A review of articular cartilage modeling

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Articular cartilage is a type of tissue vital in the protection of the ends of diarthrodial joints, distributing loads evenly to the subchondral bone to prevent damage. Cartilage damage and diseases like osteoarthritis alter the mechanical response of cartilage, reducing its effectiveness and changing the synthesis behaviour of chondrocytes. For this reason it is vital to understand the stresses and strains that present themself in cartilage during loading conditions. Due to the complexity of articular cartilage it is almost impossible to do this analytically, requiring the need of computational models. Many types of models exist, having different functions and expressing different aspects of the structure and composition. They can range from basic linear and isotropic models to complex poroviscoelastic models that are reinforced with fibrils. This review serves as an overview of the different models that currently exist, highlighting their limitations and applications, and explaining when a model should be used.

Introduction

Structure

Articular Cartilage is a type of hyaline cartilage overlying the end of diarthrodial joints. It functions as a load bearing tissue, providing a smooth lubricated surface to reduce friction and transmit loads evenly to the underlying bone.[17] Articular cartilage consists of a low amount of chondrocytes and an extracellular matrix (ECM) filled with an interstitial fluid of mostly water. Fluid makes up around 80% of the cartilage composition. There are no blood vessels, nerves or lymph nodes present in the tissue.[31,37] Due to the lack of these structures, the capability for natural large-scale self-repair and healing is severely diminished.

Chondrocytes are the native cells of cartilage, their main function being the maintenance of the ECM by synthesizing important components like collagen, glycoproteins and proteoglycans.[2,37] Mechanical loads, hydrostatic pressures, growth factors and free flowing ions are the main components in regulating chondrocytes. Chondrocytes do not form direct physical contact with each other, but are almost always surrounded by the ECM, creating a localized microenvironment of distinct regions.[37] The cells are responsible for the maintenance of this local area. The area directly adjacent to the cells is called the pericellular matrix and mainly contains proteins. Around this matrix lies a second layer consisting of small woven collagen fibrils forming a network to protect the cells against stresses. The outermost layer is the overall matrix, making up the remainder and is thus the largest. It is built from larger collagen and contributes the most to the overall biomechanical properties of cartilage. Chondrocyte cells cannot replicate freely, which impedes large scale self-healing capability of cartilage as a response to injuries or disease.

Chondrocytes only make up around 5% of the cartilage tissue. Most of the dry mass comes from the ECM matrix. The ECM matrix consists mostly of collagen fibrils with proteoglycans resting inside. Proteoglycans are large, negatively charged glycosylated proteins.[16] Their charge causes a negative fixed-charge density and heightened ion concentration within the tissue. Due to this an osmotic pressure gradient is created that causes fluid to flow into the cartilage tissue, resulting in swelling.[20,21,35] Proteoglycans have many charge sites that repel each other and cause further swelling. This swelling is inhibited by the collagen fibers and causes a tensile stress even in rest.

Collagen is the largest solid component of cartilage, making up around 60% of the dry weight.[22,37] Type II collagen is most common and forms the base of the primary fibrils throughout the cartilage and traps the proteoglycan aggregates to form a network. This creates a strong composite matrix of both materials. The collagen fibrils are further stabilized by crosslinking of mainly type IX and XI collagen.[14] Other collagen types are present in smaller amounts.[1,2,37] The orientation of these major fibrils differs throughout the depth of the cartilage and gives different tensile properties.
Cartilage can be divided into four different zones that differ in mechanical properties, fiber orientations and chondrocyte densities (Figure 1).

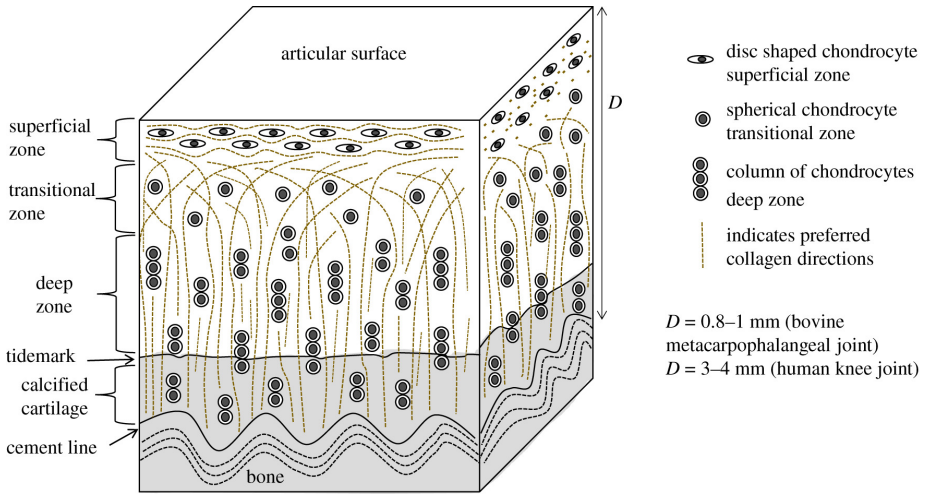

Figure 1: A schematic overview of the collagen orientations and chondrocyte densities in each cartilage zone.[30]

The first and outermost zone is the superficial zone, also known as the articular surface. It is in direct contact with the synovial fluid. It acts as a protective layer of the inner zones, and has the highest resistance against tensile stresses.[29,37] The collagen fibers are orientated parallel to the surface. This zone has the highest water density and lowest proteoglycan concentration. Chondrocytes are the most abundant in this area and have flattened shapes.[2,27,32] An extensive network of elastin fibers in the same direction as the collagen fibers is present.
The middle or transitional zone is the largest zone, making up around 40 to 60% of the cartilage thickness. It connects the superficial with the deep zone. A lower amount of chondrocytes are present. The collagen fibrils in this zone are thicker than those in the superficial layer, and have diagonal orientations connecting the fibrils in the areas above and below.
In the deep zone the collagen fibrils are aligned vertically, perpendicular to the surface. They are rooted in the calcified cartilage and subchondral bone below, adhering the cartilage to the bone. These fibrils have the biggest diameters and are the main component when handling loads. The chondrocytes in this area consist of vertical columns. Conversely to the superficial zone, this layer has the lowest water density and highest proteoglycan concentration.[32] Below the deep zone rests calcified cartilage, separated by the tide mark. This area forms the connection to the bone by rooting the collagen fibrils and forming a secure connection.

Biomechanical Function

The key function of cartilage is to transmit loads evenly across the underlying bone, preventing damage to the bone when forces are applied. By maximizing the contact area stresses will be lowered and energy can dissipate more evenly.[9,16] It has to be able to withstand highly cyclic loads like walking, absorbing these forces without resulting in permanent deformation. As articular cartilage is a porous and viscoelastic material, it is difficult to analytically calculate the exact force responses. This is further hindered by the inhomogeneous and anisotropic nature of cartilage, each zone exhibiting different mechanical properties. The local microenvironments around chondrocytes have their own localized response that differs from the overall bulk tissue

response. Force responses are nonlinear and the tissue always has stresses acting on it, even at rest.

