



Computational Modelling for Managing Pathways to Cartilage Failure

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Abstract

Over several decades the perception and therefore description of articular cartilage changed substantially. It has transitioned from being described as a relatively inert tissue with limited repair capacity, to a tissue undergoing continuous maintenance and even adaption, through a range of complex regulatory processes. Even from the narrower lens of biomechanics, the engagement with articular cartilage has changed from it being an interesting, slippery material found in the hostile mechanical environment between opposing long bones, to an intriguing example of mechanobiology in action. The progress revealing this complexity, where physics, chemistry, material science and biology are merging, has

been described with increasingly sophisticated computational models. Here we describe how these computational models of cartilage as an integrated system can be combined with the approach of structural reliability analysis. That is, causal, deterministic models placed in the framework of the probabilistic approach of structural reliability analysis could be used to understand, predict, and mitigate the risk of cartilage failure or pathology. At the heart of this approach is seeing cartilage overuse and disease processes as a ‘material failure’, resulting in failure to perform its function, which is largely mechanical. One can then describe pathways to failure, for example, how homeostatic repair processes can be overwhelmed leading to a compromised tissue. To illustrate this ‘pathways to failure’ approach, we use the interplay between cartilage consolidation and lubrication to analyse the increase in expected wear rates associated with cartilage defects or meniscectomy.

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6.1 Introduction

Over the past ~40 years, incredible advances have been made in cartilage biology. We are thinking about the finding that transient compressive stiffness arises from low hydraulic conductivity of cartilage and collagen network stiffness, how the equilibrium cartilage compressive stiffness arises primarily from repulsion between negatively charged aggrecan, the interplay between the aggrecan compression and the collagen tension to maintain normal cartilage stiffness, and how turnover of these ECM components is regulated by chondrocytes via chemical, electromechanical and mechanical signals [1–8]. These insights, often gained by patient work on individual processes or isolated molecules, have been integrated to present a compelling story of how this tissue functions in both the short term (to an individual loading) and the long-term (to repeated cyclic loadings), and potential pathways to pathology [8]. With the insight made possible by understanding this integrated system, we are only just beginning to develop rational strategies to intervene at the tissue scale to maintain or reverse cartilage damage.

Meanwhile great advances have also occurred in imaging and computational biomechanics, genetics and genetic manipulations that may soon enable patient (or cohort) specific data to be incorporated into cartilage treatment strategies [9, 10]. How best to do this is still in its infancy, and so largely an open question, but it holds such promise. Our belief is that this way forward will no doubt be computational (*i.e.* based on deterministic quantitative mechanistic models of cartilage tissue turnover in response to its mechanical and chemical environment), but will also necessarily include statistical aspects (*e.g.* variable loadings and model tissue parameters over time and/or population). More to our point, we believe the concepts of risk analysis borrowed from reliability engineering, provides a promising framework to shepherd our hard-won understanding of cartilage biology into the clinic [11, 12]. Here we will expand on these ideas. In doing so we will necessarily review some cartilage biology.

However, the focus will be on identifying strategies cartilage uses to maintain and repair itself, and the pathways to cartilage ‘failure’, however failure may be defined. This approach promises to enable the risk associated with various ‘disease pathways’ in an individual or patient cohort to be rationally quantified, and then managed.

6.2 Articular Cartilage, an Extraordinary Tissue

Articular cartilage faces extraordinary mechanical challenges during daily physical activities. For example, knee cartilages in adults experience contact forces up to 5 times the body weight during stair climbing [13], leading to contact stresses up to 18 MPa. To get this loading in perspective, we note that a large stiletto heel exerts about 10 MPa pressure on the ground, and this contact stress is well-known for damaging some wooden floors—while cartilage tissue repeatedly experiences stresses that are almost twice as great. Probably due to this harsh mechanical environment, cartilage is an avascular tissue with a sparse chondrocyte to extracellular matrix (ECM) distribution, which limits its repair capacity. All tissues that normally repair quickly have abundant blood supplies, while in contrast, cartilage relies solely on diffusion/advection of nutrients and oxygen from synovial fluid that bathes its contact surface, with the subchondral bone-cartilage interface generally considered impermeable in healthy joints. Consequently, articular cartilage function and homeostasis largely rely on complex interactions between its main extracellular components: interstitial fluid, aggrecan and a Type II collagen network [5, 8]. For example, the rate of tissue strain under sustained load largely depends on the interstitial fluid movement through the cartilage tissue and across the cartilage surfaces, influencing the mechanical and chemical microenvironments continually being sensed by chondrocytes, while the fluid contributes to synovial joint lubrication [5, 14]. When cartilage is subjected to compressive loading, it consolidates. The load is initially carried by the fluid phase, which is slowly squeezed out of the

