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Review

Finite element modeling of soft tissues: Material models, tissue interaction and challenges

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ABSTRACT

Background: Musculoskeletal soft tissues, such as articular cartilage, ligaments, knee meniscus and intervertebral disk, have a complex structure, which provides elasticity and capability to support and distribute the body loads. Soft tissues describe an inhomogeneous and multiphasic structure, and exhibit a nonlinear, time-dependent behavior. Their mechanical response is governed by a substance composed of protein fiber-rich and proteoglycan-rich extracellular matrix and interstitial fluid. Protein fibers (e.g. collagen) give the tissue direction dependent stiffness and strength. To investigate these complex biological systems, the use of mathematical tools is well established, alone or in combination with experimental in vitro and in vivo tests. However, the development of these models poses many challenges due to the complex structure and mechanical response of soft tissues.
Methods: Non-systematic literature review.
Findings: This paper provides a summary of different modeling strategies with associated material properties, contact interactions between articulating tissues, validation and sensitivity of soft tissues with special focus on knee joint soft tissues and intervertebral disk. Furthermore, it reviews and discusses some salient clinical findings of reported finite element simulations.
Interpretation: Model studies extensively contributed to the understanding of functional biomechanics of soft tissues. Models can be effectively used to elucidate clinically relevant questions. However, users should be aware of the complexity of such tissues and of the capabilities and limitations of these approaches to adequately simulate a specific in vivo or in vitro phenomenon.

1. Introduction

The mechanical function of musculoskeletal soft tissues, such as articular cartilage, ligaments, meniscus or intervertebral disk, is in supporting and distributing the loads generated by muscles, body weight and inertial forces and allowing for the controlled motion of the human body. In order to investigate the mechanics of these biological systems, mathematical tools, such as finite element methods act as a complementary approach to in vivo and in vitro studies. It provides valuable insights into the behavior of the structures' function and are helpful for explorative preclinical investigations.

As a matter of fact, soft tissues exhibit mechanical characteristics with a higher complexity than most engineering materials and structures. For modeling purposes it is crucial to select a material law as well as material parameters that well describe the mechanical properties of the soft tissue with regard to the investigation scope.

The mechanical behavior of soft tissues is governed mainly by the major phases of these materials. The solid phase with collagen fibers, proteoglycans, other proteins and cells as well as an interstitial fluid phase composed of water and electrolytes (Mow and Huiskes, 2005). While substances like proteoglycans bind water to form a firm gel and give the tissue its resiliency, the collagen fibers give the tissue its tensile strength. The specific arrangement and hierarchical organization of the fibers have major influences on the mechanical behavior of the tissue (Fung, 1993). It is naturally optimized to fulfill the specific mechanical function of each tissue (Schneck and Bronzino, 2003). Hyaline cartilage for example is highly hydrated and is comprised of fine collagen fibrils oriented isotropically in planes parallel to the articular contact. This specific orientation gives the cartilage its high resistance to compressive loads and provides good lubrication to highly mobile joint surfaces (Bell et al., 2006). Differently, soft tissues made of fibrocartilage, e.g. annulus fibrosus of the intervertebral disk, knee meniscus or temporomandibular joint, are made up of compact collagen fiber bundles oriented in the circumferential direction of the tissue. However, a closer look at the fiber distribution reveals not only circumferentially oriented fibers. For example, the meniscus also

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Table 1
Material formulations for statically responding simulations.

Linear material formulations (Hooke's law)

General formulation (*anisotropic material*)

$\sigma = C \cdot \varepsilon$

with

$$\sigma = \begin{bmatrix} \sigma 11 \\ \sigma 22 \\ \sigma 33 \\ \sigma 23 \\ \sigma 13 \\ \sigma 12 \end{bmatrix}, \varepsilon = \begin{bmatrix} \varepsilon 11 \\ \varepsilon 22 \\ \varepsilon 33 \\ 2\varepsilon_{23} \\ 2\varepsilon_{13} \\ 2\varepsilon_{12} \end{bmatrix}, C = \begin{bmatrix} C_{1111} & C_{1122} & C_{1133} & C_{1123} & C_{1113} & C_{1112} \\ C_{2211} & C_{2222} & C_{2233} & C_{2223} & C_{2213} & C_{2212} \\ C_{3311} & C_{3322} & C_{3333} & C_{3323} & C_{3313} & C_{3312} \\ C_{2311} & C_{2322} & C_{2333} & C_{2323} & C_{2313} & C_{2312} \\ C_{1311} & C_{1322} & C_{1333} & C_{1323} & C_{1313} & C_{1312} \\ C_{1211} & C_{1222} & C_{1233} & C_{1223} & C_{1213} & C_{1212} \end{bmatrix}$$

σ: stres vector; ε: strain vector; C: 4th-order stiffness tensor

For orthotropic, transversal isotropic and isotropic materials:

$$C = \begin{bmatrix} C_{1111} & C_{1122} & C_{1133} & 0 & 0 & 0 \\ C_{2211} & C_{2222} & C_{2233} & 0 & 0 & 0 \\ C_{3311} & C_{3322} & C_{3333} & 0 & 0 & 0 \\ 0 & 0 & 0 & C_{2323} & 0 & 0 \\ 0 & 0 & 0 & 0 & C_{1313} & 0 \\ 0 & 0 & 0 & 0 & 0 & C_{1212} \end{bmatrix}$$

Orthotropic material	Transversal isotropic material	Isotropic material
$C_{2211} = C_{1122}$	$C_{2211} = C_{1122}$	$C_{1111} = C_{2222} = C_{3333}$
$C_{3311} = C_{1133}$	$C_{3311} = C_{3322} = C_{1133} = C_{2233}$	$C_{2323} = C_{1313} = C_{1212}$
$C_{3322} = C_{2233}$	$C_{1111} = C_{2222}$	$C_{1122} = C_{1133} = C_{2233} = C_{2211} = C_{3311} = C_{3322}$
	$C_{2323} = C_{1313}$	
	$C_{1212} = \frac{1}{2}(C_{1111} - C_{1122})$	

