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## **FORMULATION OF A BIPHASIC MODEL CONSIDERING DONNAN'S OSMOTIC PRESSURE FOR INVESTIGATIONS OF THE SWELLING PHENOMENON IN SOFT TISSUES**

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**Abstract.** *The biomechanical behavior of soft tissues evolves a series of biochemical phenomena that are directly related to the structures that compose the tissue, as well as the environment that it permeates. Tendons are highly hydrated and poorly vascularized connective tissues. Its morphological composition is mainly composed of an extracellular matrix formed by a combination of fibers (collagen and elastin) together with a ground substance constituted by a set of hydrophilic macromolecules. These molecules include glycosaminoglycans and proteoglycans. In addition to having various properties and performing different morphological functions, these molecules are also responsible for providing tissues with a negative electrochemical charge called fixed charge density (FCD). This property is directly related to a series of biochemical phenomena that influence the chemical and mechanical response of the tissue. Due to the presence of these macromolecules, an electrochemical imbalance is established, creating a potential difference called osmotic pressure. This osmotic pressure imposes a mechanical loading on the tissue, affecting on its kinematic responses and acting directly on the fluid flow. In many studies, triphasic models are commonly used to describe the biomechanical behavior of soft tissues under chemical loading. However, these models are quite complex and computationally costly. Alternatively, poroelastic biphasic models have been modified to include electrochemical effects in research where the variable of interest does not include the ionic field. In this case, instead of considering a third field (ionic), the models incorporate the osmotic pressure phenomenon through a local update of the total pressure term. In this context, the main objective of the present study is to use a poroelastic biphasic model to study the swelling phenomenon observed in tendon tissues when subjected to chemical stimuli. For this purpose, a poroelastic model has been developed that takes into account the osmotic pressure caused by chemical solicitation based on Donnan's equation. The proposed model was implemented in an in-house finite element code and the results and accuracy of the model were compared with the FEBio software.*

**Keywords:** *Soft tissues biomechanics, biphasic formulation, Poroelasticity, osmotic pressure, finite element method*

### **1. INTRODUCTION**

Tissue engineering is an important multidisciplinary field that has been widely studied in recent decades. When pathological conditions compromise the functionality of tissues and organs of the human body, tissue engineering offers alternative treatments, assisting regenerative medicine through the development of artificial biomechanical structures capable of efficiently perform the functions of natural organs and tissues. Therefore the tissue engineering has the main objective to investigate the biomechanical behavior of tissue and organs of the human body in order to develop synthetic structures that replace or stimulate the regeneration of natural tissues of the human body.

In this context, aiming the continuous development of the clinic treatments related to regenerative medicine, there is a large number of recent studies related to the biomechanical behavior of tissues in the human body. Among these, conjunctive soft tissues like tendons, cartilages and ligaments constitute an important research group. These structures are highly hydrated and poorly vascularized, composed by extracellular matrix of collagen and elastin fibers among with a ground substance that contains a large group of hydrophilic macromolecules called glycosaminoglycans (GAG's) and proteoglycans. Besides the heterogeneous morphological composition, connective tissues present a complex structural organization. The fibers that constitute the extracellular matrix have preferential directions in strain, featuring an anisotropic

biomechanic behavior. When submitted to stress these tissues can present large deformations, featuring a non linear and viscous mechanic behavior. Furthermore, the biomechanic response of these tissues can be influenced by several factors, such as morphology, age, species, temperature, osmotic pressure, pH, strain rate, among others.

Another important feature of connective soft tissues is related to the glycosaminoglycans present in the ground substance. These large molecules are retained to the extracellular matrix and provide an electronegative charge to the tissue, called fixed charge density (FCD). When the tissue is submerged in an ionic bath, the presence of the GAGs attracts counter-ions in order to obtain electroneutrality. The movement of these ions, causes a phenomenon of osmosis that increases the concentration of solute internal to the tissue. The chemical imbalance results in a internal fluid pressure known as Donnan osmotic pressure. These pressure, contributes directly with the swelling behavior observed in connective soft tissues, influencing in his biomechanic responses and morphological/chemical features.

Therefore, as the biomechanical behavior of connective soft tissues is directly related to a vast range of morphological and constructive features, the characterization of this variables and his phenomenological impacts contributes directly with the computational modeling of theses structures. Specifically, consider the electrochemical effects of charge concentration in the tissues and the resultant osmotic pressure can improve the representativeness of numeric models.

