} = \frac{\partial \mathcal{W}}{\partial p_E} = 0$ and $I_{el} = \frac{\partial \mathcal{W}}{\partial \phi_E} = 0$.

The constitutive form of the energy $\mathcal{W}$ here proposed is decomposed into a coupled chemo-mechanical contribution and a purely chemical contribution, $\mathcal{W} = W_{ch-mech} + W_{ch}$.

The coupled chemo-mechanical contribution is, in turn, decomposed into a coupled chemo-mechanical term $W_{ch-mech,1}(\mathbf{E}, N_{kE}) = -p_{ch}(N_{kE}) (\det \mathbf{F} - 1)$ and by a product of a purely chemical term $W_{ch,2}(N_{kE})$ by a purely mechanical term $W_{mech}(\mathbf{E})$, corresponding to the strain energy of the tissue matrix and proteins (PGs, collagen and other proteins), as

$$W_{ch-mech}(\mathbf{E}, N_{kE}) = W_{ch-mech,1}(\mathbf{E}, N_{kE}) + W_{ch,2}(N_{kE}) W_{mech}(\mathbf{E}). \quad (2.15)$$

The purely chemical term is given by:

$$W_{ch}(N_{kE}) = RT \left( \sum_k N_{kE} \ln N_{kE} - N_{kE} \ln N_{E} \right), \quad k \in E \quad (2.16)$$

where $N_{E} = \sum_{k \in E} N_{kE}$ and $N_{E} = \frac{N_{E}}{V_0} = \sum_{k \in E} N_{kE}$, $T$ is the temperature and $R$ is the gas constant.
The mole based electro-chemical potentials of the species are then written as follows:

\[
g_{kE}^{ec} = \frac{\partial W}{\partial N_{kE}} + \dot{v}_k p_E + F \phi_E \xi_k
\]

\[
= \frac{\partial W_{ch-mech}}{\partial N_{kE}} + \frac{\partial W_{ch}}{\partial N_{kE}} + \dot{v}_k p_E + F \phi_E \xi_k
\]

\[
= \frac{\partial W_{ch-mech}}{\partial N_{kE}} + RT \ln x_{kE} + \dot{v}_k p_E + F \phi_E \xi_k
\]

which, in the absence of chemo-mechanical couplings \(\frac{\partial W_{ch-mech}}{\partial N_{kE}} = 0\), present their classical form, composed by a mechanical \((\dot{v}_k p_E)\), a chemical \((RT \ln x_{kE})\) and an electrical \((\xi_k F \phi_E)\) term.

As usual, in the definition of the electro-chemical potentials of the ionic species, only the chemical and electrical terms are retained, thus:

\[
g_{kE}^{ec} = RT \ln x_{kE} + F \xi_k \phi_E, \quad k \in \mathcal{E}^{ions}.
\]

(2.18)

In the case of the electrically neutral \((\xi_w = 0)\) water molecule, its electro-chemical potential, neglecting again the chemo-mechanical couplings, is defined as:

\[
g_{wE}^{ec} = \dot{v}_w p_E + RT \ln x_{wE}.
\]

(2.19)

The Cauchy stresses may be defined as a function of the 2\(^{nd}\) Piola-Kirchhoff stress tensor, and thus:

\[
\sigma = \frac{1}{\det F} F S F^T
\]

\[
= \frac{1}{\det F} (F \frac{\partial W}{\partial \mathcal{E}} F^T - \dot{p}_E \det F F^{-1} F^{-T} F^T)
\]

\[
= \frac{1}{\det F} F \frac{\partial W}{\partial \mathcal{E}} F^T - \dot{p}_E I
\]

\[
= \frac{1}{\det F} F \frac{\partial W_{ch-mech}}{\partial \mathcal{E}} F^T - \dot{p}_E I
\]

\[
= \frac{1}{\det F} F \left( -p_{ch} \frac{\partial \det F}{\partial \mathcal{E}} F^T + \frac{\partial W_{ch,2}}{\partial \mathcal{E}} \frac{\partial W_{mech}}{\partial \mathcal{E}} F^T - \dot{p}_E I \right)
\]

\[
= \frac{1}{\det F} F (-p_{ch} \frac{\partial \det F}{\partial \mathcal{E}} F^T + \frac{\partial W_{ch,2}}{\partial \mathcal{E}} \frac{\partial W_{mech}}{\partial \mathcal{E}} F^T - \dot{p}_E I)
\]

\[
= -p_{ch} I + \mathcal{E}_{ch,2} : \mathcal{E} - \dot{p}_E I
\]

(2.20)

with \(\frac{\partial \det F}{\partial \mathcal{E}} = \det F F^{-1} F^{-T}\) and \(\frac{\partial W_{ch,2}}{\partial \mathcal{E}} \frac{\partial W_{mech}}{\partial \mathcal{E}} F^T = \mathcal{E}_{ch,2} : \mathcal{E}\). Rewriting equation (2.20) one obtains:

\[
\sigma + \dot{p}_E I = -p_{ch} I + \mathcal{E}_{ch,2} : \mathcal{E}
\]

(2.21)

where \(\mathcal{E}\) is the 4\(^{th}\) rank mechanical constitutive tensor of the tissue immersed in a saturated bath and \(I\) is the 2\(^{nd}\) order identity tensor.
In the absence of chemo-mechanical couplings \((p_{\text{ch}} = 0 \text{ and } W_{\text{ch,2}} = 1)\), the classical constitutive equation of an inert porous medium is obtained, \(\sigma + p_E I = E : E\), which corresponds to the classical definition of the Terzaghi’s effective pressure used in Soil Mechanics. Therefore, the first chemo-mechanical term \(W_{\text{ch-mech,1}}\) gives rise to an isotropic chemical stress \(p_{\text{ch}} I\), while the term \(W_{\text{ch,2}}\) is intended to amplify the stiffness of the tissue for small ionic concentrations, thus reflecting the shielding effect.

In order to obtain the final form of the constitutive equation, the concept of “fictitious bath” needs to be introduced, that is a bath whose composition and pressure \(\tilde{p}_B\) may vary in time and space so that, at any time, it is in electro-chemical equilibrium with any point of the tissue. Thus, the pressure \(p_E\) can be defined as \(p_E = \tilde{p}_B + \tilde{\pi}_{\text{osm}}\), where \(\tilde{\pi}_{\text{osm}}\) is the osmotic (or Donnan) pressure between the tissue’s point and the corresponding fictitious bath. Therefore, the constitutive equation can be written as:

\[\sigma + \tilde{p}_B I + \tilde{\pi}_{\text{osm}} I + p_{\text{ch}} I = W_{\text{ch,2}} E : E.\]  \(2.22\)

Since the properties of the fictitious bath are obtained from those of the tissue, the osmotic pressure \(\tilde{\pi}_{\text{osm}}\) can be seen as a function of the primary variables and, therefore, it is eligible to enter in the constitutive equation. Due to the fact that the osmotic pressure \(\tilde{\pi}_{\text{osm}}\) varies with the ionic concentration, it will be used to define both \(p_{\text{ch}}\) and \(W_{\text{ch,2}}\). In this sense, the following expressions are suggested:

\[p_{\text{ch}} = \alpha_p \tilde{\pi}_{\text{osm}}\]  \(2.23\)

\[W_{\text{ch,2}} = 1 + \alpha_w \tilde{\pi}_{\text{osm}}\]  \(2.24\)

where \(\alpha_p\) and \(\alpha_w\) are chemo-mechanical parameters, with \(\alpha_p\) being non-dimensional.

It is important to notice that when the composition of the tissue is uniform and the tissue is in equilibrium with an external bath of known pressure and chemical composition, \(\tilde{p}_B\) and \(\tilde{\pi}_{\text{osm}}\) become the real bath \((p_B)\) and osmotic \((\pi_{\text{osm}})\) pressures (the fictitious bath then becomes the real one), and the fluid pressure at any point of the tissue is:

\[p_E = p_B + \pi_{\text{osm}}.\]  \(2.25\)

However, when there is no equilibrium, the pressure \(p_E\) and the chemical composition are obtained, at every time, from the primary variables and never from the properties of the surrounding bath, since those properties are not constitutive, and, thus, should not be involved in the definition of the constitutive equations.

The notion of the “fictitious bath” is then particularly useful during transient states (e.g. when changes of the chemical composition of the bath occur) or when the external bath is inhomogeneous.

### 2.4.2 Equations of Generalized Diffusion

In Loret and Simões (2007) [2], two equivalent forms of the generalized diffusion equations, that satisfy the dissipation inequality \(D_2 \geq 0\) in equation (2.7), were proposed. The first one relates the vector \(j\), containing the volume fluxes of the species in the fluid phase relative to the solid phase, with the vector
of their electro-chemical gradients by an isotropic, semi-definite positive, generalized diffusion matrix $\kappa$:

$$j = -\kappa \mathbf{f} \quad (2.26)$$

where

$$\mathbf{j} = \begin{bmatrix} J_{wE} \\ J_{NaE} \\ J_{ClE} \end{bmatrix} \quad \text{and} \quad \mathbf{f} = \begin{bmatrix} \rho_w \nabla \mu_{wE} \\ \rho_{Na} \nabla \mu_{NaE} \\ \rho_{Cl} \nabla \mu_{ClE} \end{bmatrix}, \quad \kappa = \begin{bmatrix} k_{ww} & k_{wNa} & k_{wCl} \\ k_{Naw} & k_{NaNa} & k_{NaCl} \\ k_{Clw} & k_{ClNa} & k_{ClCl} \end{bmatrix}. \quad (2.27)$$

In equation (2.27), the electro-chemical potentials $\mu_{kE}^{ce}$ are related to the electro-chemical potentials per unit of mole by $\mu_{kE}^{ce} = \gamma_{k}^{ce}/n_{k}$.

The second proposed form relates the vector $\mathbf{J}$, containing the volume flux of the water and the diffusive fluxes of the ionic species $J_{k}^{d} = n_{kE}(v_{kE} - v_{wE})$ with respect to the water velocity, with the vector $\mathbf{F}$, containing the gradients of the fluid pressure, of the ionic concentrations or molar fractions and of the electric potential, by a matrix $\mathbf{K}$:

$$\mathbf{J} = -\mathbf{K} \mathbf{F} \quad (2.28)$$

where

$$\mathbf{J} = \begin{bmatrix} J_{w} \\ J_{Na}^{d} \\ J_{Cl}^{d} \\ I_{e} \end{bmatrix} \quad (2.29)$$

with $I_{e}$ the electrical current density within the tissue and

$$\mathbf{F} = \begin{bmatrix} \nabla P_{E} - RT \nabla c_{PG} \\ RT \nabla \ln x_{NaE} \\ RT \nabla \ln x_{ClE} \\ \nabla \phi_{E} \end{bmatrix}. \quad (2.30)$$
The matrix \( K \) governs the coupled motions of water and ionic species inside the tissue that result from Darcy’s law of seepage (due to a water pressure gradient), Fick’s law of diffusion (due to an ionic concentration gradient) and Ohm’s law of electrical flow (due to an electrical potential gradient). Since the electrical current density \( I_e \) is a linear combination of the water volume flux \( J_w \) and of the ionic diffusion fluxes \( J_{d,k} \), matrix \( K \) is a symmetric, isotropic and, at best, positive semi-definite and its form is given in Loret and Simões (2007) by:

\[
K = \begin{bmatrix}
  k_{EE} & 0 & 0 & k_e \\
  0 & k_{NaNa}^d & 0 & k_{Nae}^d \\
  0 & 0 & k_{ClCl}^d & k_{Cle}^d \\
  k_e & k_{Nae}^d & k_{Cle}^d & \sigma_e
\end{bmatrix}
\] (2.31)

where

\[
\begin{align*}
  k_{EE} &= \frac{K_h}{\rho_w g} \text{ is the "short-circuit" permeability which is proportional to the hydraulic conductivity } K_h, \\
  k_e &= -k_{EE} F \tilde{e}_{PG} \text{ is the electro-osmotic coefficient,} \\
  \sigma_e &= n^E F \sum_{k=E^{ions}} c_{kE} u_{kE}^* + k_{EE} F^2 \tilde{e}_{PG}^2 \text{ is the electrical conductivity of the tissue,} \\
  k_{kl}^d &= \hat{v}_k \hat{v}_l n^E c_{kE} u_{kE}^* \frac{u_{kE}^*}{F} I_{kl}, \\
  k_{ke}^d &= \hat{v}_k n^E c_{kE} u_{kE}^* sgn(\xi_k), \\
  \tilde{e}_{PG} &= e_{PG} \frac{n^E}{n_w^E} \approx e_{PG} = \xi_{PG} c_{PG} \text{ is the fixed charge density (FCD)}
\end{align*}
\]

and \( u_{kE}^* \) is the effective ionic mobility of species \( k \in E^{ions} \) related to the corresponding coefficient of diffusion \( D_{kE} \) by the Nernst-Einstein relation \( u_{kE} = D_{kE} |\xi_k| \frac{F}{RT} \), being \( u_{kE}^* = \tau u_{kE} \), with \( \tau \) representing the tortuosity factor.