Nonlinear fiber reinforced material formulations

$\sigma = \sigma_{gs} + \sigma_{fib}$ with $E_{fib} = \begin{cases} E^0_{fib} + E^{\varepsilon}_{fib}\varepsilon_{fib} & for\ \varepsilon_{fib} > 0 \\ 0 & for\ \varepsilon_{fib} < 0 \end{cases}$

σ_{gs}: ground substance stress; σ_{fib}: fibril stress; E_{fib}: fibril tensile strain dependent modulus; ε_{fib}: fibril strain; E^0_{fib}: initial fibril stiffness; E^{ε}_{fib}: fibril stiffness

consists of a few radial tie fibers in the central portion (Petersen and Tillmann, 1998). In the superficial layer the fibers are randomly distributed (Petersen and Tillmann, 1998). Such locally varying collagen fiber arrangement can also be found in other soft tissues and are of major interest in modeling soft tissues since the collagen fibers are quantitatively the major organic component (Mow and Huiskes, 2005). Proteoglycans are the second most abundant organic component (Mow and Huiskes, 2005). With their fixed charge density, they are involved in osmotic swelling (Schneck and Bronzino, 2003), which regulates the pressure and tissue hydration, hence, contributing to the viscoelastic nature of the soft tissue. The fluid phase also plays an important role in terms of viscoelasticity. The pressure of the interstitial fluid due to osmotic imbibition and mechanical loads creates a stress in the solid phase, which contributes to the stiffness and the apparent incompressibility of the soft tissue (Mow and Huiskes, 2005).

Simulations of musculoskeletal structures are usually not limited to one specific soft tissue. Instead, most studies are focused on the interaction between the various anatomical components, such as contact between cartilage layers or ligament wrapping, which introduces a nonlinearity in a numerical model and can be particularly critical in biphasic models or when considering friction.

Moreover, simulations of musculoskeletal tissues targeted to achieve a clinical impact are not usually limited to modeling the complexity of the response of these materials or their interaction. Modeling of pathologies, like continuous degeneration, damage, failure or crack propagation introduces geometric discontinuity in the tissue and constitutes another challenge.

The present non-systematic review discusses different modeling strategies with associated material properties, contact interactions between articulating tissues, validation and sensitivity analyses of soft tissues and provides some salient clinical findings of reported finite element simulations with special focus on the soft tissues of the knee and the intervertebral disk. Nevertheless, as soft tissues exhibit analogous structure and properties in all anatomical regions, modeling approaches and material constitutive laws can be adapted to other soft tissues with little effort.

2. Material laws for soft tissues

2.1. Static response

Static analyses can be used to investigate the behavior of the soft tissue at one certain time point, for example instantaneous or equilibrium response. In this case the time-dependent behavior, e.g. creep or relaxation, of the soft tissue is neglected.

2.1.1. Isotropic, linear elasticity

The simplest way to model the mechanical response of a soft tissue is to use a linear elastic and isotropic formulation (Table 1). In such case it is assumed that the stress–strain curve is linear and not dependent on the direction of load. Due to their simplicity, linear elastic isotropic materials can be used to limit numerical difficulties in challenging contact formulations when the investigation of the response of the tissues in the proximity of the contact is not the main focus, e.g. in kinematic analyses of the knee, as well as for debugging purposes of more complex models.

One of the first finite element simulations of the meniscus used a linear elastic and isotropic material model in a strongly geometrically simplified, axisymmetric model (Sauren et al., 1984). Later studies also included linear elastic isotropic material formulations for e.g. articular cartilage, menisci (Beillas et al., 2001; Pena et al., 2005a; Perie and Hobatho, 1998) or nucleus pulposus of the intervertebral disk (Ueno and Liu, 1987) and considered a more detailed geometry. In a sensitivity study, in which the linear elastic material properties of e.g. cartilaginous and meniscal tissue were varied in a physiological range (Beillas et al., 2007) it was shown that the variation of articular cartilage properties highly influenced the cartilage contact pressure response. In general, higher elasticity and Poisson's ratios of the cartilage tissue caused higher maximal contact pressure (Beillas et al., 2007).

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Table 2
Advantages and disadvantages of different material models.

	Advantages	Disadvantages
Static response		
Isotropic elasticity	+ Limiting computational cost + Limiting numerical difficulties	− Only certain time point (instantaneous or equilibrium response) − Neglecting time-dependent behavior − Neglecting direction dependency − Neglecting nonlinearity
Orthotropy and transverse isotropy	+ Taking collagen fiber directions into account	− Effects of architecture of collagen fibers not included − Neglecting time-dependent behavior − Neglecting nonlinearity
Fiber reinforced models and nonlinear behavior of the fibers	+ Nonlinear behavior of fibers can be considered + It can be distinguished between fibrillar and non-fibrillar phase	− Neglecting time-dependent behavior − Convergency problems due to large differences in stiffnesses between ground substance and fibers especially for higher loads
Time dependent behavior		
Monophasic models	+ Limiting numerical difficulties + Limiting computational cost	− Solid and fluid phases are modeled in one continuum
Biphasic models	+ Distinguishing between solid and fluid phases + Strain dependent permeability can be included	− Free osmotic swelling is neglected or simplified
Osmotic swelling	+ Including free swelling in unloaded conditions + Diffusion of moving ions is included	− Computationally intensive − Difficult to validate

The fact that these soft tissues are fiber reinforced with a predominant natural fiber direction, e.g. circumferential or radial, dictates that a more accurate material formulation should be considered; Haut Donahue et al. (2003) reported that the contact pressure distribution of the knee is better described with a more detailed material law than an isotropic constitutive law. This conclusion is based on a finite element model which was validated with experimental measurements of the contact pressure distribution of the tibial plateau. Moreover, simulations of a physiological compression of the knee lead to a compression of cartilage and a tension in the meniscus, for which a linear elastic law would incorrectly estimate the strains in the naturally fiber reinforced direction, as the fibers stiffen the material in the direction of reinforcement.