In most cases the biomechanics are approximated by using a biphasic theory. Although in some cases the more complex triphasic theory is used. The biphasic theory uses two phases, a solid phase and a fluid phase. The solid phase is composed of the collagen fibers and proteoglycans of the ECM. The solid matrix has elastic or viscoelastic properties and is porous, allowing fluid to flow through it. It is incompressible, deformation is only a result of fluid flowing out of the tissue. The fluid phase consists of the interstitial fluid. This interstitial fluid is water with free flowing ions often being ignored. With the biphasic theory the flow-dependent viscoelastic properties can be explained. The biphasic theory has 3 acting components namely; the stress and deformation of the collagen and proteoglycan matrix in the solid phase, the fluid phase pressure, and the frictional drag between these two phases. The total acting stress is the sum of the stresses in both phases. As stated before, proteoglycans are responsible for swelling of the cartilage tissue. This is kept in check by the collagen fiber network. The main function of the collagen network is to provide tensile stresses that reduce the overall swelling expansion. Even at rest these collagen fibrils have a tensile stress as cartilage is swollen at rest.[21,32,41,42] Collagen behaves as a nonlinear elastic but can sometimes be thought of as linear because the toe region is skipped due to these prestresses.[19] Collagen also helps with the shear stress response, because of the random distribution of these fibers they are deformed easily and can withstand these stresses. However because the individual collagen fibers are quite small they are relatively weak in compression. Most of the compressive forces are handled by the pressure caused by the fluid phase.

When a load is applied to the articular cartilage, the pressure increases immensely, causing fluid to flow out of the tissue into the synovial cavity. The fluid cannot flow out in every direction, as it is blocked by the bones and surrounding cartilage of the joint capsule.[30,37] The flowing speed is quite low, due to the small pore size of the cartilage. The viscosity decreases even more over time as pores become smaller when the matrix gets compressed. This results in a nonlinear fluid flow. When the fluid is flowing out of the cartilage a large frictional drag is created. This frictional drag creates further pressure gradients and is responsible for the majority of the load bearing.[22,31] Over time the force gradually transitions to the solid phase, when most of the fluid has exited the tissue. Equilibrium is reached when all the fluid is outside the tissue, and all forces are supported by the solid phase. Under normal circumstances this never occurs in the human body. After the load is removed again the tissue recovers and water slowly flows back into the cartilage tissue. When subjected to cyclic loading there is a limited amount of time for the cartilage to recover before the next load is applied. At a low frequency adaptation is easily acquired. Under high frequency cyclic loading cartilage tissue won't have the time to reform completely, causing an elevation in hydrostatic pressure when the next load is applied.[38]

Modeling of cartilage

The composition of cartilage tissue varies with depth. Swelling behaviour changes due to proteoglycan concentrations and stress responses vary because of collagen orientation and density. This causes the mechanical properties of cartilage to become depth dependent. Because of this it is difficult to analytically calculate the force responses of cartilage tissue.

Models are an alternative approach to calculate the reaction forces and strains of cartilage. Models are used to determine the material properties of cartilage under different loading conditions and with different factors.
Other reasons to construct these models are to study the progress of cartilage degeneration. Disease and trauma can dramatically alter the force response of the tissue. Diseases are one of the most common causes for cartilage degeneration. Osteoarthritis for example is a common disease that causes degeneration of the collagen matrix. This results in pain and stiffness and increases the swelling of the tissue. Even age alters the cartilage composition. Because the self repair of cartilage is limited it is important to study the changes in structure, function and biomechanical properties. By obtaining the response of cartilage to constant or cyclical forces degeneration can be better understood and new treatments can be developed for treating these changes.
The complexity of the model needed depends on the focus of the research. Single phase models exist but in most cases at least a biphasic approach is used. Biphasic models exist in a wide range of varieties. Simpler models assume the tissue to be isotropic and homogeneous and use a linear stress relationship. In some generic cases this is sufficient. In most cases however using this model gives inaccuracies and additional changes need to be considered. Factors such as nonlinearity, anisotropy and heterogeneity can improve the approximation of the model and allow it to be valid under multiple loading conditions.[25,39,43] It is difficult to include the swelling behaviour in a biphasic model so a triphasic approach could be used for this. Fibril-reinforcement can be used to explain the anisotropic nature and show the effects of degeneration due to osteoarthritis.
Models can be based on just the localized cartilage structure, or expanded for full joint analysis. All of these factors need to be considered when designing a model. The complexity required depends on the focus and use of the model. The more complex the model is, the more computation it requires. When determining the changes that occur during osteoarthritis a different model is required than when looking at the localized response of chondrocytes. As it was found that tissue anisotropy decreases with osteoarthritis, this factor would need to be included in a model focussing on this disease.[8] A simpler isotropic model is accurate when looking at static forces but fails to predict the tensile stresses, and shows inaccuracies during indentation testing.[23] Another major benefit of modeling is the ability to establish the response using conditions that cannot be measured using real cartilage experiments. All of this makes models a good base when developing artificial engineered cartilage. For this review a look will be taken at the many models that exist for articular cartilage and their uses.

Materials & Methods

For this review a literature search about different cartilage models has been conducted. An introductory research about the physiology and biomechanical function of healthy and diseased cartilage stood as a basis. This information was used to validate the relevance of found models, and understand their accuracy and limitations. A broad scope of models was used to showcase the wide variety that exist. Differences in phases, linearity and tissue composition were studied to show their relevance when modeling. Older models are included to show the progression over time. Criteria were placed on the amount of citations an article had, as to not include unused models. Niche models were excluded in favour of models that showcased the broader effect of varying parameters and approaches. Models more simplistic than linear biphasic were excluded. Focus was placed on cartilage models, with only a few full joint models for support. To study the effects of fibril-reinforced models background literature about fibril orientation was used. Responses to different loading tests were compared, as some model theories cannot account for multiple situations at the same time. For each model their properties and functions will be assessed. A look will be taken at the properties included and excluded, and the reasoning behind it. The goal is to make an overview of the many different model types and list their respective uses, limitations and advantages.

In almost all model studies the model parameters were obtained from literature, or results obtained from cartilage experiments. For this three common experimental setups exist: Confined compression, unconfined compression and indentation testing (Figure 2). Unconfined compression looks at the lateral deformation and reaction forces of cartilage when compressed between two non permeable plates. This is commonly used to highlight the effects of tissue anisotropy. For confined compression round cartilage plugs are surrounded by a confining chamber, inhibiting lateral displacement. In this case a porous plate is used, allowing fluid to flow out during compression. Often a compression test is performed in a saline solution to simulate physiological conditions. Indentation testing can be performed directly on bone and doesn't require extraction of cartilage plugs. This leads to a closer approximation of the real physiological environment and can be used to test the health of the tissue. When obtaining the elastic properties using indentation testing the Young's modulus and Poisson's ratio are coupled and require other tests to distinguish them.[35] Using the parameters obtained during one of these tests, the model is validated by comparing the theoretical results to further experimental values, by curve fitting the model response. In most cases a model is unable to predict the response for all tests, but only for one or two of the situations. The tests show the accuracy of a model. Based on the agreement with experimental results the model may be deemed valid for certain conditions, and its limitations are highlighted. When the limitations of a model are determined further research can be conducted to upgrade the model theory, and alleviate these problems. This can be useful as the upgrades are done to an already verified model, giving a direct overview of the improvements. Swelling tests are another important method in determining the cartilage behaviour, especially in triphasic models. Free swelling is determined by suspending cartilage-bone samples in various solution concentrations, and checking the changes in weight or dimensions.[3]