The coefficients of the matrices \( \kappa \) and \( K \) are related to each other, and so there is a compatibility relation between these two matrices. In this way, the coefficients of \( \kappa \) are given by:
\[ \kappa = \begin{bmatrix} 1 & L_{Na} & L_{Cl} \\ L_{Na} & L_{Na}^2 & L_{Na}L_{Cl} \\ L_{Cl} & L_{Na}L_{Cl} & L_{Cl}^2 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & k_{NaNa}^d & 0 \\ 0 & 0 & k_{ClCl}^d \end{bmatrix} \] (2.33)

where \( L_k = \frac{n_k^E}{w} \), \( k = L^{ions} \).

### 2.5 Osmotic Equilibrium (Fictitious Bath)

From the electro-chemical potentials of the ionic species \( Na^+ \) and \( Cl^- \), one may obtain additionally the chemical potential of the salt \( NaCl \).

\[
g_{NaCl} = g_{NaE}^{\infty} + g_{ClE}^{\infty} = \mu_{NaE}^{\infty}\tilde{m}_Na + \mu_{ClE}^{\infty}\tilde{m}_Cl = RT \ln x_{NaE} + F\phi_E + RT \ln x_{ClE} - F\phi_E = RT \ln(x_{NaE}x_{ClE})
\] (2.34)

with \( \tilde{m}_Na \) and \( \tilde{m}_Cl \) the molar masses of \( Na^+ \) and \( Cl^- \), respectively, and \( x_{kE} \) the molar fraction of the species in the EF compartment.

The electroneutrality condition of the (fictitious) bath requires that \( \tilde{x}_{ClB} = \tilde{x}_{NaB} \) (with \( \tilde{x}_{ClB} \) and \( \tilde{x}_{NaB} \) the molar fractions of the species in the fictitious bath), and the electroneutrality condition of the tissue imposes that \( x_{ClE} = x_{NaE} + y_{PG} \) where \( y_{PG} = \xi_{PG} x_{PG} < 0 \). Although \( x_{PG} \) is very small when compared to the molar fractions of the ionic species, \( y_{PG} \) is a significant quantity since the PGs valence is a very large number and, therefore, \( y_{PG} \) can’t be neglected. Imposing the chemical equilibrium between the two phases (bath and cartilage tissue), \( \tilde{g}_{NaCl} = g_{NaCl} \), one obtains:

\[
x_{NaE}x_{ClE} = \tilde{x}_{NaB}\tilde{x}_{ClB}
\]

or

\[
\tilde{x}_{NaB} = \tilde{x}_{ClB} = \sqrt{x_{NaE}(x_{NaE} + y_{PG})}
\] (3.35)

and

\[
\tilde{x}_{wB} = 1 - \tilde{x}_{NaB} - \tilde{x}_{ClB} = 1 - 2\sqrt{x_{NaE}(x_{NaE} + y_{PG})}
\]

\[
x_{wE} \approx 1 - x_{NaE} - x_{ClE} = 1 - 2x_{NaE} - y_{PG}.
\] (2.36)

Note that \( x_{PG} \) was neglected in the first equality of equation (2.36).
From the chemical equilibrium of water (\( \tilde{g}_w = g_w \)), the fictitious Donnan osmotic pressure is thus defined as:

\[
\tilde{\pi}_{osm} = p_E - \tilde{p}_B = \frac{RT}{\tilde{v}_w} \ln \left( \frac{\tilde{x}_{wB}}{\tilde{x}_{wE}} \right)
\]

\[\approx \frac{RT}{\tilde{v}_w} (x_{NaE} + x_{ClE} - \tilde{x}_{NaB} - \tilde{x}_{ClB}) \tag{2.37}\]

from which results \( \tilde{p}_B = p_E - \tilde{\pi}_{osm} \).

In order to obtain the quantities necessary to formulate the finite element method we need to differentiate the expression of \( \tilde{\pi}_{osm} \):

\[
\delta \tilde{\pi}_{osm} \approx \frac{RT}{\tilde{v}_w} (\delta x_{NaE} + \delta x_{ClE} - 2\delta \tilde{x}_{NaB})
\]

\[= \frac{RT}{\tilde{v}_w} \left( \delta x_{NaE} + \delta x_{ClE} - 2\left( \sqrt{x_{NaE}x_{ClE}} \right) \right)
\]

\[= \sum_{k \in E_{ions}} P_k \delta x_{kE} \tag{2.38}\]

with

\[
P_{Na} = \frac{RT}{\tilde{v}_w} \left( 1 - \frac{1}{\sqrt{x_{NaE}x_{ClE}}} \right) x_{ClE} = \frac{RT}{\tilde{v}_w} \left( 1 - \frac{x_{ClE}}{x_{NaB}} \right)
\]

and

\[
P_{Cl} = \frac{RT}{\tilde{v}_w} \left( 1 - \frac{1}{\sqrt{x_{NaE}x_{ClE}}} \right) x_{NaE} = \frac{RT}{\tilde{v}_w} \left( 1 - \frac{x_{NaE}}{x_{NaB}} \right).
\]

Then, using equation (A.15) of appendix A, one obtains:

\[
\delta \tilde{\pi}_{osm} = Q_u \text{ div} \tilde{u} + \sum_{l \in E_{non}} Q_l \tilde{m}_l \delta \mu_{lE}^c
\]

with

\[
Q_u = \sum_{k \in E_{ions}} P_k \frac{3y_{PG} \tilde{z}_{kE}}{4 \tilde{v}_w z_E} \tag{2.39}\]

and

\[
Q_l = \sum_{k \in E_{ions}} P_k \frac{x_{kE} \tilde{z}_{kl}}{RT} z_{kl},
\]

with \( z_{kl} = 1_{kl} - \xi_k \tilde{\xi}_l \frac{x_{IE}}{z_E} \) and \( z_E = x_{NaE} + x_{ClE} \).

As the system evolves towards the equilibrium, which occurs when the tissue is in balance with the (homogeneous) real bath (the fictitious bath then becomes the real bath), the electro-chemo-mechanical equilibrium conditions (equations (2.35), (2.36) and (2.37)) can also be used to obtain the equilibrium concentrations within the tissue and the osmotic pressure as a function of the known (real) bath composition \( x_{NaB} = x_{ClB} = x^* \), as:
\[
x_{NaE} = \frac{-y_{PG}}{2} + \frac{\sqrt{y_{PG}^2 + 4x^2}}{2}
\]

\[
x_{ClE} = \frac{y_{PG}}{2} + \frac{\sqrt{y_{PG}^2 + 4x^2}}{2}
\]

\[
x_{wE} = 1 - x_{NaE} - x_{ClE} = 1 - \sqrt{y_{PG}^2 + 4x^2}
\]

\[
\pi_{osm} = \frac{RT}{\nu_w} (\sqrt{y_{PG}^2 + 4x^2} - 2x^*)
\]
3

Finite Element Formulation

Contents

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3.1 Element Contributions of the Field Equations

The field equations developed in the previous sections 2.2 and 2.3, and that are going to be used from here forward to govern the cartilage tissue behavior under different mechanical and chemical conditions, are summarized in table 3.1. There are 4 different equations that need to be verified (momentum balance of the porous medium, mass balance of each of the ions Na\(^+\) and Cl\(^-\), and the global mass balance of the medium as a whole), from which are obtained the 4 unknowns of the problem: solid displacement and the electro-chemical potentials of the EF species \(w, Na^+, Cl^-\).

**Table 3.1:** Field equations and the primary unknowns that can be obtained from each equation.

<table>
<thead>
<tr>
<th>Field Equation</th>
<th>Unknown (degree of freedom)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance of Momentum (\text{div } \sigma = 0)</td>
<td>displacement (u)</td>
</tr>
<tr>
<td>Total Mass Balance (\text{div } v_S + \text{div } J_E = 0)</td>
<td>electro-chemical potential of the EF water (\mu_{wE}^{ec})</td>
</tr>
<tr>
<td>Mass Balance of each Ionic Species (\frac{dv_{kE}}{dt} + \text{div } J_{kE} = 0)</td>
<td>electro-chemical potential of the EF ionic species (\mu_{kE}^{ec}, k = Na^+, Cl^-)</td>
</tr>
</tbody>
</table>

In order to solve these equations, so the values of the primary unknowns are obtained, a finite element analysis will be conducted.

To formulate the problem in its weak form, the field equations need to be multiplied by virtual fields \((u^*, \mu^*)\), and integrated by parts over the body \(V\), which results in the following formulation:

\[
\begin{align*}
\int_V \nabla (u^*) : \sigma \, dV &= \int_{\partial V} u^* \cdot \sigma \cdot \hat{n} \, dS \\
\int_V \mu^* \text{div } v_S - \nabla (\mu^*) \cdot J_E \, dV &= - \int_{\partial V} \mu^* J_E \cdot \hat{n} \, dS \\
\int_V \mu^* \left( \frac{dv_{kE}}{dt} \right) - \nabla (\mu^*) \cdot J_{kE} \, dV &= - \int_{\partial V} \mu^* J_{kE} \cdot \hat{n} \, dS, \quad k \in E^{ions}
\end{align*}
\]

(3.1)

where \(\hat{n}\) is the unit outward normal to the boundary \(\partial V\) of the volume \(V\).

The replacement of the virtual fields in equation (3.1), for each element, by its approximation with the shape functions \(\psi (u^* = \psi_u u^*, \mu^* = \psi_\mu \mu^*)\) results in the elemental non-linear first order semi-discrete equation

\[
\mathcal{F}^{int}_e = \mathcal{F}^{ext}_e
\]

(3.2)

where the contribution of the element \(e\) to the global vectors \(\mathcal{F}^{int}_e\) and \(\mathcal{F}^{ext}_e\) is:

31
\[ F_{\text{ext}}^e = \begin{bmatrix} \int_{\partial V^e} \psi_u^T \sigma \cdot \hat{n} \, dS^e \\ - \int_{\partial V^e} \psi_{\mu}^T J_E \cdot \hat{n} \, dS^e \\ - \int_{\partial V^e} \psi_{\mu}^T J_{NaE} \cdot \hat{n} \, dS^e \\ - \int_{\partial V^e} \psi_{\mu}^T J_{ClE} \cdot \hat{n} \, dS^e \end{bmatrix} \] (3.3)

\[ \begin{bmatrix} \int_{V^e} B_u^T \sigma \, dV^e \\ \int_{V^e} \psi_{\mu}^T \text{div} \, v_S - \nabla \psi_{\mu}^T J_E \, dV^e \\ \int_{V^e} \psi_{\mu}^T \frac{dJ_{NaE}}{dt} - \nabla \psi_{\mu}^T J_{NaE} \, dV^e \\ \int_{V^e} \psi_{\mu}^T \frac{dJ_{ClE}}{dt} - \nabla \psi_{\mu}^T J_{ClE} \, dV^e \end{bmatrix} \] (3.4)

From the elemental vector of the internal forces \( F_{\text{int}}^e \), the elemental stiffness and diffusion matrices may be retrieved through their definition, \( K^e = \frac{\partial F_{\text{int}}^e}{\partial \chi^e} \) and \( C^e = \frac{\partial F_{\text{int}}^e}{\partial \psi^e} \), with \( \chi^e \) and \( \psi^e \) representing, respectively, the vectors of the elemental degrees of freedom and their time derivatives:

\[ \chi^e = \begin{bmatrix} u^e \\ \mu_{wE}^e \\ \mu_{NaE}^e \\ \mu_{ClE}^e \end{bmatrix}, \quad \psi^e = \dot{\chi}^e, \] (3.5)

\[ C^e = \begin{bmatrix} 0 & 0 & 0 & 0 \\ C_{\mu_{wE}^e} & 0 & 0 & 0 \\ C_{\mu_{NaE}^e} & C_{\mu_{NaE}^e \mu_{Na}^e} & C_{\mu_{NaE}^e \mu_{Cl}^e} \\ C_{\mu_{ClE}^e} & C_{\mu_{ClE}^e \mu_{Na}^e} & C_{\mu_{ClE}^e \mu_{Cl}^e} \end{bmatrix}, \] (3.6)
The non-zero components of the matrices $K^e$ and $C^e$ are then:

$$K^e_{uu} = \int_{V^e} \psi^T_u \mathbf{tr} \mathbf{B}_u \, dV^e,$$

$$K^e_{u\mu} = \int_{V^e} \psi^T_u \left[ \frac{3 \nu_k E}{4 \nu E} z_{kE} \right] \mathbf{tr} \mathbf{B}_u \, dV^e, \quad k \in E^{ions},$$

$$K^e_{\mu\mu} = \int_{V^e} \psi^T_\mu \left[ \frac{\mu_i}{RT} v^k E z_{kE} \right] \mathbf{tr} \mathbf{B}_u \, dV^e, \quad k \in E^{ions}, \quad l \in E^{ions},$$

$$C^e_{\mu w} = \int_{V^e} \mathbf{tr} \left[ \rho \sum_{k \in E} k_{kl} \nabla \psi_\mu \right] \nabla \psi_\mu \, dV^e, \quad l \in E^{mo},$$

$$C^e_{\mu k l} = \int_{V^e} \mathbf{tr} \left[ \rho_i \psi_\mu \right] \nabla \psi_\mu \, dV^e, \quad k \in E^{ions}, \quad l \in E^{mo}$$

where $\mathbf{B}_u$ is defined as the strain-displacement matrix, $Q_u$ and $Q_l$ are given by equation (2.39) and $R_u$ and $R_l$ are given by equation (A.20). To obtain each of the components of the elemental matrices it is necessary to resort to the constitutive equations developed in section 2.4, taken additionally into account the manipulations described in detail in appendix A.