2.1.2. Orthotropy and transverse isotropy

In contrast to an isotropic material formulation, an orthotropic material formulation has different mechanical properties in the three coordinate directions due to different linear stress–strain curves in each direction (Tables 1, 2). A special case of orthotropic material is the transverse isotropic material law, for which the material has the same properties in two orthogonal directions (Table 1). The transverse isotropic constitutive law is the most common way to describe the static soft tissue response of the meniscus; as such a formulation takes the predominant fiber direction into account. The comparison of an isotropic (direction independent) and a transversely isotropic (direction-dependent) constitutive law, through optimization of certain material properties of the knee soft tissues, showed that a transversely isotropic elastic material law is crucial for predicting a plausible response (Haut Donahue et al., 2003). This was confirmed by a comparison with experimental results on the contact pressure distribution on the tibial plateau (Haut Donahue et al., 2003) as well as performing a sensitivity analysis to fit the results of a finite element model to experimental data of meniscal motion and deformation (Yao et al., 2006). Concerning the meniscus, it was shown that an orthotropic material model does not provide significant advantage in comparison with a transverse isotropic law (Haut Donahue et al., 2003). Furthermore, the choice of the material laws in modeling the knee tissues was found to be less significant than geometrical parameters (Meakin et al., 2003). A transverse isotropic constitutive law in combination with other modeling approaches was utilized by different groups (LeRoux and Setton, 2002; Spilker et al., 1992; Vadher et al., 2006; Vaziri et al., 2008; Wilson et al., 2003).

The aforementioned studies were not able to distinguish between the individual role of collagen fibrils and the other components of the soft tissue (Table 2). Moreover, all soft tissues respond nonlinearly to increasing loads, which is not captured by a linear ortho- or transversal isotropic material formulation. As Yao et al. (2006) suggested that many research questions about modeling of the meniscus also require a focus on nonlinear properties and inhomogeneity.

2.1.3. Fiber reinforced models and the nonlinear behavior of the fibers

Fiber reinforced models describe the soft tissues' material behavior with special attention to the nonlinear behavior of the fibers characterized by a toe region, linear region and failure (Fig. 1, Table 1). When a tensile test of a soft tissue specimen is performed, the nonlinear toe region is caused by the straightening of the collagen fibers. During the linear region the fibers perform a linear stretch until failure of the collagen fibers. The properties of the fibers can be simulated with elastic springs (Li et al., 1999; Schmidt et al., 2006; Shirazi-Adl et al., 1986), truss elements (Bendjaballah et al., 1995), rebars (Gupta et al., 2009; Lubomierski, 2013; Schmidt et al., 2010) (Fig. 2), membrane elements (Shirazi and Shirazi-Adl, 2005), a mixture of membrane and continuum elements (Shirazi et al., 2008) or continuum elements (Li and Herzog, 2004; Pena et al., 2008; Vena et al., 2005). Spring elements can either be linear or nonlinear, coupling a force with a relative displacement. The cross sectional areas of the fibers cannot be separately defined. In contrast, truss elements allow the definition of cross sectional areas. Membrane or solid elements with rebar properties allow the definition of different layers with uniaxial reinforcement as a part of host elements. The cross sectional areas of the fibers can be defined and nonlinear tensile stress–strain behavior can be described. An advantage compared to the other fiber implementation methods is the distinct definition of the fiber angle, independently of the shape of the underlying host element. If the fibers are included in continuum elements, the strain-energy function incorporates the matrix as well as the nonlinear fiber properties with their direction dependency (e.g. Holzapfel et al., 2000). Collagen fibers in soft tissues are stiffer in tension than in compression (Fig. 1), and numerical models take this aspect into consideration with strain-dependent nonlinear formulations. Therefore, compressive stress states are carried by the ground substance and tensional stresses lead to a mixture carriage dependent on the fiber volume fraction and stiffness of the fibers. In addition to the strain-dependent formulation, a depth dependency might also be included, e.g. for cartilage (Li et al., 2000).

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The nonlinear elastic stress–strain dependent behavior (hyperelasticity) of soft tissues can only be described using the large strain theory. A strain energy density function is used to define a hyperelastic material. Different forms of strain energy functions can be emphasized, for example, the neo-Hookean (Ogden, 1997). It is the simplest model to describe an initial linear behavior, similar to Hooke's law, which at some point turns into a nonlinear behavior. The strain energy function for an incompressible neo-Hookean material is shown in Table 3. A more general model is the Mooney–Rivlin model, where the strain energy density function is a linear combination of two invariants of the left Cauchy–Green deformation tensor and is more accurate for larger strains than the neo-Hookean model. The two parameter Mooney–Rivlin model (Mooney, 1940; Rivlin, 1948) is usually valid for strains less than 100%, whereas the neo-Hookean material is typically accurate only for strains less than 20% (Gent, 2001). Another model to describe the stress–strain relationship of hyperelastic materials is the Ogden model (Table 3) (Ogden, 1972). It is more advanced than the other two models and is expressed in terms of principal stretches. These models with their increasing level of complexity are mostly applied for the non-fibrous ground substance of soft tissues (e.g. Shirazi et al., 2008). However, there are also anisotropic hyperelastic material models which distinguish between ground substance and fibers in one continuum (Holzapfel et al., 2000; Weiss and Gardiner, 2001), e.g. for ligaments (Pena et al., 2006a).