extracellular matrix, helping to sustain very low frictional force between two opposing cartilage surfaces. As cartilage interstitial fluid exudes through the tissue surface, load is gradually transferred to the solid matrix, resulting in a gradual increase in friction at contacting surfaces.

6.3 Cartilage Damage Mechanics

The ability of cartilage to maintain its physiological function in this hostile mechanical environment depends on the tissue's ability to continually synthesize extracellular matrix components, while avoiding excessive strain, an attribute normally conferred by its composite structure. Aggrecans are negatively charged molecules that have counter ions in a diffuse double-layer to maintain overall electroneutrality. Overlapping double-layers repel and so normally expand and imbibe water. However, this expansion is resisted by the collagen network [15]. The aggrecan molecules within the collagen network normally provide the equilibrium compressive stiffness for cartilage tissue [16], and ensure a very small hydraulic permeability which delays consolidation of the tissue to its equilibrium state. Consequently, when loaded, a long consolidation time follows (e.g. up to three or more hours).

As shown schematically in Fig. 6.1, a damaged collagen network is not able to effectively retain a high enough concentration of aggrecan molecules within the collagen network, which leads to cartilage softening [17]. Reduced aggrecan content also leads to larger hydraulic conductivity, more rapid consolidation and larger strains. This means the aggregate, collagen tissue network and chondrocytes are more likely to be damaged by excessive strain (following even normal load), leading to further loss of aggrecan [18]. This positive feedback cycle is just one important pathway that can lead to disease such as osteoarthritis. One can imagine many more and so osteoarthritis is not just one disease [8, 19]. Its management is likely to also differ depending on the etiology.

6.4 Role of Computational Modelling to Capture Complex Interactions

A key attraction of computational modeling is that it can be employed to reveal the spatial and temporal distribution of tissue microenvironments experienced by chondrocytes embedded within articular cartilage. This involves interpolating sparse experimental data sets, often measured at tissue boundaries, to define local conditions experienced by chondrocytes throughout the cartilage tissue. This immediately opens up the possibility of beginning to define previously inaccessible variables that are likely to be driving local ECM damage and chondrocyte repair processes within articular cartilage. This new capability, together with experimentally calibrated computational damage and repair functions, then naturally leads to predictions about the integrity of cartilage under various short and long-term scenarios.

Through this process, computational modeling can provide a pathway from laboratory data to quantitative predictions about future tissue states under various scenarios. This should be of great interest to clinicians, as they are in the business of advising patients as to the optimal path to follow in response to their problem. The process of building and calibrating computational models of cartilage tissue also offers up the possibility of a new pathway to more effective use of the new data being generated by 'precision medicine' for individual patients.

There are many chemical molecules and mechanical cues that regulate articular cartilage homeostasis. Therefore, to realistically define cartilage microenvironments requires consideration of interactions between many specific and rather detailed computational modules (involving multi-physics and multiphase modelling). The theory of porous media has been widely employed to simulate the mechanical behaviour of biological soft tissues, such as articular cartilage [20–25] and fracture callus [26–28]. Here the extracellular matrix and interstitial fluid interaction contributes to the time-dependent observed tissue stiffness and deformation behaviour. By