In the present work, for the finite element simulation, a one dimensional bar element will be used, with three nodes for the displacement unknown, and two nodes in the case of the electro-chemical potentials. In this way, each variable may be approximated, within a generic element $e$, by the predefined shape functions multiplied by the nodal values of the respective variables: $u = [\psi_u] \{u^e\}$ and $\mu_{\mu c} = [\psi_\mu] \{\mu_{\mu c}^e\}$ with

$$u^e = \begin{pmatrix} u^1 \\ u^2 \\ u^3 \end{pmatrix} \quad \text{and} \quad \mu_{\mu c}^e = \begin{pmatrix} \mu_{\mu c 1}^e \\ \mu_{\mu c 2}^e \end{pmatrix},$$

The shape functions for the displacement and electro-chemical potentials will differ, since the number of nodes per element for each of these two degrees of freedom is different as well. Thus, the equations...
that define each shape function, in function of the position $X$ along the element, are presented below:

$$\psi_\mu = \begin{bmatrix} \psi_1^\mu & \psi_2^\mu \end{bmatrix}, \quad \text{with} \quad \begin{cases} \psi_1^\mu = \frac{1}{2} - \frac{1}{L} \left( X - \frac{X_1 + X_2}{2} \right) \\ \psi_2^\mu = \frac{1}{2} + \frac{1}{L} \left( X - \frac{X_1 + X_2}{2} \right) \end{cases}$$

and

$$\psi_u = \begin{bmatrix} \psi_1^u & \psi_2^u & \psi_3^u \end{bmatrix}, \quad \text{with} \quad \begin{cases} \psi_1^u = -\frac{1}{2} \frac{2}{L} \left( X - \frac{X_1 + X_2}{2} \right) \left( 1 - \frac{2}{L} \left( X - \frac{X_1 + X_2}{2} \right) \right) \\ \psi_2^u = 1 - \frac{4}{L^2} \left( X - \frac{X_1 + X_2}{2} \right)^2 \\ \psi_3^u = \frac{1}{2} \frac{2}{L} \left( X - \frac{X_1 + X_2}{2} \right) \left( 1 + \frac{2}{L} \left( X - \frac{X_1 + X_2}{2} \right) \right) \end{cases}$$

where $L$ is the element length (see figure 3.1).

![Figure 3.1: Illustration of the one dimensional bar element, with two (top) and three (bottom) nodes per element. The $X$ represents the axis of the position along the element, with $X_1$ and $X_2$ representing, respectively, the coordinates in the axis of the first and last node of the element. In the case of the presence of three nodes, the position of the middle one is defined as $(X_1 + X_2)/2$.](image)

From the classical finite element formulation, the displacements unknowns require a quadratic interpolation for a proper approximation of the results, being, therefore, considered three nodes per element for this unknown. Regarding the electro-chemical potentials, these unknowns comprise further quantities, namely: electrical potentials, molar fractions and water pressures. In the case of a porous medium, in which the nodal degrees of freedom also comprise the water pressure, a linear interpolation is usually used to approximate the behavior of this variable along the element. Thus, although the electro-chemical potentials depend also on electrical potentials and molar fractions, a linear interpolation with two nodes per element was considered for these variables.

In order to obtain the non-zero components of the stiffness and diffusion matrices, the Gaussian Quadrature rule is applied, where two integration points will be used for both displacement and electro-chemical potentials unknowns. In the case of the electro-chemical potentials, since these unknowns were defined to vary linearly along the element, only one integration point would be required. However,
as a way to simplify further calculations, two integration points were chosen for all cases, even though this means an increase in the computational work.

In a 1D (uniaxial strain) analysis, the 4th rank mechanical constitutive tensor \( \mathbf{E} \) defined in equation (2.21) and used in equation (3.9), involves just one constitutive constant. Formally, the \( \mathbf{E} \) tensor will be replaced by a constant \( (E_{\text{eq}}) \) to be obtained later, in chapter 4, from experimental results.

### 3.2 Time Integration

For the integration of the semi-discrete equations previously developed, within the finite element framework, both an incremental and an iterative process will be applied, where the steps in the incremental process are denoted by \( n \), and the iterations by \( i \). Moreover, a midpoint scheme will be used for the numerical integration, meaning that, for each step \( n + 1 \), the equations are evaluated at the time \( t_{n+1} = t_n + \alpha \Delta t \), with \( \alpha = 0.5 \), where \( \Delta t = t_{n+1} - t_n \).

Within each step \( n + 1 \), several iterations will be performed until the system convergence is reached, which is translated by the evolution of the residual towards zero, as:

\[
\mathbf{R}_{n+1} = \mathbf{E}^\text{ext}(\mathbf{S}_{n+\alpha}, \mathbf{X}_{n+\alpha}) - \mathbf{E}^\text{int}(\mathbf{X}_{n+\alpha}, \mathbf{V}_{n+\alpha}) = 0, \quad (3.10)
\]

with \( \mathbf{X} \) and \( \mathbf{V} \) representing, respectively, the vectors of the nodal primary variables (displacement and electro-chemical potentials) and the nodal velocities of change of the primary variables and \( \mathbf{S} \) representing the nodal "loads". The quantities \( \mathbf{Z} = \mathbf{S}, \mathbf{X}, \mathbf{V} \), evaluated at the time \( t_{n+\alpha} \), are defined as \( \mathbf{Z}_{n+\alpha} = (1 - \alpha) \mathbf{Z}_n + \alpha \mathbf{Z}_{n+1} \), with \( \mathbf{X}_{n+1} \) and \( \mathbf{V}_{n+1} \) the values of \( \mathbf{X} \) and \( \mathbf{V} = d\mathbf{X}/dt \) evaluated, respectively, at the time \( t_{n+1} \).

In the present problem, the internal forces are a non-linear function of the nodal primary unknowns. In this way, the Newton-Raphson method will be applied, with the previous linearization of equation (3.2) around the solution’s guess in the current iteration \( (\mathbf{X}^i \text{ and } \mathbf{V}^i) \), for \( i \geq 1 \), through the development of the internal forces into a Taylor series, neglecting the higher order terms, which results in:

\[
\mathbf{E}^\text{ext}(\mathbf{S}_{n+\alpha}^i, \mathbf{X}_{n+\alpha}^i) - \mathbf{E}^\text{int}(\mathbf{X}_{n+\alpha}^i, \mathbf{V}_{n+\alpha}^i) \simeq \mathbf{R}_{n+\alpha}^i - \mathbf{E}^*(\mathbf{S}_{n+\alpha}^i, \mathbf{V}_{n+\alpha}^i) = 0, \quad (3.11)
\]

with \( \mathbf{R}_{n+\alpha}^{i+1} \), the residual at step \( n + 1 \), evaluated at time \( t_{n+\alpha} \), and at iteration \( i + 1 \), which recalling equation (3.10), has the form

\[
\mathbf{R}_{n+\alpha}^{i+1} = \mathbf{E}^\text{ext}(\mathbf{S}_{n+\alpha}^i, \mathbf{X}_{n+\alpha}^i) - \mathbf{E}^\text{int}(\mathbf{X}_{n+\alpha}^i, \mathbf{V}_{n+\alpha}^i), \quad (3.12)
\]

where, \( \mathbf{Z}^{i+1}_{n+\alpha} = (1 - \alpha) \mathbf{Z}_n + \alpha \mathbf{Z}_n^{i+1} \), with \( \mathbf{Z} = \mathbf{S}, \mathbf{X}, \mathbf{V} \).

With all the above relations formulated, the iterative process is then conducted as follows:

\[
\begin{align*}
\text{for } i &= 0 \quad \mathbf{V}_n^0 = \mathbf{V}_n, \quad \mathbf{X}_n^0 = \mathbf{X}_n + (1 - \alpha) \Delta t \mathbf{V}_n \\
\text{for } i &\geq 1 \quad \mathbf{V}_{n+1}^i = \mathbf{V}_{n+1}^{i-1} + \Delta \mathbf{V}, \quad \mathbf{X}_{n+1}^i = \mathbf{X}_n + \Delta t \mathbf{V}_{n+1}^i = \mathbf{X}_{n+1}^0 + \alpha \Delta t \mathbf{V}_{n+1}^i
\end{align*}
\quad (3.13)
\]
where the velocity update $\Delta V$, in each iteration, is obtained from the linearized equation (3.11), forcing the residual to vanish. The effective diffusion matrix $C^*$ is expressed in terms of the diffusion matrix $C$ and of the stiffness matrix $K$ as:

$$C^* = C + \alpha \Delta t \, K \quad \text{with} \quad C = \frac{\partial F^{\text{int}}}{\partial V}(x_i^n + \alpha), \quad K = \frac{\partial F^{\text{int}}}{\partial X}(x_i^n + \alpha).$$  (3.14)

While the choice of the steps’ number used in the incremental process may be variable and free, the number of iterations within each step will depend on a predefined criteria of convergence. As the iteration process progresses, returning in each iteration an increment $\Delta V$ that updates the velocity vector, it is expected that the system converges until the residual becomes zero (or, equivalently, $\Delta V \approx 0$). Thus, the criteria here proposed is the following:

$$\frac{||\Delta V||_n^{(i)}(\Delta V)}{||\Delta V||_n^{(0)}} \leq TOL,$$  (3.15)

where $||\Delta V||_n^{(i)}$ represents the norm of the normalized $\Delta V$ vector, at the step $n$ and iteration $i$, and $TOL$ represents the threshold which is a very small number.

The normalization of the $\Delta V$ vector is required since either $X$ and $V$ contain nodal values both related to the displacements and to the electro-chemical potentials, and these two primary variables have different physical dimensions and orders of magnitude. In this way, the $\Delta V$ vectors over iterations, in the positions related to the displacements, are normalized by the maximum value among the $\Delta V$ values at iteration $0$, in the positions corresponding to the displacements, and the same for the positions related to the electro-chemical potentials,

$$(\Delta V_n^i)_u = \frac{(\Delta V_n^0)_u}{(\Delta V_n^0)_{\max,u}} \quad \text{and} \quad (\Delta V_n^i)_\mu = \frac{(\Delta V_n^0)_\mu}{(\Delta V_n^0)_{\max,\mu}}.$$

Once this is performed, the same threshold $TOL$ may be used for both variables.
4

Chemo-Mechanical Model

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37
For the simulation of the mechanical behavior of the cartilage tissue, under different physiologic and loading conditions, the equation (2.22), which dictates the stress-strain relationship, is considered.

At an equilibrium condition, the constitutive equation, under a uniaxial strain state, becomes
\[\sigma = -p_E (1 + \alpha_p) + (1 + \alpha_w p_E) \, E_{\text{sat}} \, \epsilon,\]
where the constitutive tensor $E$ is represented, in a one-dimensional formulation, only by the material parameter $E_{\text{sat}}$. In this way, this equation is composed by three mechanical parameters that have to be properly defined so that this model well simulates the cartilage mechanical behavior: $\alpha_p$, $\alpha_w$ and $E_{\text{sat}}$, the latter being the confined compression modulus at the tissue’s saturation state.

4.1 Initial Considerations

In a state where the equilibrium between the tissue and the surrounding medium is verified, the fictitious bath corresponds to the real bath, and thus $\tilde{\pi}_{\text{osm}} = \pi_{\text{osm}}$ and $\tilde{p}_B = p_B$. Taking additionally the real bath pressure as the reference value (formally considering the atmospheric pressure $p_B = 0$), one obtains: $p_E = \pi_{\text{osm}}$, and the constitutive equation (2.22), under a uniaxial strain state, becomes:
\[\sigma = -p_E (1 + \alpha_p) + (1 + \alpha_w p_E) \, E_{\text{sat}} \, \epsilon. \quad (4.1)\]

From equation (2.37), under equilibrium, the equation for the real osmotic pressure $\pi_{\text{osm}}$, arises, with the quantities of the fictitious bath becoming the ones at the real bath: $\pi_{\text{osm}} = \frac{RT}{v_w} (x_{NaE} + x_{ClE} - x_{NaB} - x_{ClB})$. By approximating the total volume of the EF phase by the volume of the EF water (water is the most abundant constituent of the tissue) and replacing the molar fractions by molar concentrations as $x_{kE} \approx c_{kE} v_w$, further taking into account equation (2.40), the equation for the water pressure used in the current simulation is:
\[p_E = RT \left( \sqrt{c_{\text{PG}}^2 + 4c^2} - 2c^* \right), \quad (4.2)\]
with $c_{\text{PG}} = \xi_{\text{PG}} c_{\text{PG}}$ being the tissue FCD and $c^* = c_{NaB} = c_{ClB}$ being the ionic strength of the bath that the tissue is in contact with.

The definition of the proper values for the material parameters in the mechanical model is conducted by adjusting this model to real experimental results, and for that, the experimental work performed by Eisenberg and Grodzinsky [17] is considered. In this work, an extraction of a cylindrical graft of articular cartilage and bone was performed, followed by several cuts, thus obtaining a final sample of cartilage from the middle zone, for posterior tests, with 6.4 mm of diameter and 600 $\mu m$ of thickness.