## 2. BIPHASIC FORMULATION AND OSMOTIC PRESSURE

### 2.1 Integral form of biphasic osmotic formulation

The homogenized biphasic formulation has been commonly utilized in a vast number of soft tissues researches in the past decades (Ateshian and Weiss, 2010; Thiesen, 2021; Klahr, 2022; Carniel *et al.*, 2023; Lanzendorf, 2023). This formulation consider the tissue constituted by solid matrix along with a inviscid and incompressible fluid phase. Additionally, the principles of poroelasticity and poroviscoelasticity are well known in the literatura, based on classical references like Lanir (1987) and Mow *et al.* (1980). In this research, some important assumptions was made in order to simplify the model and maintain its representativeness regarding the biomechanical behavior of soft tissues. These hypothesis are listed below:

1. Incompressibility of the  $i$  phases:  $\dot{\rho}_\mu^i = 0$ .
2. Mixture fully saturated:  $\nu^s + \nu^f = 1$ .
3. Total stress composed of two parts referring to the solid and fluid phases:  $\boldsymbol{\sigma} = \boldsymbol{\sigma}^s + \boldsymbol{\sigma}^f$ .
4. Hydrostatic stress dependent on pore pressure:  $\boldsymbol{\sigma}^f = -p\mathbf{I}$ .
5. Zero inertial and body forces:  $\rho^i \mathbf{a}^i = \mathbf{0}$  and  $\mathbf{b}_x = \mathbf{0}$ ,

where  $\dot{\rho}_\mu^i$  is the time derivative of each phase  $i$ ,  $\nu^s$  is the tissue solidity,  $\nu^f$  is the tissue porosity,  $\boldsymbol{\sigma}$  is the Cauchy stress tensor,  $\boldsymbol{\sigma}^s$  is the stress of the solid matrix,  $\boldsymbol{\sigma}^f$  is the stress on the fluid phase,  $p$  is the pore pressure,  $\mathbf{I}$  is the identity tensor,  $\rho^i$  is de density of each phase  $i$ ,  $\mathbf{a}^i$  is the acceleration of each phase  $i$  and  $\mathbf{b}_x$  represents the body forces.

In order to add the osmotic pressure in the biphasic formulation its necessary to utilize a constitutive equation for it similarly to the formulations used in the works of Wilson *et al.* (2005) and Galbusera *et al.* (2011). In that case, the pore pressure will be composed by two parts: the chemical potential of the fluid  $\mu^f$  and the osmotic pressure  $\Delta\pi$  (whose constitutive equation will be demonstrated latter). Therefore, the pore pressure is defined by:

$$p = \mu^f + \Delta\pi \quad (1)$$

The consideration of the osmotic pressure requires some changes in the classical biphasic poroelastic formulation. For instance, the boundary condition of the fluid phase no longer refers to the pore pressure, but to the chemical potential of that phase that represents a measure of hydrostatic pressure related to the Gibbs free energy contained in each fluid particle. The osmotic pressure is generated by a chemical imbalance induced by negative chargers present in the tissue solid matrix. This pressure is calculated according to a constitutive model like Donnan's osmotic pressure considering ideal conditions. Therefore, the integral formulation of the biphasic model considering the osmotic pressure can be represented by the following equations:

$$\begin{cases} \delta W^s = \int_{\Omega_x} \boldsymbol{\sigma}^s : \delta \mathbf{e} \, dv - \int_{\Omega_x} (\mu^f + \Delta\pi) \text{tr}(\delta \mathbf{e}) \, dv - \int_{\partial\Omega_x} \bar{t} \cdot \delta \mathbf{u} \, ds = 0 \quad \forall \delta \mathbf{u} \in \mathcal{K}^u, \\ \delta W^f = \int_{\Omega_x} \text{div}(\mathbf{v}^s) \delta \mu^f \, dv - \int_{\Omega_x} \boldsymbol{\omega} \cdot \nabla_x \delta \mu^f \, dv + \int_{\partial\Omega_x} \bar{q} \delta \mu^f \, ds = 0 \quad \forall \delta \mu^f \in \mathcal{K}^{\mu^f}, \end{cases} \quad (2)$$

## 2.2 Donnan's osmotic pressure

The theory of membrane equilibria of Donnan (1924) present the case where a ionic solution composed by two phases is separated by a membrane that is permeable to solvent and ions but restricts the movement of larger molecules. In that scenario a heterogeneous distribution of ions causes a electrochemical phenomena, as well as the appearance of an osmotic pressure and chemical potential difference between phases (Overbeek, 1956).