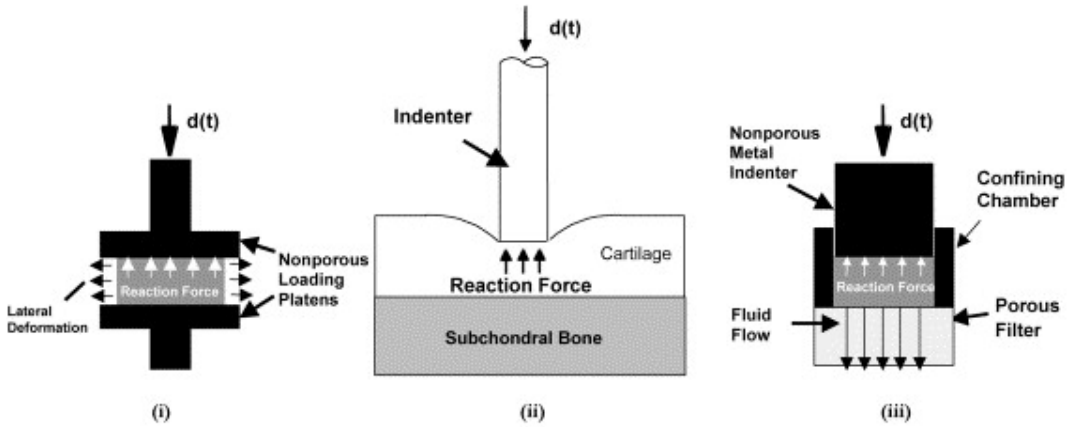

Figure 2: A schematic representation of the three most common model validation tests; unconfined compression (i), indentation testing (ii) and confined compression (iii).[12]

Literature

When conducting the research multiple articles showed up on multiple search engines and with multiple criteria, these models are included for every time they appeared. It was found that isotropic linear biphasic models are almost nonexistent in the current landscape of cartilage modeling. Research was conducted using Google Scholar and PubMed. Relevant studies found are shown in table 1. Not all relevant studies have been included in this review as some were very closely related to each other. This does not include the entire literature search, but only the larger overview.

Search Terms	**Relevant Articles found**	**Articles used**
Biphasic cartilage / model	17	10
Linear cartilage model	4	1
Triphasic cartilage / model	4	2
Transverse isotropy cartilage	3	2
Collagen model cartilage	9	5
Chondrocytes cartilage	5	3
Biphasic poroviscoelastic	6	3
Biotribology cartilage	3	1
Poroelastic cartilage model	5	3
Viscoelastic cartilage model	7	2
Fibril model cartilage	5	3
Fluid model cartilage	1	1
Citations*	16	13

* citations means the articles were found using citations found in other articles

Results

Simple biphasic

The most basic model for articular cartilage is the linear, homogeneous biphasic model. The theory for this model was first developed in 1980 and is one of the first to apply the biphasic theory using the solid and fluid phases described earlier.[23] Cartilage is assumed as a porous incompressible solid filled with water. This means the tissue can only be compressed as a result of fluid flowing out of the tissue. It uses an uniform structure with no discernment for the different zones resulting in isotropic properties. Pore size does not change over time resulting in a constant fluid velocity. Linear elasticity is used for the solid phase, ignoring the toe region present in the stress-strain curves. The reason for this is because the stress-strain relationship is nonlinear in the toe region, with the strain increasing more rapidly than the stress. The total stress is the sum of the stresses of the fluid and solid phase.[7,12] The downside of this model is however that it is unable to account for swelling behaviour, underestimates the peak stresses during unconfined compression, and cannot predict the strain-dependent permeability.[9,43] For this reason most models add in anisotropic or nonlinear stress-strain behaviour, changing to a hyperelastic or nonlinear elastic model. A hyperelastic material is a nonlinear material where the strain increases quicker than in a linear model. add in fibre reinforcement or switch to a triphasic theory. The biphasic theory is still the most common theory used as in most cases it requires less computations than triphasic models, and triphasic behaviour can be substituted through other means.

One application of the biphasic theory was done by developing a biphasic poroviscoelastic (BPVE) model. By including poroelastic and viscoelastic behaviour the two different stress-relaxation times can be added.[12] Parameters were obtained from curve fitting against unconfined compression stress-relaxation experiments. During all tests a small preload was added before measuring, to skip the toe region of the stress-strain curve and allow a linear approach. The obtained parameters were in line with data found in literature. Using these parameters the model was able to accurately predict the behaviour during indentation testing. However when using these parameters for confined compression a large overestimation of the reaction force was found (Figure 3). This data shows a close accuracy between experimental data and unconfined compression. For confined compression however, the one dimensional result shows the largest deviation from the experimental values. When assuming perfect lubrication or perfect adhesion closer results were obtained, but they still showed significant errors, with perfect lubrication underpredicting the stresses, and perfect adhesion showing a slight overprediction. The tests show that a linear isotropic biphasic model can be used to predict the linear responses of unconfined compression and indentation testing, but failed to predict the confined compression response when using the same parameters. To alleviate these limitations a switch to nonlinearity and anisotropy would need to be made.

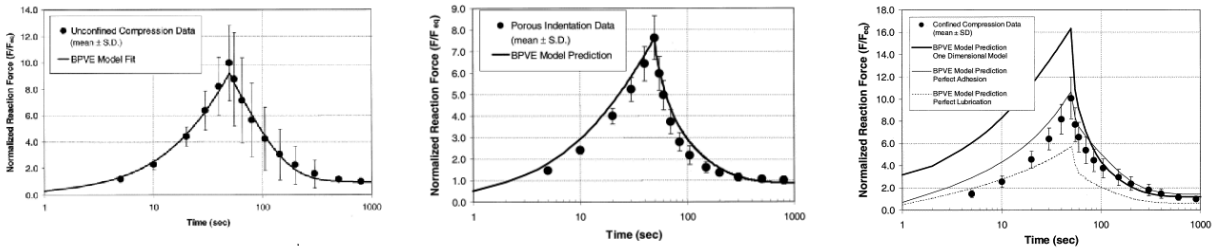

Figure 3: Reaction forces measured during indentation testing, confined compression and unconfined compression using the BPVE model.[12]

Another study used the biphasic theory to predict the pressure and strain curves during cyclic loading using confined compression.[38] Results showed that at lower frequencies the tissue had time to fully recover, resulting in a lower average pressure. At higher frequencies the tissue could not fully recover which led to a pressure and strain increase. The importance of the subchondral bone was also tested by creating a gap and comparing the differences in both situations. It was found that the subchondral bone is important in maintaining the fluid pressure by preventing fluid outflow at the bottom. Results were in agreement with experimental data and showcase that the linear biphasic theory is accurate when looking at the responses during cyclic loading. It was also found that the fluid flow was higher near the superficial area, but to be able to determine the reason an anisotropic model would need to be used.
The research into cyclic loading using this type of model was later extended by including tissue composition factors. Collagen, cell and glycosaminoglycan (GAG) concentrations were added and modeled as a function of time. The synthesis of these elements was coupled with multiple variables like the solid matrix deformation. The Young Modulus was linearly dependent on these concentrations. Using a 2D representation the concentrations and force responses over a time of 24 hours was modeled. This research showed an increase in fluid velocity at the surface as well. The Collagen and GAG concentrations increased over time, as did the cell concentration until a certain density was reached. A maximum error of 8% was found, leading to the conclusion that this model was accurate in tracking solid element concentrations. The resulting model is able to determine the change in ECM production based on different loading conditions and can be used for further research in this topic.