With the tissue sample described above, the initial volume considered henceforth is $V_0 = 0.0193 \times 10^{-6}$ m$^3$. Supposing that, initially, 80% of the total volume of the articular tissue is water, one can obtain the initial total volume of water in the sample: $V_0^w = 0.8V_0$. However, as mentioned before in chapter 1, section 1.2, part of the water is contained in the IF space and the remaining in the EF space, being the percentage of water, with respect to the total amount, in the IF and EF phases, 25% and 75%, respectively, as indicated in chapter 1, section 1.4. In this way, the initial EF water volume is $V_{wE}^0 = $
1.1580 \times 10^{-8} \text{ m}^3 and the respective number of moles, considering the water density and the water molar mass (table 4.1), is \( N_{wE}^0 = 6.4333 \times 10^{-4} \text{ mol} \). Regarding the PGs, their mass percentage from the total tissue’s mass is considered to be 5%, thus resulting in a number of moles of \( N_{PG}^0 = 5.3075 \times 10^{-10} \text{ mol} \) and in a volume of \( V_{PG} = 5.8913 \times 10^{-10} \text{ m}^3 \), considering, once again, the PGs’ molar mass and volume shown in table 4.1 and a tissue’s density of 1.1 g/cm\(^3\). Since PG molecules aren’t able to leave the EF space, both PGs’ mass and volume always remain constant.

<table>
<thead>
<tr>
<th>Table 4.1: Chemical constants.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \hat{v}_k ) (m(^3) mol(^{-1}))</td>
</tr>
<tr>
<td>( w )</td>
</tr>
<tr>
<td>( Na )</td>
</tr>
<tr>
<td>( Cl )</td>
</tr>
<tr>
<td>( PG )</td>
</tr>
</tbody>
</table>

The density values of each specie may be retrieved from the values of the molar volumes and masses as \( \rho_k = \frac{\hat{m}_k}{\hat{v}_k} \).

The bath concentration is initially set to 1000 mol/m\(^3\) = 1 M (practically near to saturation), with its pressure and electrical potential being set to zero (reference values). Due to the equilibrium between the bath and the tissue, the electro-chemical potentials of the water and ions inside and outside the tissue are equal. In this way, the initial number of moles of the ionic species in the EF phase is: \( N_{NaE}^0 = 1.28381 \times 10^{-5} \text{ mol} \) and \( N_{ClE}^0 = 1.04497 \times 10^{-5} \text{ mol} \), from which the respective initial EF volumes may also be calculated, resorting to the molar volumes presented in table 4.1: \( V_{NaE}^0 = 3.0426 \times 10^{-11} \text{ m}^3 \) and \( V_{ClE}^0 = 1.6113 \times 10^{-10} \text{ m}^3 \). Moreover, the initial values of the EF water pressure and EF electrical potential are, respectively, \( p_{E}^0 = 2.6413 \times 10^4 \text{ Pa} \) and \( \phi_{E}^0 = -2.64283 \times 10^{-3} \text{ V} \).

From the number of moles defined for the water, ionic species and PG molecules, the initial molar fraction of the PGs, in the EF phase, is given by: \( x_{PG}^0 = \frac{N_{PG}^0}{N_{wE}^0 + N_{NaE}^0 + N_{ClE}^0 + N_{PG}^0} = 7.9618 \times 10^{-7} \). Moreover, it was considered that the initial EF total volume, \( V_{E}^0 \), is given by the contributions of the initial volumes of each of its constituents (water, ions and PGs), and so its value is \( V_{E}^0 = 1.2361 \times 10^{-8} \text{ m}^3 \). Due to the fact that the volume percentage of water and ions, with respect to the total amount, in the IF and EF phases, is 25% and 75%, respectively, the total initial volume of the IF phase is 1/3 of the total EF phase initial volume, without the PGs contribution: \( V_{I}^0 = 3.9239 \times 10^{-9} \text{ m}^3 \).

Multiplying the PGs’ molar fraction, \( x_{PG} \), by the PGs’ valence, one obtains \( y_{PG}^0 = -0.0036 \) and the initial value of the FCD is \( e_{PG}^0 = -200 \) moles of charge/m\(^3\), or, equivalently, \( e_{PG}^0 = -200 \times 10^{-6} \) moles of charge/g = - 0.2 mEq of charge/g, which is within the values of the FCD pictured in figure 1.6 of chapter 1. Moreover, note that the PGs’ initial molar fraction, \( x_{PG}^0 \), can be neglected when compared to the molar fractions of the other constituents, but \( y_{PG}^0 \) is a significant quantity and can’t be neglected in
the electroneutrality condition.

Table 4.2: Initial values.

<table>
<thead>
<tr>
<th>$V_0$ = 0.0193$\times 10^{-6}$</th>
<th>$V_w^0$ = 1.544$\times 10^{-8}$</th>
<th>$p_E^0$ = 2.6413$\times 10^4$</th>
<th>$\phi_E^0$ = -2.64283$\times 10^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{PG} = 5.8913\times 10^{-10}$</td>
<td>$V_w^0 = 1.1580\times 10^{-8}$</td>
<td>$V_{NaE}^0 = 3.0426\times 10^{-11}$</td>
<td>$V_{ClE}^0 = 1.6113\times 10^{-10}$</td>
</tr>
<tr>
<td>$N_{PG} = 5.3075\times 10^{-10}$</td>
<td>$N_{wE}^0 = 6.4333\times 10^{-4}$</td>
<td>$N_{NaE}^0 = 1.28381\times 10^{-5}$</td>
<td>$N_{ClE}^0 = 1.04497\times 10^{-5}$</td>
</tr>
<tr>
<td>$x_{PG}^0 = 7.9618\times 10^{-7}$</td>
<td>$x_{wE}^0 = 0.9651$</td>
<td>$x_{NaE}^0 = 0.0193$</td>
<td>$x_{ClE}^0 = 0.0157$</td>
</tr>
</tbody>
</table>

Units: volume = m$^3$; number of moles = mol; electrical potential = volt; water pressure = pascal.

All the quantities defined so far, and that are summarized in table 4.2, result from an initial condition under equilibrium, which applies to all the simulations conducted in this work. Therefore, these initial values will also be used in chapter 5, where the main simulations take place. Yet, one should notice that, since in the simulations of the current chapter, the EF water pressure is always calculated using equation (4.2), there is no need to consider here the initial EF water pressure value outlined in table 4.2. Nevertheless, the difference between these two values is insignificant and it is due to approximation factors conducted while obtaining equation (4.2). Similarly, the initial value of 200 moles of charge/m$^3$ for the FCD is also not used directly in the current simulation, being $e_{PG}$ computed as:

$$e_{PG} = \xi_{PG} \frac{N_{PG}}{V_E}. \quad (4.3)$$

The error involved in these simplifications is only around 10%.

The adjustment of the model to the experimental points was performed in two different stages, considering in all cases that the system was under an equilibrium state:

1. The first stage was performed under a no deformation condition, in which the bath composition was changed, decreasing the concentration from the initial value (chosen to be 1000 mol/m$^3$) to a given final target concentration, depending on the experimental data of figure 4.1;

2. During the second stage, the bath composition didn’t undergo any alteration, and instead, for each final fixed salt concentration in the bath, a negative deformation was imposed.

The experimental points obtained in the Eisenberg and Grodzinsky work, and that were used for the model fitting, are presented in figure 4.1, where different curves, for different final target concentrations are presented.

During the compressive stage, it had to be considered that the collagen fibers (solid phase) and the PG molecules are incompressible, and thus their volume after the compression is the same as the one at the initial state. In this way, the final volume of the fluid phases (without the PGs contribution), after
Figure 4.1: Stress-strain points, for five different articular cartilage samples tested, at the equilibrium stage, for different final bath concentrations: 0.005M, 0.01M, 0.025M, 0.05M, 0.1M, 0.15M, 0.5M and 1M. A linear fitting to these points was performed, and the best fits are presented in the figures by solid lines. Adapted from S. R. Eisenberg and A. J. Grodzinsky [17].

The deformation, is the total final volume without the volumes of the PGs and collagen fibers. The final EF volume is obtained considering again 75% of the final volume of the fluid phase (that only accounts for the water and ions), adding additionally the PGs volume. As the compression is applied, between the initial and final deformation, the FCD value is gradually updated considering intermediate values for the total EF volume: \( V_{E}^{\text{int}} = V_{E}^{0} + \Delta V_{E} \ast (\epsilon / \epsilon_{\text{max}}) \), with \( \Delta V_{E} = V_{E}^{0} - V_{E} \), where \( V_{E}^{\text{int}} \) is an intermediate value of the total EF volume for a respective intermediate deformation percentage, and \( V_{E} \) is the total EF volume correspondent to the final deformation, \( \epsilon_{\text{max}} \). Since the deformation is contractive, \( \epsilon \) is a negative value. After updating \( e_{PG} \) using equation (4.3), the water pressure and the corresponding stress are obtained from equation (4.2) and equation (4.1), respectively.

The values used for the chemical and physical constants in the simulations performed in both chapter 4 and chapter 5 are presented in table 4.1 and table 4.3. The pH was considered to be neutral.

| Table 4.3: Temperature of the test and physical constants. |
|-----------------|-----------------|-----------------|
| Temperature, \( T \) | Faraday’s Constant, \( F \) | Gas Constant, \( R \) |
| 298 K | 96485 Coulomb mol\(^{-1}\) | 8.314 J mol\(^{-1}\) K\(^{-1}\) |

In order to complete the material constants of the model, the values used for the transport parameters required for the calculation of the generalized diffusion matrix components to be used in the finite element simulations in chapter 5, and which were retrieved from Loix et al. [22], are presented in table 4.4.
Table 4.4: Transport parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydraulic Conductivity, $K_h$</td>
<td>$9.8 \times 10^{-12}$ m/s</td>
</tr>
<tr>
<td>Sodium Diffusion Coefficient, $D_{Na}$</td>
<td>$13.3 \times 10^{-10}$ m$^2$/s</td>
</tr>
<tr>
<td>Chloride Diffusion Coefficient, $D_{Cl}$</td>
<td>$20.3 \times 10^{-10}$ m$^2$/s</td>
</tr>
<tr>
<td>Tortuosity, $\tau$</td>
<td>0.4</td>
</tr>
</tbody>
</table>

4.2 Stage 1: Variation of the bath composition under no deformation

The variation of the salt concentration in the bath, considering a zero deformation, allows to set the first mechanical parameter in the mechanical model, $\alpha_p$, since, during this stage, the stress is only governed by $\sigma = -p_E (1 + \alpha_p)$.

The simulation starts at a zero stress and strain, and thus the initial value of the bath’s concentration ($c_0^*$) needs to be set at a very high value (near saturation condition), here set to 1000 mol/m$^3$. From this point, the bath concentration is decreased in small steps, until the target concentration is reached. During this decrease of the bath concentration, one can verify a successive increase in the absolute value of the stress due to the increase of the water pressure. This trend of the model, to increase the water pressure as the salt concentration in the bath surrounding the sample decreases, well simulates the tendency of water to flow from mediums with lower to mediums with higher salt concentration. In this way, a higher pressure exerted by water is felt against the tissue walls as the outer concentration decreases, and so, in order to maintain the equilibrium of forces, an opposite force needs to be applied by the wall, resulting in a compressive stress, which is higher as the water pressure increases. The lower the final concentration is, the higher is the water pressure felt, and consequently, the higher will be the compressive stress.

Therefore, the value for $\alpha_p$ is set in order to approximate the stress obtained by the proposed constitutive model, with zero deformation, to the values of the stress in figure 4.1 for the correspond final concentrations, at zero strain. The value of $\alpha_p$ that most accurately approximates the model to the experimental results is -0.95.

4.3 Stage 2: Variation of the deformation under fixed bath composition

During stage 2, under a constant bath concentration (the target one at the end of stage 1), a successively increased negative deformation is applied. At this point, the stress is defined accounting also for the strain contribution. With the $\alpha_p$ parameter defined, the remaining mechanical parameters, $\alpha_w$ and $E_{sat}$, may also be determined, which further determine, for each salt concentration in the bath, the slope of the stress-strain curves.

In addition to the flow of water, there is also the presence of flow of ions in and out of tissue, as
discussed before. Thus, when the concentration of ions outside the tissue is very large, there is a tendency of ions to move inside the tissue due to chemical equilibrium purposes, meaning that more $\text{Na}^+$ ions will surround the proteoglycans molecules, increasing the shielding effect and decreasing the repulsive forces. Therefore, for the same applied strain, but different concentration of the bath, one can see a higher compressive stress in the case of lower outer concentration, since the repulsive forces are less shielded, reflecting the dependence of the tissue stiffness with the chemical environment that is surrounding it. Moreover, as the contractive strain increases, while maintaining the same chemical conditions, the proteoglycans will get closer to each other, increasing the inter repulsive forces. All these aspects are well reproduced by the model, as one can see in figure 4.2.

The curves obtained in figure 4.2 are adjusted in order to fit, as accurately as possible, the real experimental data (figure 4.1), and the values for $\alpha_w$ and $E_{sat}$ that allow the best interpolation are, respectively, $5.4 \times 10^{-6} \text{ Pa}^{-1}$ and 250000 Pa.