The challenging task to include these material formulations into a whole knee joint model was accomplished by several authors (Bendjaballah et al., 1995; Gu and Li, 2011; Mononen et al., 2012; Shirazi and Shirazi-Adl, 2005; Shirazi et al., 2008). Despite the complexity of these approaches compared to isotropic or transversely isotropic models, fiber-reinforced models are still a simplification of the real microstructural arrangement of the soft tissue, since a realistic fibril arrangement is hard to capture and to represent in a simulation model. Nevertheless, differentiating between the fibrillar and the non-fibrillar phase allows for capturing separately the mechanics of both phases and their respective influences on the tissue response can be assessed. Moreover, if validation experiments show a good agreement with the simplified fiber-reinforced model, its predictive nature still exists.

2.2. Time-dependent behavior

It is known that soft tissues exhibit a time-dependent behavior if a constant load or deformation is applied (Fig. 3). This behavior is due to the intrinsic viscoelastic behavior of the solid phase of the tissue and on the fluid exudation and imbibition.

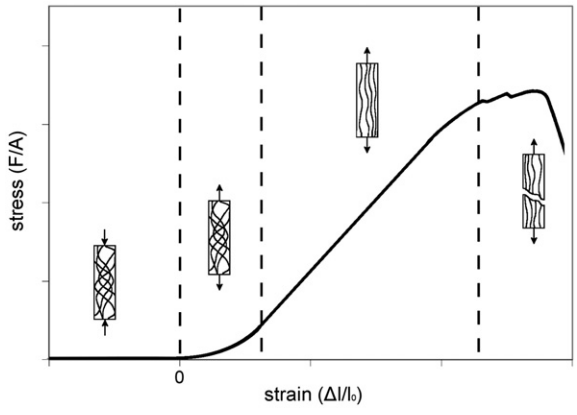

Fig. 1. Example of stress–strain curve of collagen fibers and their alignment during an experiment.

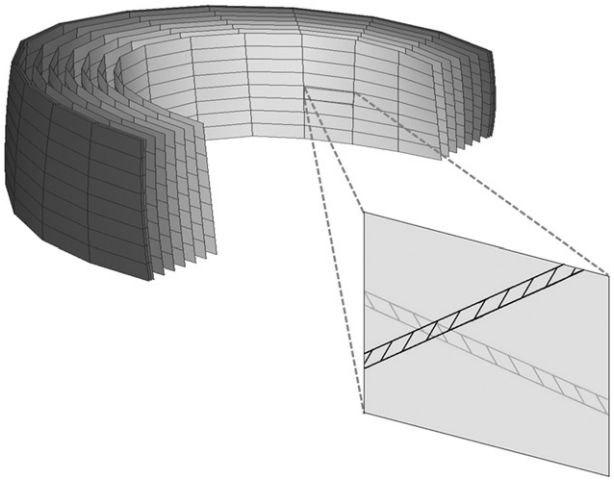

Fig. 2. Fiber reinforced model with membrane elements hosting rebars mimicking the function of the fibers.
Adapted from Schmidt et al. (2010).

2.2.1. Monophasic models

Viscoelastic materials exhibit both the properties of elasticity, i.e. the structure returns to the original unloaded configuration when a load is removed, and viscosity, i.e. strain increases with time when a load is applied and decreases similarly when it is removed, thus globally resulting in a time-dependent strain. This behavior is described by viscoelastic constitutive models, which can be used either to represent the global time-dependent response of a biological material independently on the presence and motion of an interstitial fluid, or to specifically describe the time-dependent behavior of the solid phase of a biphasic material.

A simple viscoelastic model widely used for soft tissues is the Kelvin–Voigt material law (Table 3), which was applied by Beillas et al. (2001) for ligaments and tendons and in combination with a hyperelastic model for ligaments by Pena et al. (Pena et al., 2007). The disadvantage of this model is that it does not account for the stress relaxation behavior of the soft tissues. Approaches based on the Zener model include stress relaxation as well as creep (Table 3). Wilson et al. (2005) described the Zener model with a nonlinear spring in series with a linear dashpot parallel to a linear spring to account for the viscoelastic behavior of collagen fibrils in articular cartilage. Another Zener model included two nonlinear springs and one nonlinear dashpot to describe the viscoelastic behavior of the fibers of the annulus fibrosus (Wang et al., 1998). A different approach to account for viscoelasticity gained from experiments is to integrate a discrete relaxation function, e.g. Prony series (Table 3), into the standard elastic formulation, e.g. for articular cartilage (DiSilvestro and Suh, 2002; Li and Herzog, 2004; Tang et al., 2011).

Viscoelastic models either including (e.g. Gu and Li, 2011; Gupta et al., 2009; Shirazi and Shirazi-Adl, 2005) or excluding (e.g. Bendjaballah et al., 1995; Shirazi et al., 2008) the presence of an interstitial fluid in the soft tissue were published. Note that the contact pressure and deformation predicted with the two different modeling approaches are considerably different in a whole knee joint model (Gu and Li, 2011).

2.2.2. Biphasic models

Biological soft tissues exhibit high water content, up to 80% for healthy articular cartilage and nucleus pulposus. The motion of the fluid content under loading, i.e. exudation during compression/creep and imbibitions during swelling/recovery, determines a time-dependent response of the biological structure. Despite this kind of

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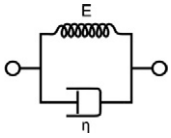
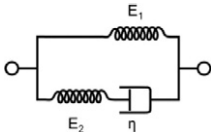
Table 3
Material formulations for hyperelastic static and time-dependent monophasic materials.