Transverse Isotropy

Because cartilage has nonlinear and anisotropic properties a basic model may not always be sufficient. A fully isotropic linear model only predicts peak stresses at the bone-cartilage interface, missing areas of high stress at the articular surface. They are also unable to explain the increased fluid velocity at the surface. By using transverse isotropy instead a different set of parameters can be used for different layers. This way the zones of cartilage can be included in a model. One study compared the stress responses found using an isotropic model and a transversely isotropic model. Their goal was to highlight the limitations of isotropic models when predicting these peak stresses in multiple areas.[13] To accomplish this the interaction between two curved cartilage layers attached to bone was created to simulate the in situ situation (Figure 4). To avoid issues with nonlinearity a force of 75 Newton was used, skipping the toe region. For both models the same parameters were used to allow direct comparison. Results showed that

the isotropic model only predicted peak stresses at the bone-cartilage interface and not at the articular surface. The transversely isotropic model had a lower contact area between the two surfaces resulting in an increase of surface stress. When decreasing the curvature the stresses at the surface increased even further. From this it was concluded that transverse isotropy is required to determine the peak stresses that occur at the articular surface. In this research the transverse layer properties were obtained using average values from literature, thus more indepth research is needed to determine the exact relationship between each layer.

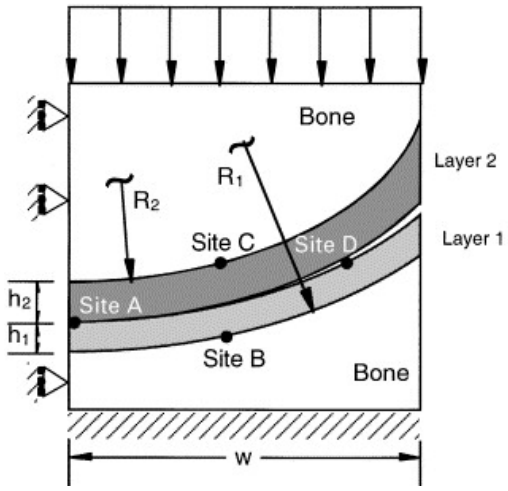

Figure 4: Model setup used for both the isotropic and transverse isotropic models.[13]

Another study utilized a transverse isotropic approach to describe the stress-relaxation response during both confined and unconfined compression.[9] Multiple ramp strains were applied and the equilibrium response was measured. As shown before a fully isotropic model cannot model the response of these at the same time. The model parameters were obtained using the confined compression experiments. With these parameters the model was unable to predict the unconfined compression response at all. When curve fitting without constraining the lateral modulus the result was more accurate (Fig 5). In this case the lateral modulus was around 3 times higher than for the confined model. The found Poisson's ratio was the same as the Poisson's ratio when using an isotropic model, leaning to the conclusion that transverse isotropy does not change this mechanical response. The results show that a linear transversely isotropic model is still unable to simultaneously explain the radial stress of confined compression and the axial force during unconfined compression, resulting in poor results when using the same parameter set for confined and unconfined compression.

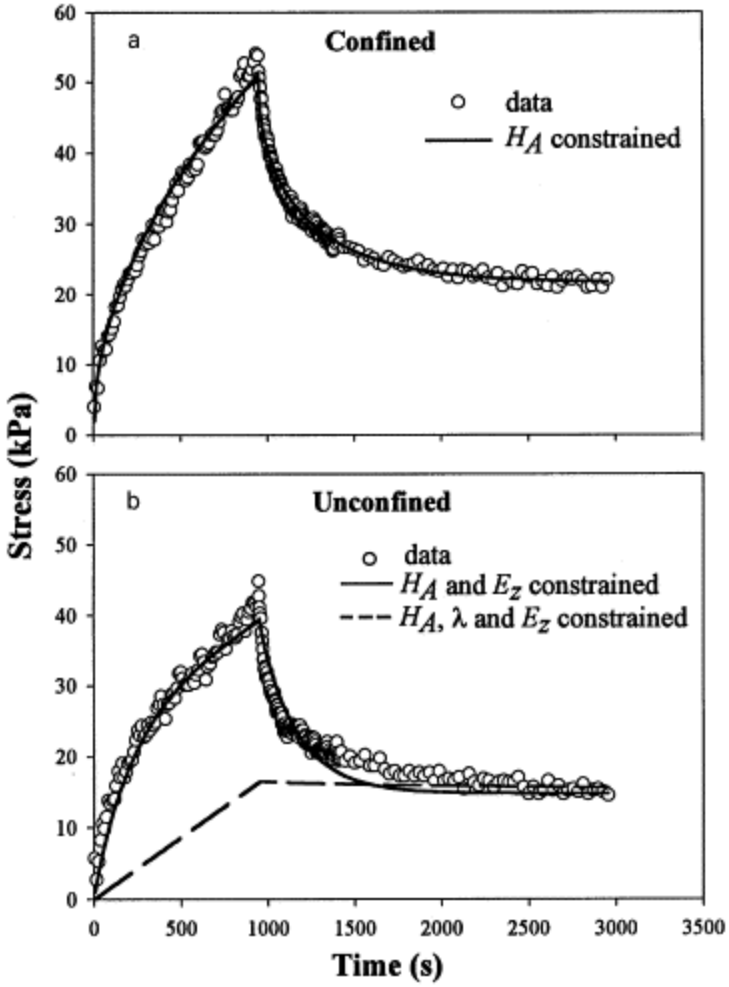

Figure 5: Predicted model stresses compared against experimental results for both confined and unconfined compression. Parameters were obtained using the confined compression dataset.[9]

Nonlinearity

A linear approach is unable to predict the mechanical behaviour in multiple situations, even when using anisotropy. Because of this models often utilize a nonlinear elastic approach to reach a broader scope and better compare forces in different circumstances. To show the significance of the elasticity method an indentation test was performed comparing a linear elastic and a nonlinear hyperelastic model during indentation testing.[34] For both setups the same material properties were used, except the elastic modulus (Figure 6). A 4th order polynomial was used for the elastic modulus in both models, but with different values so it could closely approximate the experimental indentation values. The stress in the hyperelastic model is more spread out, resulting in peak stresses that are only half as high as in the elastic model. This did result in a slightly higher stress at the cartilage-bone interface. This indentation test shows that changing the elasticity approach has major implications on how the force is distributed throughout the tissue. As the main function of cartilage is evenly distributing loads across the underlying bone, preventing high stresses in single points, the hyperelastic model is the superior approach as it spreads the force out across a wider area. It gives a better insight

into the way cartilage behaves. This model could be used to predict the propagation of stresses when subjected to high stresses.