Figure 4.2: Experimental points from S. R. Eisenberg and A. J. Grodzinsky [17] and stress-strain curves obtained by the mechanical constitutive model proposed, while changing the contractive deformation, from zero to a given final strain value, under constant bath concentration, with $\alpha_p = -0.95$, $\alpha_w = 5.4 \times 10^{-6} \text{ Pa}^{-1}$ and $E_{sat} = 250000 \text{ Pa}$.
Finite Element Simulations

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5.6 Heterogeneous Bath Simulation .................................... 57
5.1 Simulation Framework

The bath concentration is initially set at 1 M of NaCl (practically the saturation state), and the tissue sample is considered to be at zero deformation, meaning that no compressive load is applied (see figure 5.1). From this initial state, to which the variables initial values were already presented in chapter 4, alterations are imposed either through changes in the bath solution (chemical loading) or through the imposition of non-zero uniaxial confined deformation in the tissue (mechanical loading).

In order to impose the variation of the bath concentration in the tissue, velocities of the electrochemical potentials are imposed in the extremity nodes of the tissue sample, which is based on a linear variation over time of the number of moles of the salt in the bath. For the imposition of the deformation, constant velocities of displacement are applied in the nodes of the extremities.

Figure 5.1: Schematic of a cylindrical tissue sample, with 0.6 mm thickness, immersed in a homogeneous bath of a given concentration A. The specimen is in contact with the bath in the upper and lower surfaces. The alteration of the chemical composition of the bath will be felt by the tissue equally in the two surfaces in contact with it, where the tissue will undergo a transient period, as response to the changes in the surrounding medium, until an equilibrium state is reached again.

The main simulation performed in this work involves four distinct stages, with both changes in the chemical and mechanical loads:

1. **Stage 1**: in the first stage, the bath concentration is decreased from the initial value (1 M NaCl) to a given final target concentration, under zero deformation, in a given period of time \( t_1 \);
2. **Stage 2**: during another period of time \( t_2 \), the system is left at rest, so that a new state of equilibrium is reached;
3. **Stage 3**: at the third stage, under a constant bath solution, a contractive uniaxial strain is imposed in a period of time \( t_3 \);
4. **Stage 4**: once again, during a period of time \( t_4 \), no changes are applied to the system in order for the equilibrium to be reached.

The four-stages simulation described above is in part similar to the one conducted in chapter 4, to obtain the values of the material parameters of the mechanical model. However, in the simulation of chapter 4, equilibrium was assumed in all points, while in this simulation the time component is included, which allows to study the evolution in time and space of the behavior of the tissue under chemical and mechanical loads.
mechanical actions, with the equilibrium state being reached during the simulation in the two extra stages (stages 2 and 4).

5.2 Mesh Convergence Analysis

The Finite Element Analysis requires the domain of study (i.e. the articular cartilage sample of 600 µm thickness) to be subdivided along its thickness into smaller 1-D sub-domains: the finite elements. The number of elements considered can have impact in the results of the computational analysis, which means that the number of elements from which the mesh no longer influences the results needs to be found.

For the study of convergence in terms of the mesh size, several simulations were conducted, with an integration time step $\Delta t$ of 1s, for 6 meshes comprising different number of finite elements, with a successively higher refinement: 6, 12, 25, 50, 100 and 200 elements. In each mesh case, several variables (both primary and secondary) were obtained in 3 fixed points (one extremity point and two in the middle), in order to study the evolution of their values as a function of the mesh refinement. The evaluation of the variables was performed at the end of the second stage, once the equilibrium was restored, after the change of the bath composition during stage 1 to a chosen final concentration of a lower value equal to 150 mol/m$^3$.

From figure 5.2, one can see that, in this work, the spatial mesh has almost no influence on the results, since the maximum variation of the variables’ values with respect to the values of the finer mesh (with 200 finite elements) it’s only of 0.003%. Nevertheless, with a closer analysis, a convergent trend becomes perceptible for almost every considered variable. In this way, the number of elements that allows a good convergence of the results, whilst not compromising to much the computational effort, was considered to be 50.

5.3 Time Convergence Analysis

In addition to the division of the spatial domain into finite elements, during an incremental process, the time domain is also subdivided into small time steps. This means that the current problem is solved in small steps until the final goal is reached, that is, instead of considering a one-step change from the initial to the target concentration, or a one-step change from the initial to a given final sample thickness when imposing a deformation, such process is performed in small intermediate time steps.

For a fixed number of 50 finite elements, three different time steps $\Delta t = \frac{\text{Time stage}}{\text{Number of steps}}$ were tested: 1s, 0.1s and 0.01s, and the spatial profiles of several variables were obtained along the whole tissue thickness. Analysing the results presented in figure 5.3 obtained at the end of stage 2, a value of $\Delta t = 0.1s$ was chosen, since the values of the variables for the time steps of 0.1s and 0.01s are very close. Thus, a $\Delta t$ of 0.1s allows to reduce the time step influence on the results, without increasing excessively the computational cost.
Figure 5.2: Spatial convergence analysis for several variables ($\mu_{NaE}$, $\mu_{wE}$, $M^{NaE}$, $M^{wE}$, $x_{NaE}$, $x_{wE}$, $p_E$ and $\sigma$), values taken at the end of stage 2), at 3 different spatial positions: point 1 at the extremity of the sample and points 2 and 3 at 100 $\mu m$ and 300 $\mu m$ from the extremity, respectively.

5.4 Homogeneous Bath Simulation

Once obtained the proper values for the number of finite elements and for the incremental time step, a new simulation is conducted, where, after a homogeneous change of the bath composition, a certain deformation is imposed. During the first stage, the bath concentration is decreased from the initial value
of 1000 mol/m³ to a value of 150 mol/m³ during 1000s, under no variation of thickness, followed by a 50 minute equilibrium stage. At the third stage, a negative deformation of 20% is applied during 1000s, with a posterior 50 minute stage to reach the equilibrium condition again. A representative scheme of the tissue sample immersed in a homogeneous bath, of a given concentration, is presented in figure 5.1.

As the bath concentration decreases during stage 1, an outflow of mobile ions from the tissue is perceived. Therefore, there is a consequent decrease of the sodium and chloride mass contents, $m^{NaE}$.
and $m^{ClE}$, in general, throughout the tissue thickness, as pictured in figure 5.4. Nevertheless, one can see that such decrease doesn’t occur in a uniform manner over the thickness of the sample, with the impact of the decrease of the bath concentration being felt firstly in the extremities of the tissue, where the change of the bath’s concentration is imposed, with the posterior progression towards inside the sample.

Since the total volume during the first two stages of the simulation is the same as the initial one, and recalling that the solid phase is incompressible, the volume of the fluid phases must also remain constant. In this way, with the loss of ions in the EF phase and the unchanged tissue volume, the water mass content, $m^{wE}$, increases at the end of the second stage, with its profile, along the tissue thickness, following the trend of the tissue local deformation (see figure 5.5). Since in the first 4000 seconds of the simulation no deformation is imposed, one can see in figure 5.5 that the mean value of $\epsilon$ is zero. However, the deformation is not null in each of the elements individually, meaning that there are some elements with a positive deformation while others are associated with a negative one. Overall, summing up the element contributions, the initial total thickness of the tissue remains constant (see figure 5.12).

Figure 5.6 shows the evolution of the variable $y_{PG}$, which can be converted to the FCD, $e_{PG}$, through the approximation $x_{PG} \approx c_{PG} \hat{v}_w$ and, thus, $y_{PG} \approx \xi_{PG} c_{PG} \hat{v}_w = e_{PG} \hat{v}_w$. The values of $y_{PG}$ are around $-3.5/ -3.6 \times 10^{-3}$, which corresponds to a FCD value of $e_{PG} = -200$ moles of charge/m$^3$. Approximating the total fluid volume of the tissue by the water volume, one has $e_{PG} = -200 \times 10^{-6}$ moles of charge/g =
−0.2 milli-moles of charge/g = −0.2 mEq of charge/g, being this value within the range of values for the FCD presented in figure 1.6, chapter 1.

Figure 5.6: Time evolution of the spatial distribution, along the tissue thickness, of the variable $y_{PC}$, during the stages 1 and 2.

Regarding the water pressure, its value presents an increase at the end of stage 2 (see figure 5.7), being this a consequence of the increase of the water mass content in the EF phase, since more water is exerting pressure against the tissue walls.

For the EF electrical potential, at the beginning, where equilibrium is verified and the external bath has a concentration close to the saturation state, its value is almost zero. By the end of the second stage, with the migration of ions towards outside the tissue, the electrical potential in the EF phase becomes more negative.

Figure 5.7: Time evolution of the spatial distribution, along the tissue thickness, of the EF water pressure (left), $p_E$, and of the EF electrical potential (right), $\phi_E$, during the stages 1 and 2.

In stages 3 and 4 no alterations are performed in the chemical composition of the medium surrounding the tissue. Thus, changes perceived in the chemical variables are a consequence of the mechanical load applied. In figure 5.8, lower ionic mass contents are shown at the end of the simulation, although such decrease is not as significant as during the first two stages. When applying the compressive force, water will start to be expelled from the tissue, and, along with water, the dissolved ions. In this way, a decrease in the water mass content is also expected as one can see in figure 5.9, left, with the consequent decrease of the tissue volume. Once again, the trend of the water mass content curves follows the trend of the deformation profiles (figure 5.9, right). With an imposed contractive deformation of 20%, the value taken by $\epsilon$, at the end of the fourth stage, is -0.2. At first, since the imposition of the deformation occurs in the extremities of the tissue, these are the points that experience initially a larger deformation.
As the system evolves towards a new equilibrium, the deformation progresses to the inner points, until a uniform deformation, with the respective imposed value, is verified along the tissue thickness (see figure 5.9, right).

**Figure 5.8:** Time evolution of the spatial distribution, along the tissue thickness, of the sodium (left) and chloride (right) ions mass contents, $m_{NaE}$ and $m_{ClE}$, during the stages 3 and 4.

**Figure 5.9:** Time evolution of the spatial distribution, along the tissue thickness, of the water mass content (left), $m_{wE}$, and of the local tissue deformation $\epsilon$ (right), during the stages 3 and 4.

In contrast to what is verified during the change of the bath chemistry, after the application of the deformation, one can see an increase in the negative value of $y_{PG}$ at the end of stage 4. Due to the decrease in the EF water volume, the concentration of the PGs is higher in this compartment, and so the FCD and $y_{PG}$ have higher absolute values (see figure 5.10).

**Figure 5.10:** Time evolution of the spatial distribution, along the tissue thickness, of the variable $y_{PG}$, during the stages 3 and 4.

With the compression, a higher pressure is exerted by water against the tissue walls in the EF phase,
which results in a higher $p_E$. Moreover, with the exit of more ions from the interior of the EF phase, the EF electrical potential decreases once again, as one may verify in figure 5.11.

![Graph](image)

**Figure 5.11:** Time evolution of the spatial distribution, along the tissue thickness, of the EF water pressure (left), $p_E$, and of the EF electrical potential (right), $\phi_E$, during the stages 3 and 4.

Analysing the stress evolution over time (figure 5.12, left) one can see that, during the change of the bath composition, the stress suffers a slightly variation around the initial value. Due to the increase of the water mass content and of the EF water pressure, an increase of the compressive stress is expected. Once the compression starts at stage 3, with the chemical environment kept constant, the stress suffers, as expected, a significant increase in its absolute value. The higher the deformation underwent by the tissue sample, the higher will be the presented compressive stress, for the same external conditions. Only the tracking of stress over time is shown and not its spatial profile, since the stress is constant over the tissue thickness.

In the right side plot of figure 5.12, the tracking over time of the tissue thickness is presented, where one can see the thickness being kept unchanged during the first two stages, and being decreased according to the deformation imposed during the third stage. Under a negative deformation of 20% of the initial thickness (0.6 mm), its final value is 0.48 mm.

![Graph](image)

**Figure 5.12:** Time evolution of the axial stress underwent by the tissue (left) and of the tissue thickness (right), during the four-stages simulation. In the stress evolution, the reach of the equilibrium state is perceptible after each of the stages involving external chemical (stage 1) and mechanical (stage 3) changes.

Alterations in the period of time during which the bath concentration is changed (stage 1) introduce modifications in the response of the tissue. By making faster the decrease of the ionic content of the bath, the stimulus felt by the tissue is more abrupt, which is reflected in the presence of a more distinct overshoot in the stress underwent by the tissue during stage 1 (see figure 5.13, left). On the contrary, if
the alteration in the concentration of ions in the bath is made slower, the tissue has more time to adapt to the changes imposed, and thus the overshoot is almost completely absent (see figure 5.13, right). Note: the change of the time taken by a given stage requires that the number of steps used in that stage is changed accordingly, in order to maintain the time step equal to the chosen value in section 5.3 of 0.1s.

Figure 5.13: Time evolution of the axial stress underwent by the tissue, considering, for stage 1, a duration of 100s (left) and 5000s (right), during the four-stages simulation. In the stress evolution, the reach of the equilibrium state is perceptible after each of the stages involving external chemical (stage 1) and mechanical (stage 3) changes.

The hydraulic conductivity is a characteristic property of porous tissues, which describes the ease of a fluid (e.g. water) to flow through the pores (percolation), thus being an indicator of the permeability of the porous medium. This property depends on the medium by itself (i.e. pore size, pore distribution and connectivity) but also on the properties of the fluid (e.g. density and viscosity) [26]. The higher its value, the higher the permeability is.