Hyperelastic models
Neo-Hookean strain energy density function $W = \frac{\mu}{2}(I_1 - 3)$
Mooney–Rivlin strain energy density function $W = \frac{\mu_1}{2}(I_1 - 3) - \frac{\mu_2}{2}(I_2 - 3)$
Ogden strain energy density function $W = \sum_{p=1}^{N} \frac{\mu_p}{\alpha_p}(\lambda_1^{\alpha_p} + \lambda_2^{\alpha_p} + \lambda_3^{\alpha_p} - 3)$ μ, α: material constants; I: invariant of the left Cauchy–Green deformation tensor; λ: principal stretches
Models of viscoelastic behavior
Kelvin Voigt $\sigma(t) = E\varepsilon(t) + \eta\frac{d\varepsilon(t)}{dt}$  η: viscosity, E: stiffness
Zener $\frac{d\varepsilon(t)}{dt} = \frac{E_2}{\eta(E_1 + E_2)}\left[\frac{\eta}{E_2}\frac{d\sigma(t)}{dt} + \sigma(t) - E_1\varepsilon(t)\right]$ 
Basis hereditary integral for viscoelasticity
$\sigma(t) = \int_0^t 2G(\tau - \tau')\dot{e}\,dt' + I\int_0^t K(\tau - \tau')\dot{\phi}\,dt'$ with relaxation moduli as Prony series: $G(\tau) = G_0\left(g_\infty + \sum_{i=1}^{N_G} g_i e^{-\frac{\tau}{\tau_i}}\right)$ $\quad K(\tau) = K_0\left(k_\infty + \sum_{i=1}^{N_k} k_i e^{-\frac{\tau}{\tau_i}}\right)$ e: mechanical deviatoric strain; ϕ: volumetric strains; G: shear modulus; K: bulk modulus; τ: reduced time; $G(\tau)$, $K(\tau)$: relaxation moduli; g_∞, k_∞: long-term moduli; g_i, k_i: relaxation moduli; τ_i: relaxation times

response can be effectively simulated in terms of the global response by using monophasic models as those described in the previous paragraph. If the aim of the investigation requires the knowledge of the local stresses acting on the extracellular matrix e.g. for simulating failure and damage, biphasic models provide a potentially more accurate tool.

The mechanics of biphasic media can be modeled with two different approaches, poroelasticity and mixture-based models (Simon, 1992). The linear poroelasticity theory was introduced in independent works by Terzaghi and Biot (Biot, 1941; Terzaghi, 1943) (Table 4), and describes media composed by a porous, linear elastic solid phase and a liquid phase which permeates the void spaces of the solid phase. Each of the two components is assumed to be incompressible. Variables in poroelastic analyses are the displacement of the solid phase, the velocity of the fluid relative to the solid phase and the pore pressure (Table 4). This formulation is based on an equilibrium equation for the whole poroelastic structure, consisting of a standard solid equilibrium equation with an added term representing the pore pressure contribution, and the equation governing the fluid phase, e.g. Darcy's law (Terzaghi, 1943). Differently, mixture formulations consider each infinitesimal volume as a mixture of fluid and solid, each phase having different degrees of freedom expressing the displacement (Table 4). In these theories, the two phases (solid and fluid) are governed by distinct equilibrium equations (Mow et al., 1980). Both approaches can be expanded to include large deformations, and have been demonstrated to be able to provide very similar results in biomechanical problems (Prendergast et al., 1996).

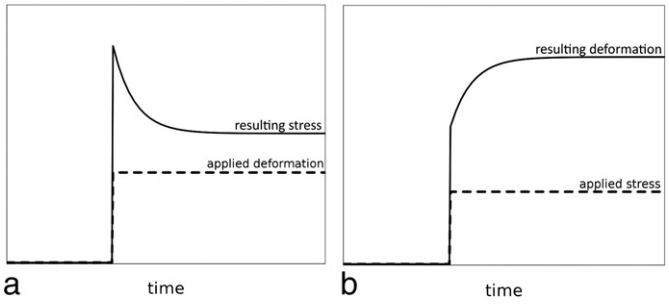


Fig. 3. Time-dependent behavior of biological soft tissues: stress relaxation (a) and creep (b).

Soft tissues typically show a strain-dependent permeability (Table 5). Permeability of articular cartilage has been experimentally shown to exponentially decrease with volumetric compression (Holmes and Mow, 1990). Since it is not possible to directly use this strain-dependent permeability in commercial codes such as ABAQUS, Argoubi and Shirazi-Adl (1996) transformed this relationship into a permeability–void ratio dependency. A similar approach based on a variety of strain–permeability relationships was used in a number of following studies (e.g. Seitz et al., 2013). Analogous formulations including anisotropy, i.e. strain- and direction-dependent permeability, were also employed (reviewed in Natarajan et al., 2006).

Many examples of biphasic models to investigate the mechanics of biological soft tissues are available in the literature (Argoubi and Shirazi-Adl, 1996; Galbusera et al., 2011b; Gu and Li, 2011; Natarajan et al., 2006; Schmidt et al., 2013). Cartilage indentation experiments are commonly modeled as a biphasic medium including collagen fibrils in the solid phase. Li et al. (2009) simulated unconfined compression and indentation of articular cartilage with a model, in which the time response was due to both poroelasticity and viscoelasticity of the collagen fibers, with the aim of assessing the dependency of the response on fiber orientation (Li et al., 2009). A similar previous model (Shirazi and Shirazi-Adl, 2005) predicted comparable results in simulations neglecting the viscous behavior of the collagen fibers. In another study (Li et al., 2003), the authors focused on the dependency of the cartilage stiffness on the strain rate, again using a fibril-reinforced poroelastic model.

Poroelastic models were also used to model whole joints or anatomical structures, with the aim of predicting the creep and relaxation behavior and the response to sustained loads such as those related to daily activities. The time-dependent response of the knee joint due to fluid flow through menisci and articular cartilage was studied in a number of papers (e.g. Kazemi et al., 2011; Vaziri et al., 2008). Another extensively investigated structure by means of poroelastic models is the intervertebral disk (Argoubi and Shirazi-Adl, 1996; Galbusera et al., 2011b; Natarajan et al., 2006; Schmidt et al., 2010).