For soft tissues Donnan's theory can be applied in order to describe the swelling phenomena observed in these structures. The swelling occurs due the existence of interns macromolecules negatively charged in the morphology of the tissue (GAGs). These molecules provide to the tissue a property called fixed charge density (FCD), establishing a flux of ions between the solid matrix and the interstitial fluid in order to maintain the chemical balance (Lai *et al.*, 1991; Huyghe and Janssen, 1997). The redistribution of charges causes a higher concentration of ions inside the tissue solid matrix than in the external bath. The ionic imbalance generate the osmotic pressure, contributing to the swelling phenomenon of the tissue. Assuming the Lanir (1987) theory related to biomechanical soft tissues behavior is considered that the intern ions movement occurs much faster than the fluid flow and solid deformation, therefore the chemical balance between the intern fluid and the external bath can be considered instantaneous.

According to other surveys such as Wilson *et al.* (2005) and Galbusera *et al.* (2011), the present research considers the theory presented previously among with swelling biphasic formulation, utilizing a simplified equation of osmotic pressure in ideal conditions described by Donnan. Therefore, the osmotic pressure can be expressed by:

$$\Delta\pi = RT \left( \sqrt{c_F^2 + \bar{c}^2} - \bar{c} \right), \quad (3)$$

where  $R$  is the universal constant of gases,  $T$  is the temperature,  $\bar{c}$  is the external bath osmolality and  $c_F$  is the fixed charge density given by:

$$c_F = c_{F0} \left[ \frac{\nu_0^f}{\nu_0^f - (1 - J)} \right], \quad (4)$$

and  $c_{F0}$  is the initial fixed charge density of the tissue,  $\nu_0^f$  is the initial fluid volume in the tissue and  $J$  stand for the volumetric Jacobian.

In order to obtain the expression demonstrated in the Eq. (3) it's necessary consider some simplifications in the original Donnan's equation. These simplifications are enumerated in the following:

1. Osmosis coefficient ( $\phi$ ): the osmosis coefficient is considered unitary. Also, this there is no differentiation between internal e external osmosis coefficient. Therefore:  $\phi_{int} = \phi_{ext} = \phi = 1$ .
2. Mean activity coefficient ( $\gamma$ ): similarly to the osmosis coefficient, the mean activity coefficient also stands for a ideal scenario of osmosis. Following the simplification utilized in many surveys (Lai *et al.*, 1991; Wilson *et al.*, 2005; Galbusera *et al.*, 2011; Zimmerman *et al.*, 2021) the ratio between these is also considered unitary in this research,  $i, g, \frac{\gamma_{ext}^{\pm}}{\gamma_{int}^{\pm}} = 1$ .
3. Temperature ( $T$ ): the internal and external temperature of the tissue was considered equivalent:  $T_{ext} = T_{int} = T$ .
4. Bath osmolality: stands for the total concentrations of solutes in the external bath. Similarly to the formulation utilized by Maas *et al.* (2012), this variable is aproximated to twice the external mass concentration of the ratio between solute and volume:  $\bar{c} = 2c_{ext}$ .

To complete the formulation is necessary utilize the constitutive equations referring to the solid matrix deformation, fluid flow and permeability. The constitutive laws considered in this study are respectively Neo Hookean, Darcy's law (applied in the chemical potential of the fluid phase) and a isotropic constant permeability.

## 3. NUMERICAL EXPERIMENTS AND RESULTS

In order to evaluate the representativeness of the formulation presented previously, a numerical sample was modeled and simulated with a laboratory program. The results obtained was directly compared with those obtained by the biomechanics finite element simulator FEBio (Maas *et al.*, 2012). The numerical sample geometry consist in a cube whose edges are 5 mm long and the boundary conditions are demonstrated in the Figure 1 and the parameters utilized in the constitutive models are displayed in the Table 1. These parameters was chosen based on literature studies like Ateshian and Weiss (2010), Galbusera *et al.* (2011), Wilson *et al.* (2005) and Zimmerman *et al.* (2021).