In order to understand the influence of the hydraulic conductivity in the behavior of the tissue, its value was changed from the base value of $9.8 \times 10^{-12}$ m/s to higher ($9.8 \times 10^{-11}$ m/s) and lower ($9.8 \times 10^{-13}$ m/s) values. As $K_h$ is assigned with successive lower values, water will tend to flow through the medium pores in a harder way, which means that one requires the application of a higher compressive stress to impose the same deformation, since it will be more challenging to expel water out of the tissue. This behavior can be verified analysing the evolution of the stress over time presented in figure 5.14, left. On the contrary, when the permeability increases (figure 5.14, right) equilibrium at stage 4 is attained very quickly with almost no overshoot. During the change of the bath composition, differences among the distinct permeability values are not as evident as during the imposition of the deformation, nevertheless, at the end of the first stage, for the case of the lower $K_h$ value, a lower stress is verified, which may be explained due to the fact that water doesn’t flow towards inside the tissue as easily, leading to a lower EF water pressure, and thus the compressive stress is lower as well. Regardless the hydraulic conductivity, in the end of the second and fourth stages, the final stresses, at the new equilibrium states, are the same.

One additional note that should be considered is that the hydraulic conductivity, and, consequently, the permeability, depends on the strain applied to the tissue, meaning that under higher deformation states, the size of the pores are reduced and it becomes more difficult for the fluid to flow (reduced permeability). In this way, although considered constant in this work, the hydraulic permeability could have been defined in a way that would depend on the available pore volume for the movement of the fluid.
Figure 5.14: Time evolution of the axial stress underwent by the tissue, considering a hydraulic conductivity, $K_h$, of $9.8 \times 10^{-13}$ m/s (left) and of $9.8 \times 10^{-11}$ m/s (right), during the four-stages simulation. In the stress evolution, the reach of the equilibrium state is perceptible after each of the stages involving external chemical and mechanical changes.

inside the tissue. Such dependence was presented by Loix et al. [22], based on the Kozeny-Carman equation [26].

The reach of the new equilibrium state after each of the chemical or mechanical modifications is not accomplished instantaneously as it is highlighted in each and every one of the figures above. Instead, the tissue response undergoes a transient period, during which the system evolves to find a new equilibrium condition. Such transient time is related with several material properties such as the percolation time described by Darcy’s Law and the diffusion time described by Fick’s Law. In the case of absence of electro-chemo-mechanical couplings, the characteristic times of the ionic diffusion and water seepage are given by $\tau_{Fick}^k = \frac{1}{4\pi^2} \frac{L^2}{D_{kE}^*}$ and $\tau_{Darcy} = \frac{1}{4\pi^2} \frac{L^2}{E_{cKE}^*}$, respectively, with $D_{kE}^* = \tau D_{kE}$, $\tau$ the tortuosity factor, $L$ the distance traveled by ions and water, $E_c$ the confined compression modulus and $k_{EE}$ the "short-circuit" permeability.

Analysing the figures related to the evolution of stress during the stages where the equilibrium is reached (second and fourth), it is possible to retrieve that the equilibrium is attained faster in stage 4 than in stage 2 (in figure 5.12 the times required to reach the plateau, in stage 2 and 4, are 474s and 203s, respectively). This trend is in agreement with the individual times of diffusion and percolation, which, in the present case, are: $\tau_{Fick}^{Na} = 4.285s$ and $\tau_{Darcy} = 3.5658s$. Since, in the second stage, the system evolution mainly depends on the ions diffusion as a response to the bath chemistry alteration, while in the fourth stage the evolution depends on the water movement as a certain deformation is applied, the faster achievement of the equilibrium during stage 4 is plausible. However, the characteristic times here presented do not account for the coupled interactions from which the tissue response depends. Of course, the time necessary to reach the equilibrium states depends on the period of time during which the modifications are introduced. The slower the changes in the bath composition or in the imposed deformation are introduced, the faster the equilibrium is reached. In these simulations the same period of time was selected for stages 1 and 3, where the chemical and mechanical actions are imposed.

From the results above, within the simulation outline, only 1000s will be used in the next simulations in order for the new equilibrium to be found during stages 2 and 4.

The time taken to conduct the four stages of the simulation, with 50 finite elements and a time
step of 0.1s within a total simulation time of 8000s, is around 4 hours, using a PC with the following characteristics: Intel Core i7-8750H 2.20 GHz processor and 8 GB of RAM.

5.5 Eisenberg and Grodzinsky Simulation

Resorting to the finite-element simulation, several stress-strain points, for different final target concentrations, and under different compressive stresses, are obtained in order to compare with the Eisenberg and Grodzinsky experimental results [17]. For this, several simulations are performed, imposing in stage 1 the final bath concentrations used in the Eisenberg and Grodzinsky experiment, and for each concentration, in stage 3, different deformations are applied.

In figure 5.15, one can see the equilibrium stress-strain points marked with a cross (values retrieved at the end of stage 4), along with the respective interpolation curves. The results show that the finite-element simulation, using the mechanical model proposed, and considering the IF phase as described before, properly simulates the real cartilage behavior captured in the Eisenberg and Grodzinsky experiments, which is something that was not possible to model in the work by Loix et al. [22].

![Figure 5.15](image_url)

**Figure 5.15:** Stress-strain curves obtained through the finite-element simulation, using the material parameters specified in chapter 4. Marked with an 'x' are the points obtained for a given bath concentration and a given deformation.

5.6 Heterogeneous Bath Simulation

The introduction of the *fictitious bath* concept in the formulation of the constitutive model makes possible the conduction of a simulation in which the tissue sample is surrounded by a heterogeneous bath (figure 5.16). In such experimental framework, the bath presents a physical horizontal separation which allows each of the sample extremities, in contact with the bath, to experience distinct variations of the salt concentrations, and so in practice there are two distinct baths.

To conduct a simulation with a heterogeneous change of the bath chemistry, two different final concentrations are imposed, starting from the initial bath concentration of 1000 mol/m$^3$: in the upper side of the bath the final concentration is set to 150 mol/m$^3$ and in the lower side it is set to 250 mol/m$^3$. Once the chemical change is performed during a time of 1000s, with the posterior 1000s stage to reach the
Figure 5.16: Schematic of a cylindrical tissue sample, with 0.6 mm thickness, immersed in a heterogeneous bath, with a horizontal physical division, separating the area of concentration A (at the top) from the area of concentration B (at the bottom). In practice, the specimen is in contact with two different baths in the upper and lower surfaces. The alteration of the chemical composition of the bath will be felt by the tissue differently in the two surfaces in contact with it.

new equilibrium, the 20% negative deformation is imposed during 1000s, followed by a second 1000s equilibrium stage.

When imposing a change in the chemical content of the bath that is different in the two sides of the tissue sample that contact with it, the behavior in the extremity nodes of the tissue in reaction to the external modifications is predictable, since it is in these nodes that the changes are imposed. However, the way the response to the stimulus will progress towards inside the tissue sample is not that straightforward.

Looking at figure 5.17, profiles similar to those in section 5.4 are obtained, with the singularity that now the distribution of the ionic mass contents, at the end of stage 2, is not uniform along the tissue thickness, but instead it presents a linear variation, meaning that the heterogeneity of the bath composition contributes to the loss of symmetry in the tissue behavior, which is also perceptible in all the figures that follow. The side of the tissue sample with the higher EF ionic mass contents corresponds to the side in contact with the bath characterized by the higher final ionic concentration.

Figure 5.17: Time evolution of the spatial distribution, along the tissue thickness, of the sodium (left) and chloride (right) ions mass contents, $m^{\text{NaE}}$ and $m^{\text{ClE}}$, during the stages 1 and 2, for a heterogeneous change in the salt concentration of the bath.

As seen for the ionic mass contents, the water mass content and the local deformation are no longer
uniform, neither symmetric, after the reach of the new equilibrium state. In figure 5.18, left, after the equilibrium is restored under a no variation of thickness condition, an increase in the water mass content can be verified in general along the tissue thickness, since in both sides of the bath there is a significant decrease in the salt concentration. Nevertheless, the water mass content is higher on the left side of the sample, where a lower final bath concentration is imposed, since it is in this extremity that a higher outflow of ions occurs. Due to this non-uniform behavior of the tissue, although maintaining an overall zero deformation, $\epsilon$ presents a shift towards the right side of the sample, resulting in a non-zero deformation value in the right extremity element (see figure 5.18, right).

Figure 5.18: Time evolution of the spatial distribution, along the tissue thickness, of the water mass content (left), $m_{wE}$, and of the local tissue deformation $\epsilon$ (right), during the stages 1 and 2, for a heterogeneous change in the salt concentration of the bath.

The $y_{PG}$ variable, which is defined in function of the variation of the nodal displacements, presents the same trend as the deformation, that results from the uneven distribution of water inside the tissue (see figure 5.19). The range of $y_{PG}$ values is maintained in comparison to previous simulations.

Figure 5.19: Time evolution of the spatial distribution, along the tissue thickness, of the variable $y_{PG}$, during the stages 1 and 2, for a heterogeneous change in the salt concentration of the bath.

In figure 5.20 the EF water pressure and EF electrical potential profiles, during the first two stages, are presented. The rational behind the curves obtained follows the same line as described in the case of a homogeneous bath.

Regarding the stages in which the deformation is applied, the evolution of the variables, with the posterior reach of the equilibrium, occurs in the same way as in the homogeneous case, the only difference is that in the current simulation the starting state of stage 3 is not uniform, and thus the results at the end of the deformation imposition (figures 5.21, 5.22, 5.23, 5.24) are not uniform as well, with all the explanations given in section 5.4 applying here as well.
Figure 5.20: Time evolution of the spatial distribution, along the tissue thickness, of the EF water pressure (left), $p_E$, and of the EF electrical potential (right), $\phi_E$, during the stages 1 and 2, for a heterogeneous change in the salt concentration of the bath.

Figure 5.21: Time evolution of the spatial distribution, along the tissue thickness, of the sodium (left) and chloride (right) ions mass contents, $m_{NaE}$ and $m_{ClE}$, during the stages 3 and 4, for a heterogeneous change in the salt concentration of the bath.

Figure 5.22: Time evolution of the spatial distribution, along the tissue thickness, of the water mass content (left), $m_{wE}$, and of the local tissue deformation $\epsilon$ (right), during the stages 3 and 4, for a heterogeneous change in the salt concentration of the bath.

The stress evolution over time is shown in figure 5.25, where it may be observed that, at the end of stage 4, the stress is a little lower than the one encountered in the case of the homogeneous bath (section 5.4). This result is expected, since one of the baths has the same final concentration as the homogeneous bath ($150 \text{ mol/m}^3$), while the second bath was attributed with a higher final concentration ($250 \text{ mol/m}^3$). In this way, in comparison to the homogeneous case, there are some points in the tissue in which the sodium mass content is higher, thus implying a higher shielding of the repulsive forces.
which is translated in a lower tissue stiffness. In this way, the required compressive stress to impose a negative deformation of 20% is lower as well.

The simulation here conducted, where the tissue is in contact with two different baths, couldn’t be performed using the previous models presented in the literature [20, 21], in which the constitutive parameters are made dependent of the bath chemical composition.

Figure 5.23: Time evolution of the spatial distribution, along the tissue thickness, of the variable $y_{PG}$, during the stages 3 and 4, for a heterogeneous change in the salt concentration of the bath.

Figure 5.24: Time evolution of the spatial distribution, along the tissue thickness, of the EF water pressure (left), $p_{E}$, and of the EF electrical potential (right), $\phi_{E}$, during the stages 3 and 4, for a heterogeneous change in the salt concentration of the bath.

Figure 5.25: Time evolution of the axial stress underwent by the tissue (left) and of the tissue thickness (right), during the four-stages simulation, for a heterogeneous change in the salt concentration of the bath during the first two stages of the simulation. In the stress evolution, the reach of the equilibrium state is perceptible after each of the stages involving external chemical and mechanical changes.
Conclusions and Future Developments
Articular cartilage is a porous medium, reinforced by collagen fibers and saturated by an aqueous electrolyte. The presence of proteoglycans (electrically charged macro-molecules) is the reason why electro-chemo-mechanical interactions occur, which enhance the tissue adaptation to physiological actions.

In previous works conducted by Loret et al. [1–3], it was proposed (1) a constitutive law and (2) a generalized diffusion model for articular cartilage. In this model, the collagen fibers constitute the solid phase of the porous medium. The fluid phase is composed by water, PGs and dissolved inorganic salts (NaCl). In the current work, two fluid compartments were considered, in order to account for the division of water in the IF and EF spaces inside the tissue, as highlighted by Maroudas and coworkers [19]. As a new feature, the IF compartment, although taken into account, was modulated in a more simplified and indirect way, distinctly to what was previously performed [1, 22–24]. This simplification avoids the definition of material parameters and functions related to the IF compartment that cannot be obtained from the existing experimental data.

In the work here conducted, a finite element program was developed, in MATLAB environment, whose formulation was based on the described model, with the purpose of numerically simulate the response of an articular cartilage sample to a combination of chemical and mechanical actions.