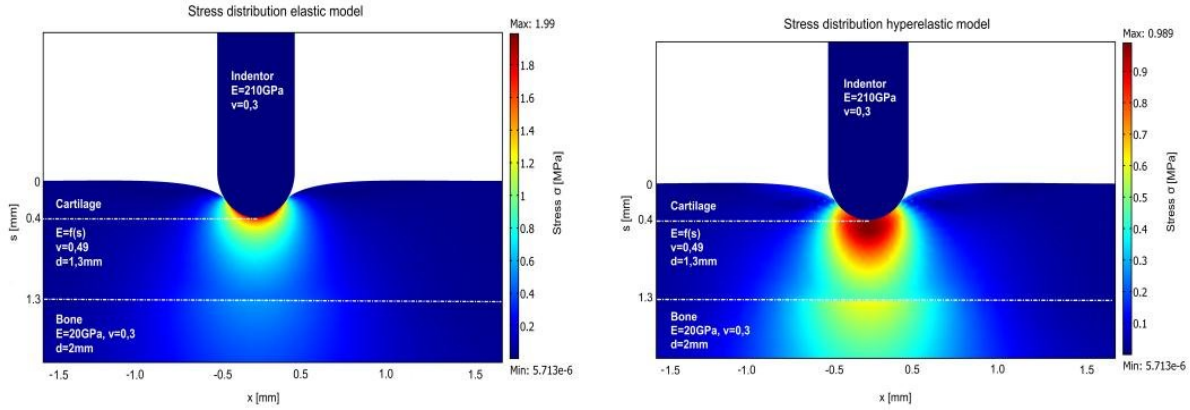

Figure 6: Stress distributions in elastic and hyperelastic models during indentation testing.[34]

To determine whether the nonlinear hyperelastic approach can be used to study the changes that present itself with osteoarthritis, two incompressible isotropic hyperelastic models, a Yeoh and a neo-Hookean model, were compared using a 3D environment.[8] A Neo-Hookean model initially assumes the stress-strain relationship to be linear, but after a certain stress it becomes nonlinear as the curve flattens. The Yeoh material model is commonly used for incompressible substances like rubber. Both models were curve fit against the instantaneous loading response when using unconfined compression. The found hyperelastic constants were higher in healthy tissue, indicating a higher stiffness. The neo-Hookean model overpredicted the contact forces and pressures at low strains, and underpredicted them at higher strains. The Yeoh model's prediction was closer to the experimental values. This leads to the belief that the Yeoh model is more accurate when investigating the change in force response in cartilage degeneration. However the material constants of the Neo-Hookean model were more in line with values present in pre-existing literature. Both models were unable to accurately predict the contact area, or give the radial strain due to their isotropic nature. From these results it was concluded that a Yeoh model can more accurately describe the changes that present itself with osteoarthritis, and that anisotropy is an important factor when investigating contact areas and radial stresses. Based on these facts both anisotropy and nonlinearity are required to accurately model cartilage tissue.

The hyperelastic theory has also been used to look at the surface interaction and solid deformation of cartilage during the gait cycle.[11] In this case dynamic porohyperelasticity was used to allow the matrix to be deformed. By using this model in a setting that resembles the in vivo situation the overall deformation and the fluid response could be predicted during the normal gait cycle. This model served as an accurate explanation for the lubrication mechanisms in the joint. For this reason anisotropy and viscoelastic effects were not included. When looking at larger timescales or physiological effects these factors would need to be included.

When using a hyperelastic theory the nonlinearity should result in an increased accuracy when predicting finite deformations. For this reason an isotropic model using the hyperelasticity was curve fit with experimental results of confined stress-relaxation, creep and oscillation tests using articular cartilage.[5] Material parameters were obtained from the stress-relaxation results, and these same parameters were used to curve fit the creep test. High accuracy was found for the stress-relaxation curve, and the creep predictions showed a small error of around 10%. When obtaining parameters using the creep test for better fitting accuracy the permeability coefficient had a different value. In both cases the permeability coefficient is derived indirectly, which may explain the inaccuracy. From these results it was concluded that a hyperelastic model is able to accurately describe the stress-relaxation and creep behaviour at the same time but is unable to derive the permeability coefficient. The isotropy of the model limits the use to simultaneously predict the results of unconfined compression however.

Multiscale

Multiscale models try to couple the overall stress response with the forces acting on chondrocyte cells. This way the influence and response of localized matrix particles could be determined. The magnitude difference between the overall matrix and chondrocyte cells is around 10^2, for this reason multiple scales are used. This way the chondrocytes do not affect the overall tissue response and can be studied independently. This is usually done by using the obtained parameters from the larger scale and using them as input and boundary parameters in the smaller model elements (Figure 7). The downside of this type of modeling is that no experimental values exist for comparison.

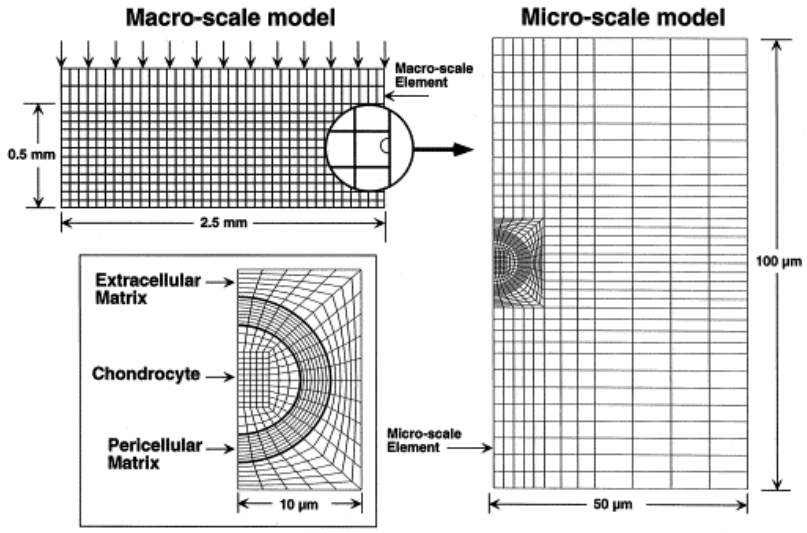

Figure 7: An overview of the ‘macroscale’ and ‘microscale’ used in a multiscale model to test the influence of chondrocytes. The values obtained on the macroscale are used as input parameters for the microscale.(17)

One application of this is to study the mechanical effects of the pericellular matrix around chondrocytes.[17] By including chondrocytes as spheres on the smaller scale the pressure

gradients could be determined. It was hypothesized that the inclusion of chondrocyte cells drastically alters the microscale pressures. In this case chondrocytes are modeled using a linear biphasic theory. The surrounding pericellular matrix followed the same equations as the overall matrix, but with different parameters to study its influence. Using unconfined compression results the relevant parameters were obtained and linearly interpolated for the microscale. To be able to use these values an assumption was made that the chondrocytes had no influence at the edge of the micromodel. This was deemed acceptable, as the obtained results showed that the chondrocytes dramatically altered the local stresses, but that it tapered quickly over distance. Without a pericellular matrix the highest stress was located around the cell-matrix border, increasing over time as the solid phase takes up a higher part of the load. If the pericellular matrix was assumed to be stiffer than the surrounding matrix the cell border stresses decreased. Based on these results it was concluded that chondrocyte cells drastically change the topology of the local stresses. This model could be highly advantageous to study the local effects when the overall tissue changes due to degeneration.