The consideration of the different phases of the soft tissue provides a more realistic description of the behavior of the tissues (Table 2). However, the sufficiency of the model always depends on the investigation scope. Poroelastic and biphasic models are commonly used when the time-dependent response of a soft tissue with high water content is of interest. They allow for the estimation of the fraction of load and stress actually supported by the solid matrix and that due to pressurization of the fluid, and are therefore useful when an accurate quantification of the local stress state is of interest, e.g. for simulating failure and crack growth. If the scope of the investigation is restricted to global variables, such as kinematics or flexibility, static models can be usually safely employed instead.

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Table 4
Material formulations for time-dependent biphasic materials.

Biphasic models
Poroelastic formulation Constitutive equation for a linear isotropic solid phase: $\sigma_{ij} = (\lambda + 2\mu)\varepsilon_{ij} + p\delta_{ij}$ Equilibrium: $\frac{\partial \sigma_{ij}}{\partial x_j} = 0$ $k_{ij}\frac{\partial p}{\partial x_j} = \frac{dw_i}{dt}$ λ,μ: Lamé parameters; k_{ij}: permeability tensor; w_i: fluid velocity relative to the solid phase
Biphasic formulation Constitutive equation for a linear isotropic solid phase: $\sigma^s_{ij} = (\lambda + 2\mu)\varepsilon^s_{ij} + \frac{\phi^s}{\phi^f}p\delta^s_{ij}$ Equilibrium: $\frac{\partial \sigma^s_{ij}}{\partial x_j} - \frac{k^{-1}_{ij}}{\left(\phi^f\right)^2}\left(\frac{du^s_i}{dt} - \frac{du^f_i}{dt}\right) = 0$ $\frac{\partial \sigma^f_{ij}}{\partial x_j} + \frac{k^{-1}_{ij}}{\left(\phi^f\right)^2}\left(\frac{du^s_i}{dt} - \frac{du^f_i}{dt}\right) = 0$ σ^s, ε^s: effective stress and strain; ϕ^s, ϕ^f: volume fraction of the solid and fluid phases; k_{ij}: permeability tensor; u^s, u^f: displacement of the solid and fluid phases respectively

2.2.3. Osmotic swelling

Soft tissue mechanics is governed by complex coupled mechanical and electrochemical phenomena, which could be successfully approximated by a monophasic elastic, poroelastic or viscoelastic behavior for some applications. If the physiological or physiopathological fluid exudation and imbibition are the focus of the investigation and local variables such as pore pressures, stresses and strains are of importance, it is generally necessary to take into account the osmotic potential of the soft tissue due to the presence of the fixed charges of matrix proteins. This topic was often taken into account in previous works with simplified approaches (Argoubi and Shirazi-Adl, 1996; Galbusera et al., 2011b; Natarajan et al., 2006; Schmidt et al., 2010). However, refined methods more strictly based on the physics of soft tissues have been presented and are shortly described in the following. These models are rarely used for applied research to their high complexity and relative novelty. Nevertheless, they constitute groundbreaking research which will probably find more vast applications in the near future.

Triphasic, fully-coupled electrochemical models, including the mechanical behavior of solid and fluid phases together with the diffusion of moving ions interacting with the fixed charges of the proteoglycans entangled in the collagenous structure of the tissue have been proposed (Gu et al., 1998; Iatridis et al., 2003; Lai et al., 1991; Yao and Gu, 2004, 2007). In these models, three distinct phases are typically simulated: the charged solid phase, the fluid phase and an ion phase representing both anions and cations of a single neutral salt (Lai et al., 1991). The gradients of the chemical potentials of the permeating fluid and of the neutral salt, which are dependent on the pore fluid pressure, salt concentration, volumetric strain of the material and the fixed charge density of the proteoglycans entangled in the solid phase, determine the motion of the fluid and of the ion phase. These complex models allow for the direct use of information about tissue composition in the model since they are able to replicate with good accuracy all the physico-chemical processes which determine the mechanical response of the tissue.

Quadriphasic models, in which both anions and cations are distinctly modeled, have been also presented (Huyghe and Janssen, 1997; Schroeder et al., 2010). These models generally consist of four different phases, namely the solid and fluid phases, cations (e.g. Na^+) and anions (Cl^-) (van Loon et al., 2003). Governing equations include the concentrations of the ions and their interaction with the fixed charges in the solid, resulting in motion of the ion and fluid phase and deformation of the solid phase. Contrastingly, simple models, which implement equivalent, homogenized material properties and boundary conditions to replicate the global behavior of the tissue without modeling all aspects of its physics and biochemistry are also commonly used. For example, a swelling-like behavior was simply simulated by imposing a non-zero pore pressure on the boundary surfaces of the model (Argoubi and Shirazi-Adl, 1996; Ferguson et al., 2004). This approach showed to be a good approximation of more sophisticated models when focusing on global quantities such as the volumetric size change of the specimen (Galbusera et al., 2013). Other simplified methods consisted of prescribing the osmotic pressure as a fixed contribution to the spherical part of the stress tensor (Olsen and Oloyede, 2002; Olsen et al., 2004) or simulating osmotic pressure gradients as locally dependent on the proteoglycan fixed charge densities, which can be in turn estimated based on the tissue volumetric deformations, assuming an instantaneous chemical equilibrium throughout the tissue (Lanir, 1987). In some benchmark cases, the latter approach was verified to yield results comparable to those obtained by considering ionic entities as independent degrees-of-freedom in a fully coupled mechano-electrochemical model (Wilson et al., 2005).

Table 5
Strain-dependent isotropic permeability.