Regarding the numerical aspects of the study, the mesh and element utilized in the numerical simulation are presented in the Figure 2. The mesh used in the simulation is composed of 8000 elements, each element is hexahedral with twenty

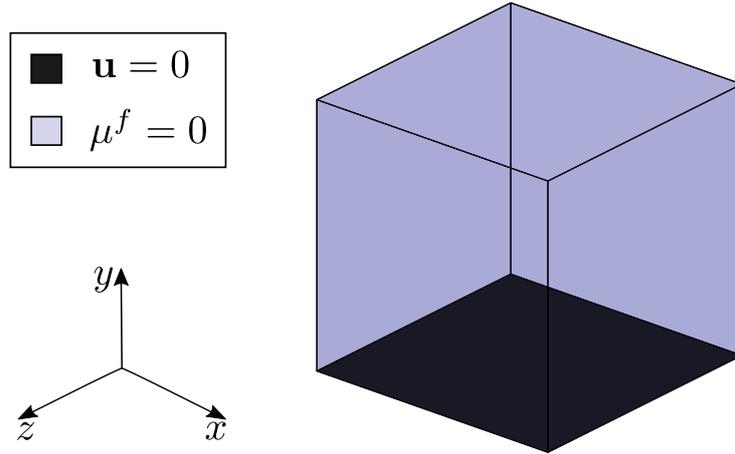


Figure 1. Validation model boundary conditions.

Table 1. Validation model parameters.

$E$ [MPa]	$\nu$	$\nu_0^f$	$cF_0$ [mM]	$\bar{c}$ [mM]	$R$ [mJ/nmolK]	$T$ [K]	$k_0$ [mm <sup>4</sup> /Ns]
2	0,4	0,8	300	150	8,3145e-6	310	0,001

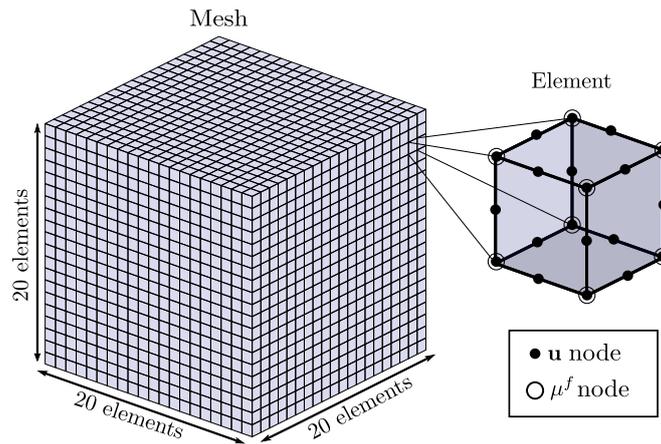


Figure 2. Mesh and element validation model.

nodes referring to the displacement degrees of freedom and eight nodes to approximate the chemical potential field of the fluid phase.

Two mesh nodes was chosen in order to verify the formulation representativeness, one to evaluate the magnitude of displacement and the second one to verify the results referring to the fluid phase chemical potential. The Figure 3 illustrates the placement of the nodes chosen for analysis, while the Table 2 presents their respective coordinates.

Table 2. Material coordinates of inspection nodes.

Node	x [mm]	y [mm]	z [mm]
A	2,5	5,0	2,5
B	2,5	0,0	2,5

The curves of magnitude displacement and chemical potential of the fluid phase obtained by the laboratorial and reference (FEBio) program are displayed in the Figure 4 a) and 4 b) respectively. Analysing the behavior of the curves a good correlation can be seen between the both formulations.

The implemented formulation was capable of representing the swelling phenomenon in an analogous way to the reference program. This finding can also be seen by analyzing the Figure 4 and Figure 6 that present the sample numerical results of displacement magnitude fields and chemical potential of the fluid phase.

therefore, in the present study, a formulation capable of including the effect of osmotic pressure and its consequent phenomenon of swelling in the behavioral investigation of soft tissues has been developed. The results were satisfactory,