Triphasic

A more complex theory for cartilage is the triphasic mixture theory.[24] In addition to the fluid and solid phase an ion phase is added. As with the biphasic theory changes in isotropy, linearity and heterogeneity can be included. The ion phase is represented by free flowing ions like Na^+, Ca^{2+} and Cl^-.[22] The fixed-charge density of the proteoglycans causes these ions to flow into the cartilage tissue, creating an osmotic pressure gradient called the Donnan osmotic pressure. The ion phase explains the effects of these ions and pressure and the resulting change in deformation and stress responses. This theory states that to reach equilibrium in cartilage 2 factors are relevant; the donnan osmotic pressure and the elastic stress of the solid matrix. The ions can be approximated using a singular ion type, or by multiple ions. Studies have shown that the Donnan osmotic pressure accounts for around half of the equilibrium response in confined axial loading.[28] During compression the fluid pressure at the confined boundaries supports most of the forces. Decoupling this fixed-charge density allows better predictions for peak stresses at the end of compression. When using the biphasic theory this fixed-charge density is included in the aggregate modulus. Both the biphasic and triphasic theory predict identical stress-relaxation responses, however there is an observable difference in the fluid pressure, dropping to 0 only when using the biphasic theory. Thus when studying fluid pressures and swelling behaviour the triphasic theory could prove to be a valuable upgrade.[16]

Swelling behaviour is an important property of cartilage tissue. Using the triphasic theory the factors affecting swelling behaviour can be determined as it mainly depends on the Donnan osmotic pressure. The tensile stress of collagen fibrils confines this swelling. Osteoarthritis causes this collagen network to degenerate, resulting in more swelling of the tissue. With the use of a free swelling test the material parameters were determined using a triphasic model. A hypertrophic solution was used as a reference as it causes ion swelling effects to become negligible. The model used only accounted for tensile properties as no compressive forces were induced.(3) A one layer and a two layer model were compared; Results showed that the 1 layer model was unable to predict the increased swelling strains caused by tissue degeneration. The

2 layer model accurately predicted the swelling stresses, showing an increased stiffness at the outermost layer. This indicates that a triphasic model can be used to accurately predict the changes in swelling behaviour, and obtain material parameters without compression experiments. To expand on the different elastic moduli found a fully depth dependent model would need to be used. This study showed that using transverse isotropy can be used in a triphasic model to explain the depth properties of swelling.

Even though the triphasic theory looks like a direct upgrade to the biphasic method, both are still used in the current day. This is likely due to the fact that the biphasic model requires less computational power and is still successful in predicting cartilage response in various loading conditions. Because of this it is useful to show the direct difference between these two approaches, in both loading response and material properties. A triphasic model can be reduced to biphasic by changing the ion phase parameters to 0.[4] Using this fact the responses of both theories were compared using multiple loading conditions. When subjected to torque both models predicted the same response, indicating that the shear stress is not influenced by the inclusion of an ion phase. To determine the compressive modulus a higher force was needed using the triphasic theory, as it assumed cartilage to be under a tensile prestress at rest. Parametric values obtained were similar, indicating that in the biphasic theory the ion phase response is included in the solid and fluid phases.

The triphasic theory uses complex mathematical equations that require more computational power. Because of this it is only used for specific conditions like swelling behaviour. Often the biphasic theory is used instead. For this reason a simplification of the triphasic theory was created, turning it back into a biphasic approach.[28] This simplification is created because the equilibrium deformation response is identical in both the triphasic model and a biphasic elastic medium. It couples the physicochemical parameters like fixed-charge density to the mechanical properties. This creates a model that can still showcase the effects of the fixed-charge density and osmotic pressure through additional modifiable parameters. Another way to include swelling behaviour is by creating a fibril-reinforced model, adding in the swelling as a function of the tensile strength.

Fibril reinforcement

The basic biphasic theory is accurate in a lot of applications, but is unable to predict the tensile behaviour of the tension-compression nonlinearity. This nonlinearity is caused by the collagen fibers that mainly act in tension and do not contribute much to the overall compressive strength. Due to this fact focus has been placed on adding in these fibrils into cartilage models. This still leads to a biphasic approach, but subdivides the solid phase into a fibrillar and a nonfibrillar part. The nonfibrillar part consists of the proteoglycans and can be modeled as linear or nonlinear. The fibrillar part consists of major collagen fibrils that curve near the articular surface and split into minor fibrils. The fibrils cause the anisotropic behaviour of the model.[10,21] The fibrils can be built using multiple methods like spring or vector setups. These fibrils cause depth dependent behaviour and the minor fibrils attribute to the articular surface. Crosslinking is often neglected in fibril models to simplify the calculations. The equilibrium response is regulated by

the nonfibrillar matrix, the fibrillar part affects the peak stresses and the permeability affects the speed of this response. Another benefit of including fibrils is the ability to study the influence of degenerative factors. Fibril length and thickness are important variables in these models, altering the exact stress response. Based on an experiment using different lengths of dry collagen fibers an equation was created that relates the viscoelastic stress response to the fiber structure.[36] By adding in fibril-reinforcement existing models can be upgraded to include nonlinear stress-strain behaviour as fibrils only contribute to the tensile stresses. One study used this to upgrade an existing viscohyperelastic model.[15] They showed that for confined compression a fibril model does not change the response, as the fibers only resist tension. In other loading situations the fibrils carried most of the tensile loads. This model also included a parameter for viscosity to show the differences between an elastic and viscoelastic approach. Combined these two parameters showed that the Young's modulus increases due to a combination of fibril stiffness and fluid pressure.

To determine the effects of damage to the collagen network a poroviscoelastic model was reinforced with collagen fibers.[42] Fibril properties were obtained from experimental indentation and unconfined compression tests. The major fibrils split up into 4 directions parallel to the surface (Figure 8). These split into short minor fibrils oriented in random directions parallel to the surface, to increase the tensile stiffness. Fiber concentrations were modeled depending on the zone, with accurate concentrations. They were modeled by 2 parallel springs with an added damper to include the viscoelastic behaviour, causing stress to act linear after full relaxation. The nonfibrillar part was modeled as linear and isotropic with strain dependent permeability. Remaining material properties were obtained from literature and older model validations.

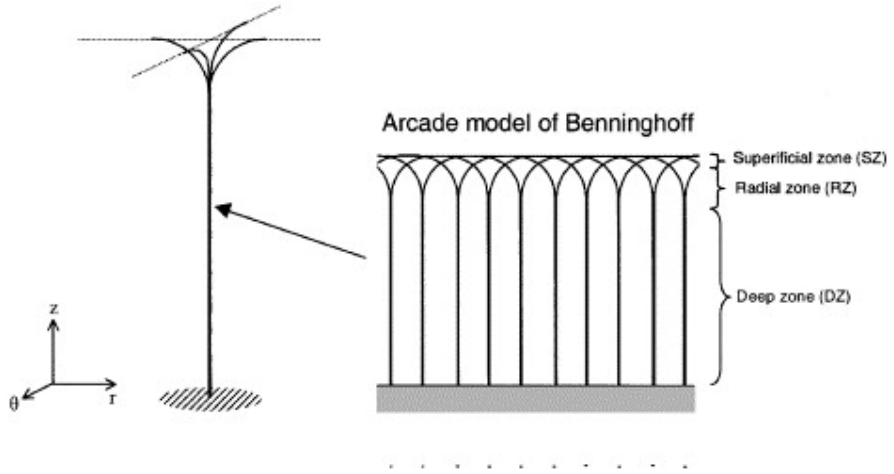

Figure 8: Directions of the major fibrils depending on zonal layer.[42]

Curve fitting to unconfined compression and indentation data showed close agreement. Slight differences were observed; A delayed force response during indentation testing and a higher lateral displacement for unconfined compression. It turned out that the orientations of the minor fibrils had a large influence on the local stresses during the indentation test, with the fibers curving away from the indentation having a larger strain. These discrepancies are most likely

caused by the isotropic and linear approach for the nonfibrillar matrix. Taking this into consideration it was still concluded that this model is able to explain the mechanical response during both unconfined compression and indentation. It also shows the influence of the size and orientation of collagen fibrils, and can show the local strains acting on these fibers based on their location.