Strain-dependent isotropic permeability
e.g.: $k = k_0 \exp\left(M\frac{e-e_0}{1+e_0}\right)$ or $k = k_0\left(\frac{J-\phi_0}{1-\phi_0}\right)^{\alpha}\exp^{\frac{1}{2}M\left(J^2-1\right)}$ with: $e = \frac{\phi}{1-\phi}$ k: permeability; k_0: permeability in the initial (unstrained) conditions; e_0: initial void ratio; e: void ratio; ϕ_0: initial porosity; J: determinant of the deformation gradient F; α, M: parameters expressing the exponential decay of the permeability

2.3. Modeling of interactions

Many biomechanical models involve multi-body contacts, for example in the diarthrodial joints and cartilage indentation tests. Commercial finite element packages provide verified algorithms for the simulation of frictionless and friction contact, which are robust and therefore employed in most studies (Donahue et al., 2003; Kazemi et al., 2011). However, these algorithms are usually not designed to deal with contact between soft tissues and may have some convergence problems, e.g. through the incongruent geometries and high deformations of the soft contact surfaces.

Contrarily, the use of contact algorithms already implemented in commercial finite element codes for poroelastic structures is generally not adequate (Galbusera et al., 2012). For example, the contact formulation for biphasic problems in ABAQUS 6.10 (Simulia, Providence, RI, USA) only prescribes continuity of the pore pressure across the interface, therefore neglecting possible tangential flow, which may be significant when large gaps are present, and leading to erroneous results (Federico et al., 2004) (improvements are being introduced in newer versions). To overcome this limitation, iterative formulations prescribing free flow on the separated areas of the contacting surface have been presented (Pawaskar et al., 2010). Open-source finite element software FEBio (Musculoskeletal Research Laboratories, Salt Lake City, UT, USA; URL: febio.org) provides a contact formulation able to simulate frictionless interaction between biphasic structures (Ateshian et al., 2010). The package allows for the simulation of mass continuity across the contacting surfaces and free draining outside the regions in contact, under large deformations and finite sliding.

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Mass continuity is enforced with a penalty method, and regularized with an augmented Lagrangian method to avoid numerical ill-conditioning for large values of the penalty factor. Other numerical methods have been presented, ranging from approximate techniques under small (Dunbar et al., 2001) and large strains (Un and Spilker, 2006) to complex methods able to simulate large deformation and finite sliding (Chen et al., 2005). However, implementations of these algorithms were not released to the public and should therefore be performed by the user.

Simulation of friction in contacting soft tissues is another challenging topic. Synovial joints have a very low friction coefficient, about 0.01, in comparison with engineering materials, due to lubrication and rehydration mechanisms (Radin and Paul, 1972). However, experimental studies testing cartilage against hard bearing materials show a time-dependent friction coefficient at least one order of magnitude higher (Forster and Fisher, 1999). As these phenomena are ongoing research and cartilage against cartilage shows a steady low value friction coefficient (Bell et al., 2006), the frictional behavior is up to date not included in computational models of the whole knee joint.

2.4. Validation of material models

A crucial step to gain confidence in the finite element model is a proper verification of the mathematical description (solving the equations right) and validation of the simulation results to demonstrate that the right equations are solved (Viceconti et al., 2005). The data proving the validity of a simulation model are obtained from in vivo and in vitro experiments, either from literature or purposely designed laboratory studies. It is important to distinguish if the validation experiments were conducted on the same specimen used as a reference to build the model or if they are averaged results of a number of specimens, since this influences the accuracy of the validation (Gardiner and Weiss, 2003). Moreover, the experiment should capture the intended simulation, considering that the geometry, physics, loads, boundary conditions and material properties (Viceconti et al., 2005) influence the validation results as well. However, one should be aware that only certain parameters can be captured during one experiment, therefore the individual experiment should properly match the purpose of the finite element model. At best the experiment captures the most critical parameters to provide certainty that the inputs to and results from a simulation model accurately define the intended system (Henninger et al., 2010). Studies analyzing the influence of experimentally derived material parameters on the finite element model results are common (e.g. Espino et al., 2003; Haut Donahue et al., 2003). The two papers mentioned conducted in vitro experiments to later optimize the material properties which best fit the experiments to validate their simulation model. A number of different experimental method can be applied to obtain validation data, for example magnetic resonance imaging (Moerman et al., 2009), optical methods (LeRoux and Setton, 2002), pressure films (Haut Donahue et al., 2003) or different setups in material testing machines, e.g. tensile, shear or compression tests (e.g. Espino et al., 2003; Gupta et al., 2009). One should be aware that a validated finite element model is only validated for the exact experimental case; further results obtained from the validated finite element model are extrapolations. More detailed descriptions about the procedures of validation are provided by Anderson et al. (2007), Erdemir et al. (2012), Henninger et al. (2010) and Viceconti et al. (2005).

2.5. Clinical applications

Finite element modeling provides a precise tool for the evaluation of clinically relevant questions. In terms of the meniscus, meniscal resection depth, the influence on adjacent tissues as well as the change in load transfer and stress distribution (Pena et al., 2005a, 2006b; Vadher et al., 2006; Wilson et al., 2003; Zielinska and Donahue, 2006) can be investigated. For example, Pena et al. (2005b) used a full knee joint model to investigate effects of meniscectomy. Soft tissues were considered as isotropic and either linear elastic (cartilage, meniscus) or hyperelastic (ligaments). Due to meniscectomy the contact stress increased which likely accelerates early cartilage degeneration (Pena et al., 2005a). A finite element model with more sophisticated material models, but using an idealized geometry, was utilized to investigate resection depth and their consequences (Vadher et al., 2006). In this model cartilage was modeled as poroelastic, depending on the location of the cartilage layer with an isotropic or transversely isotropic matrix. The meniscus was characterized with a transversely isotropic elastic material formulation. This study concluded that a medial meniscectomy, greater than 20%, drastically increases the contact stress in the knee joint (Vadher et al., 2006).