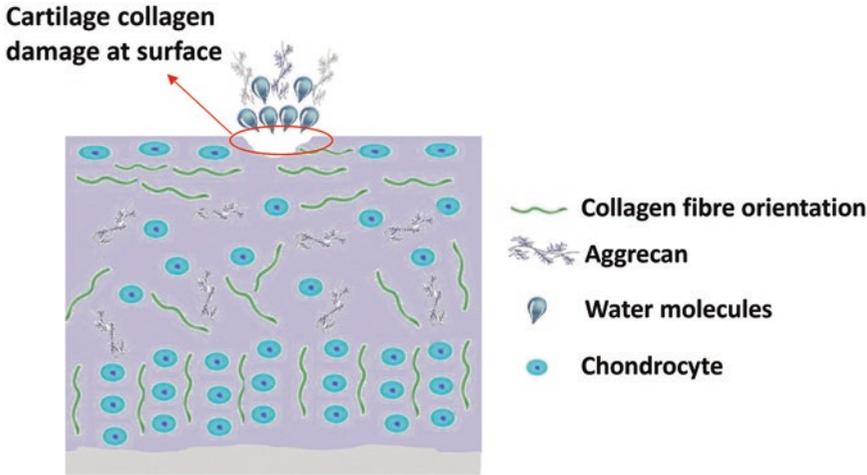


Fig. 6.1 Schematic shows damage to superficial collagen network results in escape of aggrecans and water molecules from the cartilage tissue, which may significantly

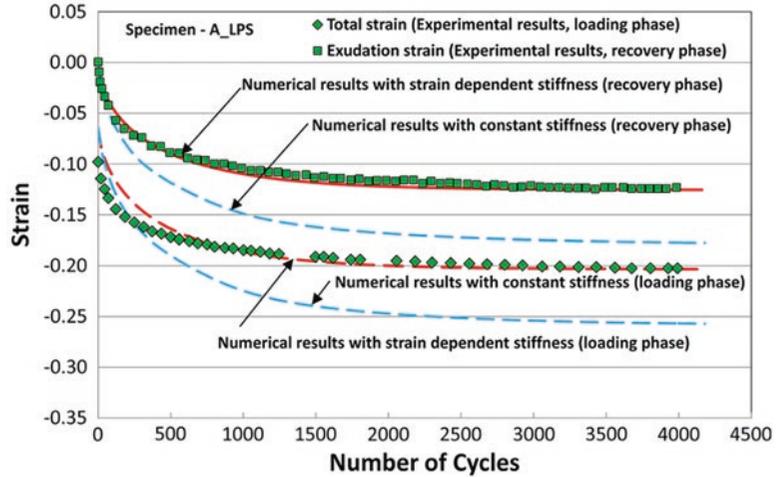
increase strain locally. This can lead to local damage of the extracellular matrix and chondrocytes

combining the porous media theory with transport models and chemical reactions, we can also simulate three-dimensional diffusion and advection of different molecules in cartilage, and use this information to predict different cellular activities [14, 29–36]. For example, insulin-like growth factors mediate cartilage cellular activities such as cell proliferation, differentiation, apoptosis and synthesis of extracellular matrix [32, 37, 38]. We have built a spatial model for IGF in cartilage tissue that includes many simultaneous chemical reactions, as well as transport parameters [36]. Each of these parameters depends on the actual chemical structure of IGF and its binding proteins, as these determine the chemical rate constants that define their interactions. These rate constants depend on the amino acid sequence in each molecule, which in turn depends on the genetic code in that individual. If the genetic code is known, as revealed by precision medicine, it should be possible to predict the effect of that person's genetic code on the chemical rate constants, enabling the creation of customized computational models for each individual's IGF system for their cartilage. By this means, we can bridge the information gap between genetic data and what this data actually means in the context of a tissue.

This same principle can be applied to all the other chemical molecules found in cartilage tissue. For example, the inflammatory cytokine IL-1 α is known to modulate biochemical degradation of cartilage tissue following a traumatic joint injury, so we built a detailed model of IL-1 β in cartilage, and calibrated the model using detailed experimental data generated exclusively in the Grodzinsky lab [37]. The model simulated the experimental observation of biochemical degradation of bovine articular cartilage explants. The developed model can help improve our understanding of in vivo events after a joint injury and potentially be employed for assessing the influence of different therapeutic molecules on osteoarthritis management [39, 40].

Since the biochemical signaling pathways are influenced by the mechanical microenvironment of cartilage, we built a mechanical model of cartilage. We have developed and published a state-of-the-art biphasic model of cartilage mechanics that is validated against ex-vivo mechanical experiments on human osteochondral plugs subject to cyclic loading [22]. The model takes into account tensile loading being carried by the collagen network, and compressive load carried by water and aggrecan. The model has a non-linear compressive stiffness and non-linear hydraulic

Fig. 6.2 Our cartilage mechanics model can accurately reproduce experimental data of time-course of deformation in both the loading and recovery phase of the experiment. (Figure adapted from Zhang et al. [22] with permission)



permeability based on the aggrecan concentration, which changes as the cartilage tissue deforms. As such this model represents a new constitutive model of articular cartilage, which helps provide a sound foundation for new models describing cartilage damage and repair modelling (Fig. 6.2).