The sample of articular cartilage is found immersed in a bath whose chemical composition may be altered, always supposing the existence of electro-chemical equilibrium in the tissue-bath interface. However, the equilibrium inside the tissue is not reached instantaneously. In fact, the time required to establish the permanent regimen depends on the problem geometry and on several material properties, such as the percolation and diffusion times related to Darcy’s and Fick’s laws, respectively. Therefore, spatial and temporal profiles were obtained, for several mechanical, chemical and electrical variables, defined in the interior of the tissue, due to either isolated or combined actions of chemical (changing of the chemical composition of the external bath) and mechanical (confined compression) loadings.

Using the finite element method, with the new constitutive equation proposed in [3], the experimental stress-strain curves presented in the work conducted by Eisenberg and Grodzinsky [17] were modelled. The real tissue behavior was well approximated by the presented model which allows, additionally, to conclude that the simplification performed regarding the contribution of the IF phase still permits to obtain good outcomes, being this an advantage of the current formulation with respect to the one developed by Loix et al. [22].

The concept of fictitious bath also allowed to obtain spatial and temporal profiles of several variables when the sample is immersed in a heterogeneous bath which gives a closer insight to the tissue’s behavior under a more diverse environment and which is something that other existing models are not able to provide. To the best of the author’s knowledge, this is the first time that this type of simulation is performed.

The results obtained in the present work were accepted for presentation in the next conference of the Portuguese Society of Biomechanics [27].

The main objective of the numerical simulations performed in this work is to understand the influence that mechanical forces and changes in the chemical composition of the synovial fluid may have on the biomechanics of articular cartilage and, in particular, in the study of the evolution of its degenerative diseases. Nevertheless, some improvements may be required when considering a more realistic de-
scription of the tissue, although such alterations may introduce complex changes in the model. During
the simulations of the present work, the pH considered was neutral, meaning that the collagen fibrils
have no charge. At a non neutral pH, the collagen will be gifted with charge, and so the IF compart-
ment, that comprises the charge of the collagen fibrils, must be fully modulated, accounting directly the
mass exchange (ions and water) between IF and EF phases. Regarding the mechanical aspects of the
simulations, it was considered that the tissue was under a uniaxial confined compression state. Thus,
simulations out of this framework must also be conducted, in order to simulate the tissue behavior un-
der different mechanical contexts, where, for example, the tensile behavior of the collagen fibers, that
introduces some degree of anisotropy, is taken into account.
Bibliography


Algebraic Manipulations

The stiffness and diffusion matrices, as previously discussed, are obtained by computing the derivative of the internal forces in order of the (nodal) primary unknowns or in order of the (nodal) velocities of the primary unknowns ($C^e = \frac{\partial F^{int}_e}{\partial \mathbf{u}_e}$ and $K^e = \frac{\partial F^{int}_e}{\partial \mathbf{x}_e}$). When the internal forces are linearly dependent on the primary unknowns, or its velocities, the components of the matrices are directly retrieved. However, when this linearity is not verified, the derivative needs to be performed with a further linearization of the solution, in which case the equations are rather written in an incremental way, to make the derivative process easier. Therefore, in the following equations the operator $\delta$ represents the difference between two solutions in an incremental process.

The constraints that must be obeyed by the molar fractions, in the EF phase, are as follows:

$$\begin{align*}
x_{wE} + x_{NaE} + x_{ClE} + x_{PG} &= 1 \\
x_{NaE} - x_{ClE} + y_{PG} &= 0
\end{align*}$$

(A.1)

where the molar fraction of proteoglycans $x_{PG}$ is considered to be approximately zero. Nevertheless, the quantity $y_{PG} = x_{PG} \xi_{PG}$ can’t be neglected, since, despite the fact that $x_{PG}$ is a very small number, the PGs’ valence $\xi_{PG}$ is a very large number, and thus $y_{PG}$ is a significant quantity.

From the electroneutrality constraints, the variations of the molar fractions ($\delta x_{kE}$) can thus be written,
in terms of the mass contents, as follows:

\[
\begin{align*}
\delta x_{wE} &= (1 - x_{wE}) \frac{x_{wE}}{m_{wE}} \delta m_{wE} - 2x_{wE} \frac{x_{NaE}}{m_{NaE}} \delta m_{NaE} \\
\delta x_{NaE} &= -x_{NaE} \frac{x_{wE}}{m_{wE}} \delta m_{wE} + (1 - 2x_{NaE}) \frac{x_{NaE}}{m_{NaE}} \delta m_{NaE} \\
\delta x_{ClE} &= -x_{ClE} \frac{x_{wE}}{m_{wE}} \delta m_{wE} + (1 - 2x_{ClE}) \frac{x_{NaE}}{m_{NaE}} \delta m_{NaE}.
\end{align*}
\]  
(A.2)

The volume content of the EF phase \(v^E\) is given by \(v^E = \frac{V^E}{V^0}\), and the variation of the volume content may be defined as \(\delta v^E = \frac{\delta V^E}{V^0}\). The volume of the EF phase is given by \(V^E = \sum_{k \in E} V_{kE}\), which can be approximated by the volume of water in the EF phase \(V_{wE}\), since water is the most abundant component in the tissue. The same is applied for the IF phase: \(v^I = \frac{V^I}{V^0} \approx \frac{V_{wI}}{V^0}\), and \(\delta v^I \approx \frac{\delta V^I}{V^0}\). The solid phase is considered to be incompressible, not presenting any volume variations, and thus variations in the total volume is only due to variations of the volume in the fluid phases.

In this way the following expression can be written:

\[
\delta v^E + \delta v^I = \frac{\delta V^E}{V^0} = \frac{\delta V^I}{V^0} \approx \frac{\delta V_{wE}}{V^0} + \frac{\delta V_{wI}}{V^0}, \text{ since } V_{wE} + V_{wI} = V_w
\]
(A.3)

Moreover, as previously described, it was also defined that the variation of the water in the IF phase was always 25% of the total variation of water, and the variation of the water in the EF water represented the remaining 75%: \(\delta V_{wI} = 0.25 \delta V_w\), and \(\delta V_{wE} = 0.75 \delta V_w\). In this way, the variation of the EF volume content is:

\[
\delta v^E = \frac{3}{4} \frac{\delta V_w}{V^0} \approx \frac{3}{4} \text{div} \delta u.
\]  
(A.4)

The volume fraction of the EF phase is given by \(n^E = \frac{V^E}{V} = \frac{1}{V} \sum_{k \in E} V_{kE} \approx \frac{V_{wE}}{V}\), and the respective variation may be written as:

\[
\delta n^E = \frac{\delta V_{wE}}{V} \approx \frac{V_{wE} \delta V}{V^2} = \frac{\delta V_{wE}}{V^0} \frac{V_0}{V} - n^E \frac{\delta V}{V^0} V_0 \approx \frac{\delta V_{wE}}{V^0} - n^E \left( \frac{\delta V_{wE}}{V^0} \frac{\delta V}{V^0} \right)
\]
(A.5)

The variation of the proteoglycans’ effective molar fraction \(y_{PG}\) can be obtained considering that the effective molar fraction may be approximated by \(y_{PG} = \xi_{PG} x_{PG} \approx \frac{N_{PG} b_w}{n^E V} \), with \(N_E \approx N_{wE}\).
\[
\delta y_{PG} = \xi_{PG} \delta x_{PG} \approx -\xi_{PG} \frac{N_{PG} \hat{v}_w \delta n^E}{n^E} - \xi_{PG} \frac{N_{PG} \hat{v}_w \delta V}{n^E} \\
\approx -y_{PG} \left( \frac{\delta n^E}{n^E} + \frac{\delta V}{n^E} \right) \approx -y_{PG} \left[ \left( \frac{3}{4} \frac{n^E}{n^E} - 1 \right) \text{div}\hat{u} + \text{div}\hat{u} \right]
\]
\[(A.6)\]

Returning to the molar fractions of the species, they can alternatively be expressed in terms of the volume contents \(v^{kE}\):
\[
x_{kE} \approx \frac{N_{kE}}{n^E} \frac{\hat{v}_w}{V} = \frac{V_{kE} \hat{v}_k}{V_{0}} = \frac{\hat{v}_k}{n^E} V_{0}
\]
\[(A.7)\]

and therefore, since \(m^{kE} = \rho_k v^{kE}\),
\[
\frac{\delta m^{kE}}{m^{kE}} = \frac{\delta \rho_k v^{kE}}{v^{kE}} = \frac{\delta \rho_k}{\rho_k} v^{kE}
\]
\[
= \frac{\delta (x_{kE} n^E V)}{v^{kE} \hat{v}_k} \frac{1}{\hat{v}_w V_0}
\]
\[
= \frac{\delta x_{kE}}{x_{kE}} \frac{n^E}{V} \frac{\hat{v}_k}{V_0} + \frac{x_{kE}}{v^{kE} \hat{v}_w} \frac{\hat{v}_k}{V_0} \delta n^E + \frac{x_{kE}}{v^{kE} n^E} \frac{\hat{v}_k}{V_0} \delta V
\]
\[
\approx \frac{\delta x_{kE}}{x_{kE}} + \frac{\delta n^E}{n^E} + \frac{\delta V}{V}
\]
\[
\approx \frac{\delta x_{kE}}{x_{kE}} + 3 \frac{3}{4} \frac{n^E}{n^E} \text{div}\hat{u}, \quad k \in E^{mo}.
\]
\[(A.8)\]

Through the electro-chemical potentials’ definitions and using the constraints imposed to the molar fractions, the variation of the EF electrical potential can also be obtained. Recalling the expressions of the electro-chemical potentials, \(\mu_{we} = p_E \frac{\hat{v}_w}{m_w} + \frac{RT}{m_w} \ln x_{wE}\) and \(\mu^{eE}_{lE} = \frac{RT}{m_l} \ln x_{lE} + \xi_l F \phi_{lE}\) with \(l \in E^{ions}\), the variations of these quantities may be retrieved:
\[
\delta \mu_{we} = \delta p_E \frac{\hat{v}_w}{m_w} + \frac{RT}{m_w} \delta x_{wE},
\]
\[(A.9)\]
\[
\delta \mu^{eE}_{lE} = \frac{RT}{m_l} \delta x_{lE} + \xi_l F \delta \phi_{lE}/m_l.
\]
\[(A.10)\]

Multiplying the variations of the electro-chemical potentials by the respective value of \(\hat{m}_l x_{lE}\) and adding all these quantities, using in addition equation (A.1), one obtains:
\[
\sum_{l \in E^{mo}} \hat{m}_l x_{lE} \delta \mu^{eE}_{lE} = RT \sum_{l \in E^{mo}} \delta x_{lE} + \delta p_E \hat{v}_w x_{wE} + F \delta \phi^{E} \sum_{l \in E^{ions}} \xi_l x_{lE}
\]
\[
= \delta p_E \hat{v}_w x_{wE} - y_{PG} F \delta \phi^{E}
\]
\[(A.11)\]
and thus

$$y_{PG} F \delta \phi^E = x_{wE} \tilde{v}_w \delta p_E - \sum_{l \in E^{mo}} \tilde{m}_l x_{lE} \delta \mu_{lE}^c.$$  \hspace{1cm} (A.12)

Using the variation of the electro-chemical potentials of the ionic species, \( \frac{RT \delta x_{kE}}{\tilde{m}_k} = \delta \mu_{kE}^c \) and

$$F \xi_k \delta \phi^E \tilde{m}_k = \delta \mu_{kE}^c - \frac{\xi_k}{\tilde{m}_k y_{PG}} (x_{wE} \tilde{v}_w \delta p_E - \sum_{l \in E^{mo}} \tilde{m}_l x_{lE} \delta \mu_{lE}^c) \quad \text{with} \quad k \in E^{ions},$$

the variation of the molar fractions of the ions may also present the following form:

$$\delta x_{kE} = \frac{\tilde{m}_k}{RT} x_{kE} \left( \delta \mu_{kE}^c - \frac{\xi_k}{\tilde{m}_k y_{PG}} \delta p_E + \frac{\xi_k}{\tilde{m}_k y_{PG}} \sum_{l \in E^{mo}} \tilde{m}_l x_{lE} \delta \mu_{lE}^c \right)$$

$$= -\frac{\xi_k}{RT} x_{kE} \frac{x_{wE}}{y_{PG}} \tilde{v}_w \delta p_E + \frac{x_{kE}}{RT} \left( \frac{\tilde{m}_k}{RT} \tilde{v}_w \delta p_E + \frac{\tilde{m}_k}{RT} \sum_{l \in E^{mo}} \tilde{m}_l x_{lE} \delta \mu_{lE}^c \right), \quad k \in E^{ions}. \hspace{1cm} (A.13)$$