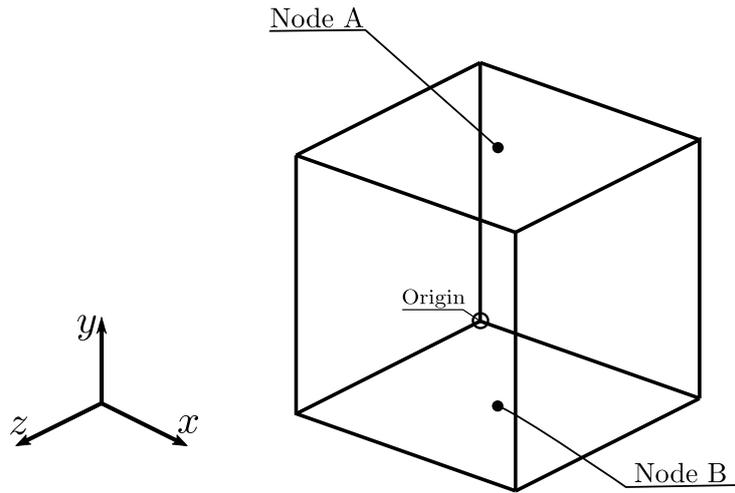


Figure 3. Analysed nodes.

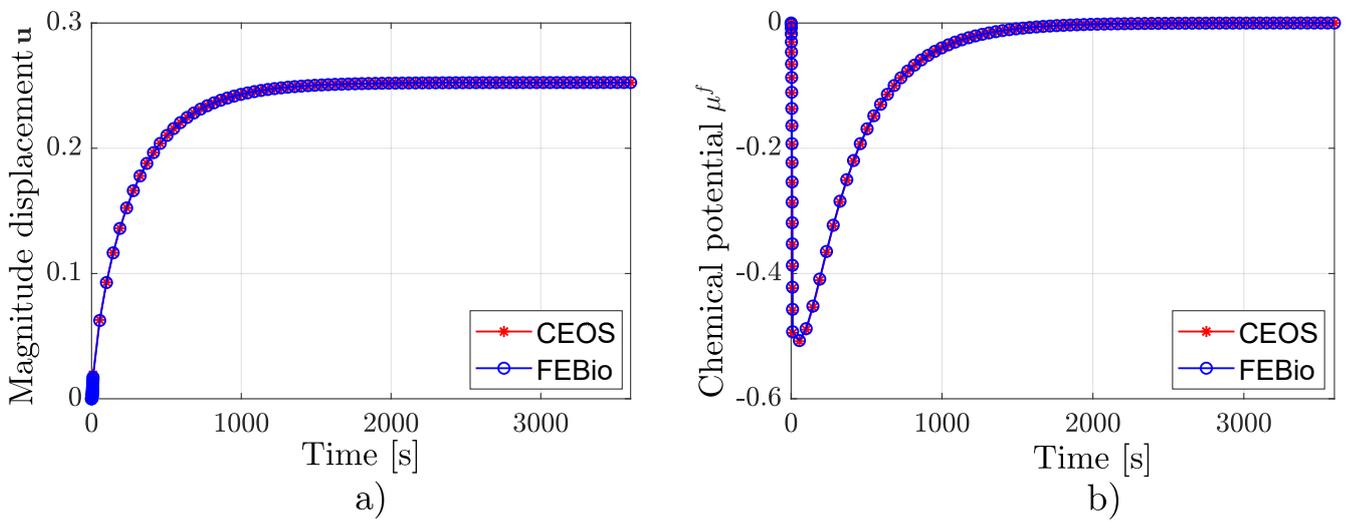


Figure 4. a) Node A magnitude displacement b) Node B Fluid phase chemical potential.