6.5 Using Models to Investigate Pathways to Cartilage Failure

Synovial joint lubrication is one of the key roles of articular cartilage. Synovial joints can experience very small frictional force, with initial friction coefficient ranging from 0.005 to 0.02, while bearing extremely large mechanical stress [41, 42]. However, experimental studies have shown that the cartilage friction coefficient can rise with time (~minutes) under loading [43, 44]. Our computational modelling in conjunction with experimental observations have shown that there is a strong correlation between cartilage friction coefficient and the degree of cartilage consolidation. This suggests that after prolonged period of loading, in particular stationary activities (e.g. standing), consolidation has occurred and friction coefficient rises (Fig. 6.3). The cartilage surface can experience relatively large friction coefficient (e.g. 0.2–0.3, with subsequent additional cartilage damage likely as motion recommences).

It is known that large frictional force at the joints can result in elevated cartilage surface wear and damage and cartilage delamination. A well calibrated and patient-specific computational modelling can help us simulate the likely impact of physical activities on synovial joint health and thereby design patient-specific physical therapy activities for management of osteoarthritis. We have incorporated different joint states such as meniscectomy and cartilage surface defects, and simulated cartilage time-dependent lubrication. As shown in Fig. 6.4, the response of damaged cartilage, to the same loading conditions, was a faster rate of consolidation and quicker increase in surface friction coefficient. The expectation then is these compromised joints will experience a higher average friction coefficient, than a healthy cartilage, and so a higher surface wear rate. Knowing this, from medical history (e.g. observation of defects in MRI) it is possible to devise activities that minimize the likelihood of these adverse situations occurring, thereby increasing the likelihood cartilage will maintain its functional integrity.

Although we have shown above that defects and meniscectomies can increase consolidation and extend the time a cartilage surface experiences high friction, we still do not know how critical this is in a particular individual. The load the joint experiences depends on factors such as body weight, joint size and shape, limb geometry and lifestyle. Some of these biomechanical

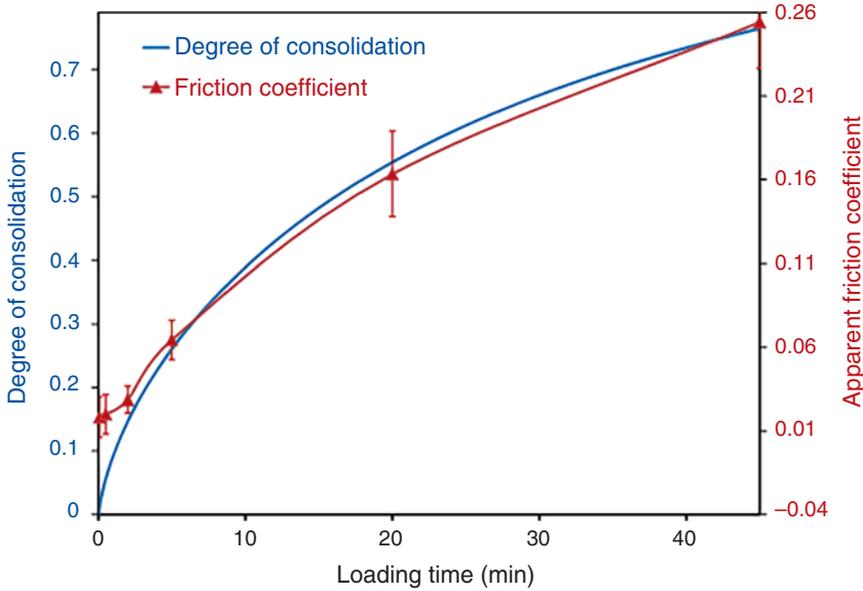
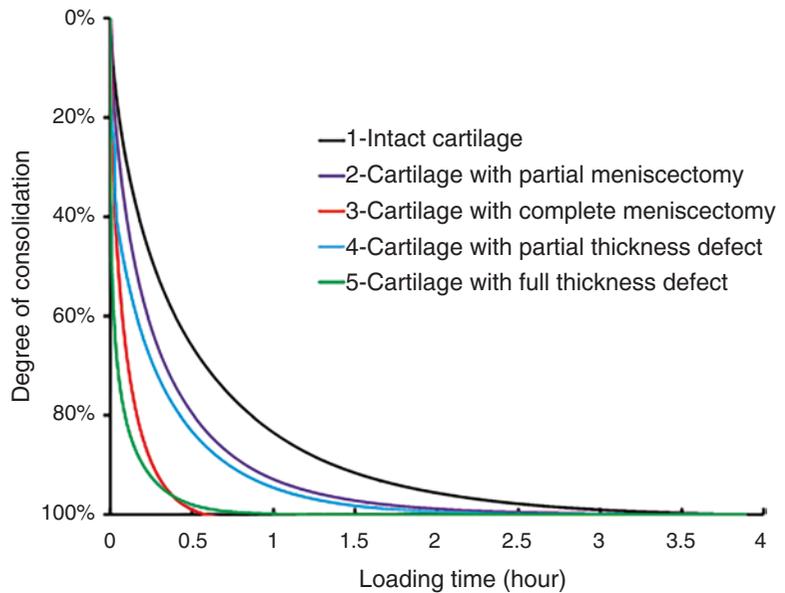