Resorting once again to the electroneutrality condition \( \sum_{k \in E^{mo}} \xi_k \delta x_{kE} + \delta y_{PG} = 0 \), the next equations follow for the deduction of the variation of the EF pressure as a function of the primary variables:

$$\sum_{k \in E^{mo}} \xi_k \delta x_{kE} = \frac{3 y_{PG}}{4 n^E} \text{div}\tilde{u}$$

$$\sum_{k \in E^{ions}} -\frac{\xi_k}{RT} x_{kE} \frac{x_{wE}}{y_{PG}} \tilde{v}_w \delta p_E + \sum_{k \in E^{ions}} \left( \frac{\xi_k}{RT} \frac{x_{kE}}{RT} \tilde{m}_k \delta \mu_{kE}^c + \frac{\xi_k}{RT} \frac{x_{kE}}{RT} \frac{\tilde{m}_k}{RT} \tilde{v}_w \delta p_E + \frac{\tilde{m}_k}{RT} \sum_{l \in E^{mo}} \tilde{m}_l x_{lE} \delta \mu_{lE}^c \right) = \frac{3 y_{PG}}{4 n^E} \text{div}\tilde{u}$$

$$- \left( \sum_{k \in E^{ions}} \frac{x_{kE}}{RT} \frac{x_{wE}}{y_{PG}} \frac{x_{wE}}{RT} \tilde{v}_w \delta p_E + \sum_{k \in E^{ions}} \xi_k x_{kE} \tilde{m}_k \delta \mu_{kE}^c + \left( \sum_{k \in E^{ions}} x_{kE} \right) \frac{x_{wE}}{y_{PG}} \frac{x_{wE}}{RT} \tilde{v}_w \delta p_E + \sum_{k \in E^{ions}} \xi_k x_{kE} \tilde{m}_k \delta \mu_{kE}^c \right) = \frac{3 y_{PG}}{4 n^E} \text{div}\tilde{u}$$

$$z_E x_{wE} \tilde{v}_w \delta p_E = -\frac{3 y_{PG}}{4 n^E} \text{div}\tilde{u} \quad \text{RT} + z_E \sum_{l \in E^{mo}} \tilde{m}_l x_{lE} \delta \mu_{lE}^c + \sum_{k \in E^{ions}} \xi_k x_{kE} \tilde{m}_k \delta \mu_{kE}^c$$

$$z_E x_{wE} \tilde{v}_w \delta p_E = -\frac{3 y_{PG}}{4 n^E} \text{div}\tilde{u} \quad \text{RT} + z_E \left( \sum_{l \in E^{mo}} \tilde{m}_l x_{lE} \delta \mu_{lE}^c + \sum_{l \in E^{ions}} \frac{y_{PG}}{z_E} \xi_l x_{lE} \tilde{m}_l \delta \mu_{lE}^c \right)$$

where \( z_E = x_{NaE} + x_{ClE} \)

$$z_E x_{wE} \tilde{v}_w \delta p_E = -\frac{3 y_{PG}}{4 n^E} \text{RT} \text{div}\tilde{u} + z_E \sum_{l \in E^{mo}} z_{lE} x_{lE} \tilde{m}_l \delta \mu_{lE}^c.$$ \hspace{1cm} (A.14)

where \( z_{lE} = 1 + \xi_l \frac{y_{PG}}{z_E} \) and from which the variation of the EF pressure is obtained.

Using the variables defined as \( z_E \) and \( z_{lE} \), further manipulations may be performed in the variations of the molar fractions of the ionic species in order for this quantities to be in function of the primary unknowns as well:
\[ \delta x_{KE} = -\frac{\xi_k x_{KE}}{RT} x_{wE} \frac{z_E}{z_E} \hat{v}_w \delta p_E + \frac{x_{KE}}{RT} \hat{m}_k \delta \mu_{KE}^{cc} + \frac{x_{KE}}{RT} \frac{\xi_k}{YPG} \sum_{\ell \in E^{mo}} \hat{m}_{\ell} x_{\ell E} \delta \mu_{\ell E}^{cc} + \delta p_E \frac{\xi_k}{RT} \hat{m}_k \delta \mu_{KE}^{cc} \]

\[ \delta x_{KE} = -\frac{\xi_k x_{KE}}{RT} y_{PG} \frac{1}{z_E} \left( -\frac{3 y_{PGE}^2}{4 n^E} \text{div} \hat{u} \right) + \frac{x_{KE}}{RT} \frac{\xi_k}{YPG} \sum_{\ell \in E^{mo}} z_{\ell E} \hat{m}_{\ell E} \delta \mu_{\ell E}^{cc} + \frac{x_{KE}}{RT} \hat{m}_k \delta \mu_{KE}^{cc} \]

\[ \delta x_{KE} = \frac{3 \xi_k x_{KE}}{4 n^E} \frac{y_{PG}}{z_E} \text{div} \hat{u} - \frac{\xi_k x_{KE}}{RT} \frac{y_{PG}}{z_E} \sum_{\ell \in E^{mo}} z_{\ell E} \hat{m}_{\ell E} \delta \mu_{\ell E}^{cc} + \frac{x_{KE}}{RT} \hat{m}_k \delta \mu_{KE}^{cc} \]

\[ \delta x_{KE} = \frac{3 \xi_k x_{KE}}{4 n^E} \frac{y_{PG}}{z_E} \text{div} \hat{u} + \frac{x_{KE}}{RT} \frac{\xi_k}{ypG} \sum_{\ell \in E^{mo}} \xi_{\ell} \frac{y_{PG}}{z_E} \hat{m}_{\ell E} \delta \mu_{\ell E}^{cc} \]

\[ \delta x_{KE} = \frac{3 \xi_k x_{KE}}{4 n^E} \frac{y_{PG}}{z_E} \text{div} \hat{u} + \frac{x_{KE}}{RT} \left( \hat{m}_k \delta \mu_{KE}^{cc} - \frac{\xi_k}{z_E} \sum_{\ell \in E^{mo}} \xi_{\ell} \hat{m}_{\ell E} \delta \mu_{\ell E}^{cc} \right) \]

\[ \delta x_{KE} = \frac{3 y_{PG} \xi_k x_{KE}}{4 n^E} \frac{z_E}{z_E} \text{div} \hat{u} + \frac{x_{KE}}{RT} \sum_{\ell \in E^{ions}} z_{\ell E} \hat{m}_{\ell E} \delta \mu_{\ell E}^{cc}, \quad k \in E^{ions} \]

where \( z_{KE} = 1_k - \xi_k \frac{x_{KE}}{z_E} \) and \( I_{kl} \), with components \( l_{kl} \), is the identity matrix.

With this final equation for the increment of the ionic molar fractions, the incremental fictitious osmotic pressure may also be defined, replacing this expression of \( \delta x_{KE} \) in equation (2.38).

Using equation (A.8) and equation (A.15), the mass content variations in terms of the primary variables become:

\[ \frac{\delta m_{KE}}{m_{KE}} = \frac{\delta x_{KE}}{x_{KE}} + \frac{3}{4 n^E} \text{div} \hat{u} \]

\[ \frac{\delta m_{KE}}{m_{KE}} = \frac{3 \xi_k y_{PGE}}{4 n^E} \frac{z_E}{z_E} \text{div} \hat{u} + \frac{1}{RT} \sum_{\ell \in E^{ions}} z_{\ell E} \hat{m}_{\ell E} \delta \mu_{\ell E}^{cc} + \frac{3}{4 n^E} \text{div} \hat{u} \]

\[ \frac{\delta m_{KE}}{m_{KE}} = \left( \frac{y_{PGE}}{z_E} + 1 \right) \frac{3}{4 n^E} \text{div} \hat{u} + \frac{1}{RT} \sum_{\ell \in E^{ions}} z_{\ell E} \hat{m}_{\ell E} \delta \mu_{\ell E}^{cc}, \quad k \in E^{ions} \]

and so,

\[ \frac{\delta m_{KE}}{m_{KE}} = \frac{3 m_{KE}}{4 n^E} \frac{z_{KE} \text{div} \hat{u}}{z_E} + \frac{m_{KE}}{RT} \sum_{\ell \in E^{ions}} z_{\ell E} \hat{m}_{\ell E} \delta \mu_{\ell E}^{cc}, \quad k \in E^{ions}. \]  

(A.16)

At last, the derivative of the volume contents of the ionic species in order of time, \( \frac{\text{d} n_{KE}}{\text{d} t} \) in equation (3.4), expressed in terms of the primary unknowns, is:
which using index notation is written as:

\[
\frac{\partial \mathbf{u}}{\partial t} = \frac{\partial \mathbf{u}}{\partial t} + m_{kE} \frac{\partial \mathbf{u}}{\partial t} + \frac{3 m_{kE}}{n_E} z_{kE} \mathbf{div} \left( \frac{\partial \mathbf{u}}{\partial t} \right) + \frac{m_{kE}}{RT} \sum_{l \in E\text{ions}} z_{kE} \hat{m}_l \left( \frac{d \mu_{IE}^{cc}}{dt} \right) \quad (A.17)
\]

With all the previous quantities defined, incrementally, in function of the primary variables, the variation of the stress can also be computed, using the mechanical constitutive equation (2.22), as well as equation (A.14) and equation (2.39):

\[
\delta \sigma = -\delta p_E \mathbf{I} - \alpha_p \delta \tilde{\pi}_{osm} \mathbf{I} + (1 + \alpha_w \tilde{\pi}_{osm}) \mathbf{E} : \delta \mathbf{E} + \alpha_w \delta \tilde{\pi}_{osm} \mathbf{E} : \mathbf{E} \quad (A.18)
\]

where

\[
\delta \sigma_{ij} = -\delta p_E \mathbf{I} - \alpha_p \delta \tilde{\pi}_{osm} \mathbf{I} + (1 + \alpha_w \tilde{\pi}_{osm}) \mathbf{E}_{ijkl} \delta \mathbf{E}_{kl} + \alpha_w \delta \tilde{\pi}_{osm} \mathbf{E}_{ijkl} \mathbf{E}_{kl} \quad (A.19)
\]

Defining

\[
\delta p_E = -R_u \mathbf{div} \mathbf{u} - \sum_{l \in E\text{ions}} R_l \hat{m}_l \delta \mu_{IE}^{cc}
\]

and

\[
R_u = \frac{3}{4} \frac{RT y_{PG}^2}{z_E x_{wE} v_w}
\]

and considering \( \mathbf{div} \mathbf{u} = (\delta u_m)_m = \delta u_{m,m} \) and \( \mathbf{E}_{ijkl} \delta \mathbf{E}_{kl} = \mathbf{E}_{ijkl} \delta u_{k,l} \), the equation gets the form

\[
\delta \sigma_{ij} = \mathbf{R}_u \mathbf{I} \delta u_{m,m} - \alpha_p Q_u \mathbf{I} \delta u_{m,m} + (1 + \alpha_w \tilde{\pi}_{osm}) \mathbf{E}_{ijkl} \delta u_{k,l} + \alpha_w Q_u \mathbf{E}_{ijkl} \delta u_{m,m} \mathbf{E}_{kl}
\]

\[
+ \left( \sum_{l \in E\text{ions}} R_l \hat{m}_l \delta \mu_{IE}^{cc} \right) \mathbf{I} + \left( -\alpha_p \sum_{l \in E\text{ions}} Q_l \hat{m}_l \delta \mu_{IE}^{cc} \right) \mathbf{I} + \left( \alpha_w \sum_{l \in E\text{ions}} Q_l \hat{m}_l \delta \mu_{IE}^{cc} \right) \mathbf{E}_{ijkl} \mathbf{E}_{kl}
\]

\[
\delta \sigma_{ij} = (\mathbf{R}_u - \alpha_p Q_u) \mathbf{I} \delta u_{m,m} + (1 + \alpha_w \tilde{\pi}_{osm}) \mathbf{E}_{ijkl} \delta u_{k,l} + \alpha_w Q_u \mathbf{E}_{ijkl} \mathbf{E}_{mn} \mathbf{I} \delta u_{k,l} + \mathbf{E}_{ijkl} \mathbf{E}_{kl}
\]

\[
\sum_{l \in E\text{ions}} (R_l - \alpha_p Q_l) \hat{m}_l \delta \mu_{IE}^{cc} \right) \mathbf{I} + \left( \sum_{l \in E\text{ions}} \alpha_w Q_l \hat{m}_l \delta \mu_{IE}^{cc} \right) \mathbf{E}_{ijkl} \mathbf{E}_{kl}.
\]

where \( \delta u_{m,m} = (\delta u_{m,m})_m = \delta u_{m,m} \) and \( Q_u \) and \( Q_l \) are defined in equation (2.39). In equation (A.21) the notation \( (\ )_m = \frac{\partial (\ )}{\partial x_m} \) is used.

In this way, the final equation becomes:

\[
\delta \sigma = \left[ (1 + \alpha_w \tilde{\pi}_{osm}) \mathbf{E} + ((\mathbf{R}_u - \alpha_p Q_u) \mathbf{I} + \alpha_w Q_u \mathbf{E} : \mathbf{E}) \mathbf{E} \right] \mathbf{div} \mathbf{u} + \sum_{l \in E\text{ions}} ((R_l - \alpha_p Q_l) \mathbf{I} + \alpha_w Q_l \mathbf{E} : \mathbf{E}) \hat{m}_l \delta \mu_{IE}^{cc}.
\]

(A.22)
In the case of a uniaxial deformation $\epsilon$ one obtains:

$$\delta\sigma = \left[(1 + \alpha_w \tilde{\pi}_{\text{osm}}) E_{\text{sat}} + ((R_u - \alpha_p Q_u) + \alpha_w Q_u E_{\text{sat}} \epsilon) \right] \frac{d(\delta u)}{dx} +$$

$$\sum_{l \in E_{\text{mo}}} \left((R_l - \alpha_p Q_l) + \alpha_w Q_l E_{\text{sat}} \epsilon\right) \tilde{m}_l \delta \mu_{\text{IE}}^c .$$

(A.23)

Using these stress equations, written incrementally, the coefficients $K_{uu}$ and $K_{u\mu l}$ of the stiffness matrix may be obtained.