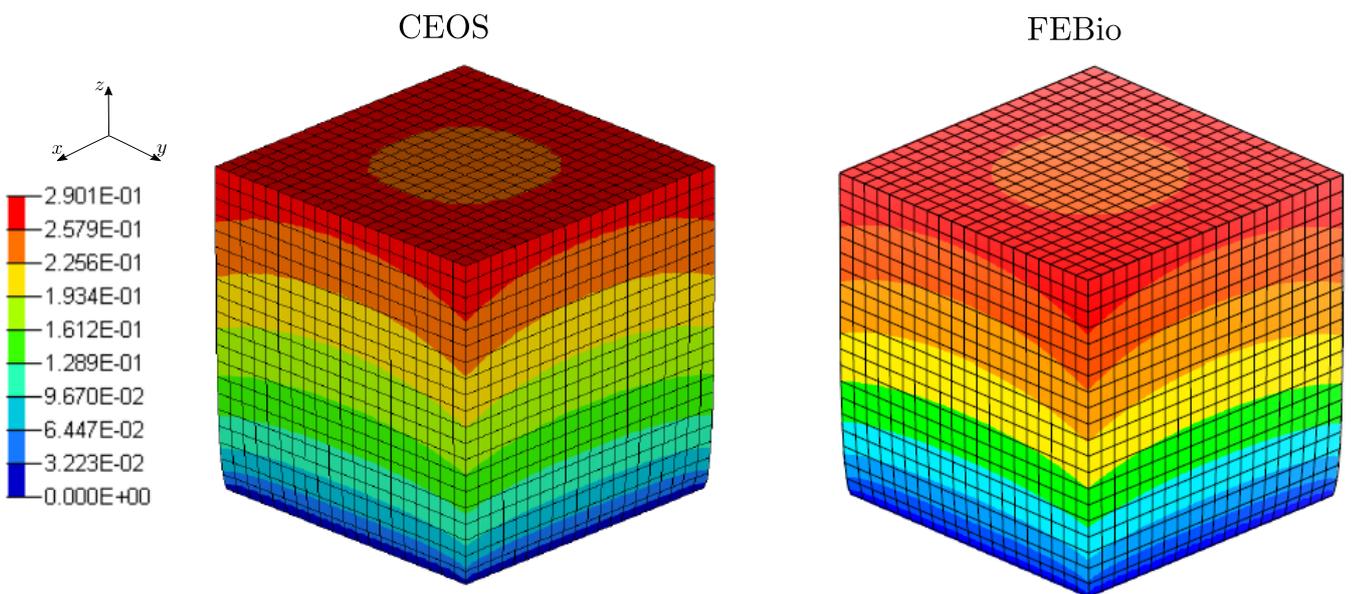


Figure 5. Numerical simulations magnitude displacement field.

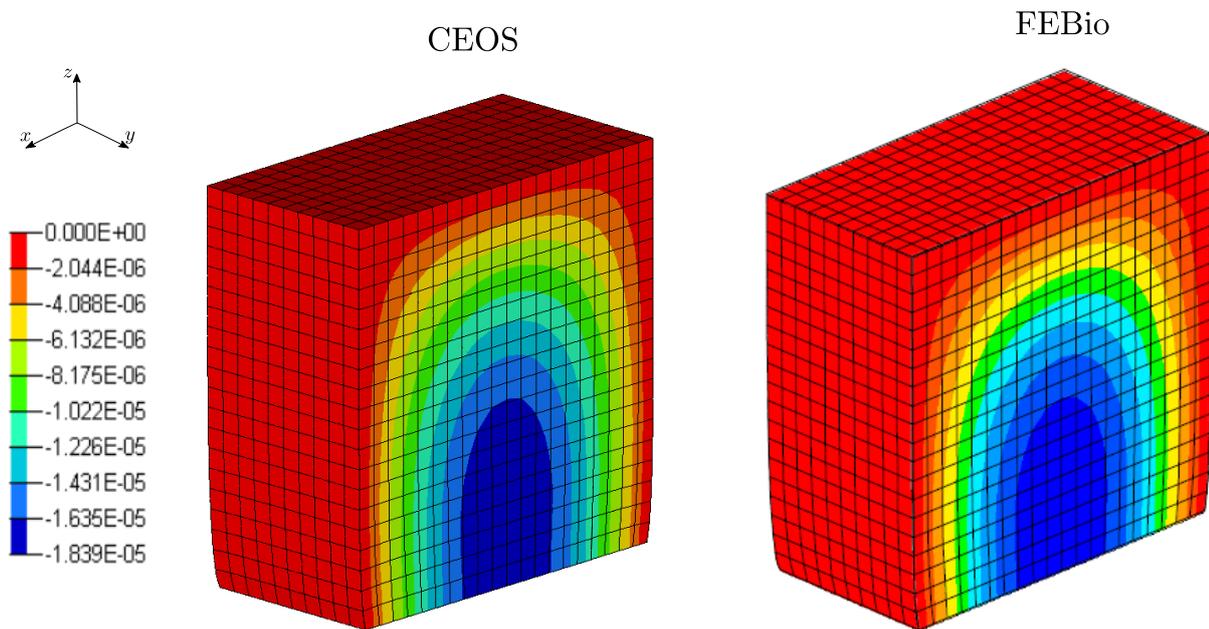


Figure 6. Numerical simulations fluid phase chemical potential.

adapting the laboratorial code to the reference program (FEBio). Additionally, the implementation of the osmotic pressure phenomenon in the laboratory code allows the continuity of studies related to the phenomenon of swelling in soft tissues, as well as the investigation of chemical solicitations occurring in these tissues.

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