This model was later extended to enable it to simultaneously predict the force responses to all 3 common loading conditions and account for swelling behaviour. This was achieved by combining the model with a previously validated biphasic swelling model.[40] Most swelling models are isotropic and thus unable to explain the compression or indentation responses. The goal of this combination was to create a model that could all of these responses with the same parameter set.[41] To save computational time the fibrils were simplified, splitting only in two directions instead of four and including less secondary fibrils. By including the swelling model the pressure gradients can be taken into account. The total stress at each point in the model is a direct combination of all substresses. The model was curve fit under all three loading conditions using the same parameters obtained from literature and the free swelling experiment. The peak stresses got slightly overpredicted in confined compression, and slightly underpredicted in unconfined compression but overall the results showed a good fit (Figure 9), unlike the linear poroviscoelastic model described above (Figure 3). The obtained Young's modulus was lower than those found in literature, most likely because the swelling contributes to the overall tissue stiffness. Similar to the unextended model a delayed force was observed in the indentation testing. The small deviations were attributed to small differences in model parameters and real cartilage parameters. Because all deviations were relatively small the model was deemed accurate in simultaneously determining all three loading conditions, as well as predicting swelling behaviour.

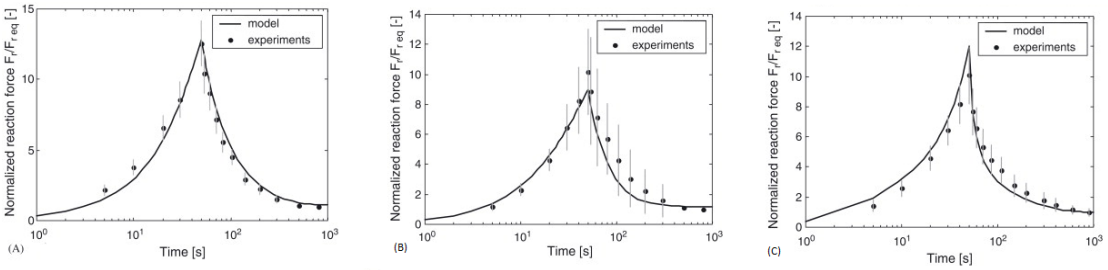

Figure 9: The upgraded fibril reinforced model fit to experimental data from (A) indentation, (B) unconfined compression and (C) confined compression tests. Experimental data was obtained using the BVPE research described above.[41]

This model was again upgraded, this time by combining it with a tissue composition model.[39] The tissue composition model allows variations in fluid and collagen concentrations, giving the nonfibrillar matrix depth dependent properties. Water was divided into intra- and extrafibrillar, altering the permeability. The fibril equation was altered to account for the stress-strain nonlinearity. This combined model would be able to relate local stresses and strains to the tissue composition, and predict the alterations in the force response as the tissue composition changes.[39] Compression results showed a high accuracy for all tests, including swelling

behaviour. The model was able to relate the permeability to the tissue composition. It was successful in analysing the changes that happen with tissue degeneration by lowering the collagen concentration and altering the zone thickness.[20]

To approach in vivo conditions a fibril-reinforced model could be used with 3D build of a complete joint.[8] This would give the ability to determine the location specific responses in a joint setup. By using realistic collagen parameters the effects of osteoarthritis could be studied.[18,26] One study showed the influence of the fibril orientation using a joint model built using MRI data. It was found that the stresses at the articular surface increase as the collagen at the surface breaks down. This highlights how fibril-reinforced models could be used in a 3D setting to simulate the in vivo effects of cartilage degeneration.

Discussion

In the current landscape of cartilage modeling many different modeling approaches exist. As can be seen above these differ wildly in properties, accuracy and uses. When choosing a model the complexity required is based on the focus of the research. It is counterproductive to always choose the most advanced model in existence, as this increases computational times and complexity. However in most cases at least some form of anisotropy or nonlinearity need to be considered as the basic isotropic linear model fails in a lot of cases. For linearity most accurate would be a poroviscoelastic approach, accounting for both flow dependent and flow independent factors. But as these have a different scale in relaxation factors one can often be ignored based on the time scale of the research.[35] The inclusion of fibril reinforcement can be used to account for the nonlinearity as well, especially when looking at the difference between compressive and tensile forces.[23] For research into cartilage degeneration the composition is an important factor, either through fibril-reinforcement or other density factors. The triphasic model is often unnecessary, it is only typically used when looking at the swelling behaviour and osmotic pressure gradients. The microscale chondrocytes can almost always be ignored, only when specifically looking at the influence of these elements are they required. When no existing model caters to the requirements of the study an existing model could be upgraded to include more properties. However in this case additional validation is required.

In conclusion, there is no one ‘best’ model. The accuracy of a model often directly correlates with the complexity and computational cost, making it counterproductive to add in every factor. It is important to first determine the focus and area of the research before creating a model. Based on this information the factors a model needs to adhere to are decided, and either a pre-existing model can be used, or a new one has to be created.

References

1. Aigner T. Collagens—major component of the physiological cartilage matrix, major target of cartilage degeneration, major tool in cartilage repair. Advanced Drug Delivery Reviews. 2003;55(12):1569-1593.

2. Akkiraju H, Nohe A. Role of Chondrocytes in Cartilage Formation, Progression of Osteoarthritis and Cartilage Regeneration. Journal of Developmental Biology. 2015;3(4):177-192.

3. armoneva D, Wang J, Setton L. A Noncontacting Method for Material Property Determination for Articular Cartilage from Osmotic Loading. Biophysical Journal. 2001;81(6):3066-3076.

4. Ateshian G, Chahine N, Basalo I, Hung C. The correspondence between equilibrium biphasic and triphasic material properties in mixture models of articular cartilage. Journal of Biomechanics. 2004;37(3):391-400.

5. Ateshian G, Warden W, Kim J, Grelsamer R, Mow V. Finite deformation biphasic material properties of bovine articular cartilage from confined compression experiments. Journal of Biomechanics. 1997;30(11-12):1157-1164.

6. Bader D, Kempson G, Egan J, Gilbey W, Barrett A. The effects of selective matrix degradation on the short-term compressive properties of adult human articular cartilage. Biochimica et Biophysica Acta (BBA) - General Subjects. 1992;1116(2):147-154.

7. Bandeiras C, Completo A. A mathematical model of tissue-engineered cartilage development under cyclic compressive loading. Biomechanics and Modeling in Mechanobiology. 2016;16(2):651-666.

8. Boschetti F, Peretti G. Mechanical properties of normal and osteoarthritic human articular cartilage. Journal of Biomechanics. 2008;41:S171.

9. Bursać P, Obitz T, Eisenberg S, Stamenović D. Confined and unconfined stress relaxation of cartilage: appropriateness of a transversely isotropic analysis. Journal of Biomechanics. 1999;32(10):1125-1130.