The adverse event of early osteoarthritis might be delayed by adequate meniscal replacements. Finite element models can help in characterizing sufficient material properties of meniscal replacements (Vaziri et al., 2008). Modeling artificial meniscal replacement with an isotropic linear elastic material and the intact meniscus with either biphasic or transversely isotropic elastic material properties revealed an optimal Young's modulus for the meniscal replacement of about 110 MPa, which corresponds to the meniscal properties in circumferential direction (Vaziri et al., 2008).

Biological soft tissues are subjected to high, repetitive loads, which may alter their structure and mechanical behavior, in combination with other non-mechanical factors. Cartilage osteoarthritis is an example of such a damage phenomenon (Knecht et al., 2006), involving cracking and wear of the tissue. However, in contrast to bone tissue, few studies modeling the progression of cartilage osteoarthritis exist, due to the high complexity, the long time scale of degenerative phenomena and the lack of in vitro data. A phenomenological model introducing cartilage damage as a fatigue effect corrected by age, body mass index and hormonal factors has been presented (Landinez-Parra et al., 2011). Another paper discussed a multiscale approach, ranging from loads acting on bones to the single cell response, to investigate the initiation of osteoarthritis (Shim et al., 2011). If cartilage defects appear to be due to osteoarthritis, implantation of osteochondral grafts might help. A finite element study modeling cartilage and meniscus with fiber reinforced material models, pointed out that predominantly the deep fibril network of the cartilage contributes to the mechanical response of cartilage (Shirazi et al., 2008). Therefore, osteochondral grafts should account for this specific fibrillar network (Shirazi et al., 2008).

The anterior cruciate ligament (ACL) is likely to be totally disrupted during traumatic events. FE studies have compared different reconstruction techniques to intact ACL knee joints to evaluate mechanical differences in the behavior. The ligaments were modeled as nonlinear hyperelastic materials (Pena et al., 2005b; Ramaniraka et al., 2007). For the grafts nonlinear hyperelastic properties, different possible graft tissues were implied (e.g. patellar tendon (Ramaniraka et al., 2007), gracilis (Pena et al., 2005b), or tendon–bone (Pena et al., 2005b)). Single and double bundles for intra-articular reconstructions showed similar kinematics of the knee joint to the intact knee (Ramaniraka et al., 2007). An extra-articular procedure alters the knee joint kinematics and overconstrains the joint, possibly leading to an earlier failure of the ACL replacement (Ramaniraka et al., 2007). The pretensioning of the reconstruction was also addressed in some studies (Mesfar and Shirazi-Adl, 2006; Pena et al., 2005b).

The annulus fibrosus of the intervertebral disk consists of concentric layers of collagen fibers. Numerical investigations of

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clinical topics in spinal surgery must therefore include anisotropic or fiber reinforced constitutive models. Schmidt et al. (2010) used fiber reinforced elements to model the response of the intervertebral disk under complex loads thereby mimicking daily activities such as weight lifting and forward bending. Annular fibers were maximally strained in the postero-lateral region for specific loads and movements such as flexion plus axial rotation, which thus determined the highest risk of disk rupture. Vena et al. (2005) used an anisotropic hyperelastic model for the annulus fibrosus to simulate the response of the lumbar spine after implantation of an interspinous spacer (Vena et al., 2005). The study showed the capability of the device to reduce the load on the facet joints, which was highly dependent of the properties of the device itself and on the annulus fibrosus.

Biphasic constitutive laws are widely used to describe the time-dependent behavior of the intervertebral disk. For example, Schmidt et al. (2010) simulated daily physiological activities by means of compressive loading cycles applied to a poroelastic model of the lumbar spine (Schmidt et al., 2010). The authors concluded that the risk of disk prolapse due to excessive intradiscal pressure is maximal in the morning, and recovery phases during the day are effective in preventing rupture of the disk due to overloading.

A more sophisticated biphasic model of the intervertebral disk, including osmotic swelling, was used to estimate the risk of crack opening due to reduced osmotic pressure (Wognum et al., 2006). The predictions of the models were validated with confocal microscopy and highlighted the possible role of depressurization as a cause of structural failure of the intervertebral disk.

Soft tissues like articular cartilage, knee meniscus and intervertebral disk are largely avascular. Due to the lack of capillaries and blood vessels, the nutrition of the population of cells living in avascular soft tissues relies on diffusion processes and convection, due to the fluid exudation and imbibitions (Grunhagen et al., 2006), from the subchondral bone or adjacent tissues (Urban et al., 1982). Concurrently, waste products such as lactic acid developed by cell anaerobic metabolism diffuse out of the tissue to avoid a pH decrease and a consequent reduced cell viability (Razaq et al., 2003). These processes have been investigated with multiphasic numerical models in which the fluid velocity has been used to calculate the convective component of the transport of nutrients and waste products (Ferguson et al., 2004; Galbusera et al., 2011a; Jackson et al., 2011; Malandrino et al., 2011; Shirazi-Adl et al., 2010). These models have primarily been developed and used for the intervertebral disk, which is the largest avascular structure of the body and the degeneration of which has been hypothesized to be linked with a reduced nutrition of the cell population (Grunhagen et al., 2006).

3. Conclusions

The mechanics of biological soft tissues can be effectively simulated with finite element models. However, the user should be aware of the complexity of the response of such tissues and of the capabilities and limitations of the approaches to model the different phenomena, which arise during the biomechanical testing. The most appropriate material model should therefore be chosen for each specific research question, taking into account that a simple model may not necessarily be inadequate. Verification and validation of the models remain a requirement prior to the clinical interpretation of the numerical predictions.

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