10. Cohen N, Foster R, Mow V. Composition and Dynamics of Articular Cartilage: Structure, Function, and Maintaining Healthy State. Journal of Orthopaedic & Sports Physical Therapy. 1998;28(4):203-215.

11. de Boer G, Raske N, Soltanahmadi S, Dowson D, Bryant M, Hewson R. A porohyperelastic lubrication model for articular cartilage in the natural synovial joint. 2019.

12. DiSilvestro M, Suh J. A cross-validation of the biphasic poroviscoelastic model of articular cartilage in unconfined compression, indentation, and confined compression. Journal of Biomechanics. 2001;34(4):519-525.

13. Donzelli P, Spilker R, Ateshian G, Mow V. Contact analysis of biphasic transversely isotropic cartilage layers and correlations with tissue failure. Journal of Biomechanics. 1999;32(10):1037-1047.

14. Eyre D. Articular cartilage and changes in Arthritis: Collagen of articular cartilage. Arthritis Research. 2002;4(1):30.

15. García J, Cortés D. A biphasic viscohyperelastic fibril-reinforced model for articular cartilage: Formulation and comparison with experimental data. Journal of Biomechanics. 2007;40(8):1737-1744.

16. Gu W, Lai W, Mow V. Transport of fluid and ions through a porous-permeable charged-hydrated tissue, and streaming potential data on normal bovine articular cartilage. Journal of Biomechanics. 1993;26(6):709-723.

17. Guilak F, Mow V. The mechanical environment of the chondrocyte: a biphasic finite element model of cell–matrix interactions in articular cartilage. Journal of Biomechanics. 2000;33(12):1663-1673.

18. Holzapfel G, Ogden R, Sherifova S. On fibre dispersion modelling of soft biological tissues: a review. Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences. 2019;475(2224):20180736.

19. Hunziker E, Quinn T, Häuselmann H. Quantitative structural organization of normal adult human articular cartilage. Osteoarthritis and Cartilage. 2002;10(7):564-572.

20. Julkunen P, Jurvelin J, Isaksson H. Contribution of tissue composition and structure to mechanical response of articular cartilage under different loading geometries and strain rates. Biomechanics and Modeling in Mechanobiology. 2009;9(2):237-245.

21. Julkunen P, Wilson W, Isaksson H, Jurvelin J, Herzog W, Korhonen R. A Review of the Combination of Experimental Measurements and Fibril-Reinforced Modeling for Investigation of Articular Cartilage and Chondrocyte Response to Loading. Computational and Mathematical Methods in Medicine. 2013;2013:1-23.

22. Katta J, Jin Z, Ingham E, Fisher J. Biotribology of articular cartilage—A review of the recent advances. Medical Engineering & Physics. 2008;30(10):1349-1363.

23. Korhonen R, Laasanen M, Töyräs J, Lappalainen R, Helminen H, Jurvelin J. Fibril reinforced poroelastic model predicts specifically mechanical behavior of normal, proteoglycan depleted and collagen degraded articular cartilage. Journal of Biomechanics. 2003;36(9):1373-1379.

24. Lai W, Hou J, Mow V. A Triphasic Theory for the Swelling and Deformation Behaviors of Articular Cartilage. Journal of Biomechanical Engineering. 1991;113(3):245-258.

25. Li L, Buschmann M, Shirazi-Adl A. A fibril reinforced nonhomogeneous poroelastic model for articular cartilage: inhomogeneous response in unconfined compression. Journal of Biomechanics. 2000;33(12):1533-1541.

26. Li L, Cheung J, Herzog W. Three-dimensional fibril-reinforced finite element model of articular cartilage. Medical & Biological Engineering & Computing. 2009;47(6):607-615.

27. LU X, MOW V. Biomechanics of Articular Cartilage and Determination of Material Properties. Medicine & Science in Sports & Exercise. 2008;40(2):193-199.

28. Lux Lu X, Miller C, Chen F, Edward Guo X, Mow V. The generalized triphasic correspondence principle for simultaneous determination of the mechanical properties and proteoglycan content of articular cartilage by indentation. Journal of Biomechanics. 2007;40(11):2434-2441.

29. Mansfield J, Bell J, Winlove C. The micromechanics of the superficial zone of articular cartilage. Osteoarthritis and Cartilage. 2015;23(10):1806-1816.

30. Mansfield J, Mandalia V, Toms A, Winlove C, Brasselet S. Collagen reorganization in cartilage under strain probed by polarization sensitive second harmonic generation microscopy. Journal of The Royal Society Interface. 2019;16(150):20180611.

31. Mononen M, Mikkola M, Julkunen P, Ojala R, Nieminen M, Jurvelin J et al. Effect of superficial collagen patterns and fibrillation of femoral articular cartilage on knee joint mechanics—A 3D finite element analysis. Journal of Biomechanics. 2012;45(3):579-587.

32. Mow V, Holmes M, Michael Lai W. Fluid transport and mechanical properties of articular cartilage: A review. Journal of Biomechanics. 1984;17(5):377-394.

33. Mow V, Kuei S, Lai W, Armstrong C. Biphasic Creep and Stress Relaxation of Articular Cartilage in Compression: Theory and Experiments. Journal of Biomechanical Engineering. 1980;102(1):73-84.

34. Reuter T, Hoffman M. Elastic and Hyperelastic Material Model of Joint Cartilage - Calculation of the Pressure Dependent Material Stress in Joint Cartilage. 2011;.

35. Richard F, Villars M, Thibaud S. Viscoelastic modeling and quantitative experimental characterization of normal and osteoarthritic human articular cartilage using indentation. Journal of the Mechanical Behavior of Biomedical Materials. 2013;24:41-52.

36. Sanjeevi R, Somanathan N, Ramaswamy D. A viscoelastic model for collagen fibres. Journal of Biomechanics. 1982;15(3):181-183.

37. Sophia Fox A, Bedi A, Rodeo S. The Basic Science of Articular Cartilage: Structure, Composition, and Function. Sports Health: A Multidisciplinary Approach. 2009;1(6):461-468.

38. Suh J, Li Z, Woo S. Dynamic behavior of a biphasic cartilage model under cyclic compressive loading. Journal of Biomechanics. 1995;28(4):357-364.

39. Wilson W, Huyghe J, van Donkelaar C. A composition-based cartilage model for the assessment of compositional changes during cartilage damage and adaptation. Osteoarthritis and Cartilage. 2006;14(6):554-560.

40. Wilson W, van Donkelaar C, Huyghe J. A Comparison Between Mechano-Electrochemical and Biphasic Swelling Theories for Soft Hydrated Tissues. Journal of Biomechanical Engineering. 2005;127(1):158-165.

41. Wilson W, van Donkelaar C, van Rietbergen B, Huiskes R. A fibril-reinforced poroviscoelastic swelling model for articular cartilage. Journal of Biomechanics. 2005;38(6):1195-1204.

42. Wilson W, van Donkelaar C, van Rietbergen B, Ito K, Huiskes R. Stresses in the local collagen network of articular cartilage: a poroviscoelastic fibril-reinforced finite element study. Journal of Biomechanics. 2004;37(3):357-366.

43. Wilson W, van Donkelaar C, van Rietbergen R, Huiskes R. The role of computational models in the search for the mechanical behavior and damage mechanisms of articular cartilage. Medical Engineering & Physics. 2005;27(10):810-826.