Fig. 6.3 There is a strong correlation between degree of consolidation of articular cartilage and friction coefficient in synovial joint. (This figure has been reproduced from Miramini et al. [45] with permission)

Fig. 6.4 A faster consolidation is predicted for cartilage with meniscectomy and the one with a full thickness defect. (This figure has been adapted from Miramini et al. [45] with permission)



aspects can be incorporated for an individual through a combination of imaging and gait analysis to predict joint loads. In addition, the functional mechanical properties of the cartilage tissue are also expected to vary in a population due to genetic and environmental histories. These factors can be also incorporated in patient-specific simulation.

Computational modelling can also assist clinicians in assessment of cartilage health. For example, we can assess cartilage tissue functional properties by combined fluoroscopic and MRI imaging of the knee in a standing still posture and measuring the degree of joint closure over time [46]. The calculated degree of consolidation of knee joint together with computational modelling

enable evaluation of knee joint ability to sustain interstitial fluid pressure and so experience a normal low surface friction coefficient [45].

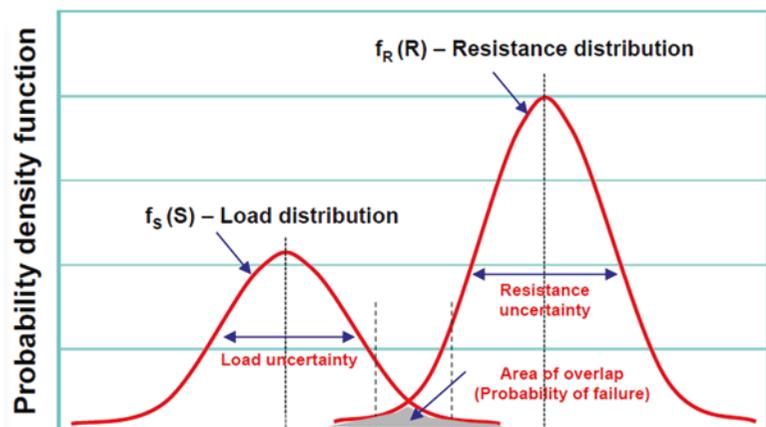
6.6 Probabilistic Modelling and Osteoarthritis Risk Assessment

As alluded to above, there are numerous uncertainties and variability associated with the parameters affecting cartilage behaviour. For example, cartilage loading condition depends on many factors including physical activity, body weight and joint anatomy. In addition, the physical properties of cartilage also remain uncertain and depend on factors such as age, joint health and genetic factors. Therefore, it is of critical importance to consider the uncertainty and variability of different factors when simulating cartilage behaviors. Probabilistic analysis has been traditionally developed and employed for reliability assessment of engineering structure such as bridges and nuclear power stations. Compared with a deterministic approach that adopts a discrete value for a specific model parameter, a probabilistic modelling approach takes into account the distribution of environmental factors and model parameters in the deterministic calculation and therefore generates a distribution of tissue trajectories (including pathways to disease) and therefore outcomes. In the context of engineering, we can define the ‘probability of failure’ as the like-

lihood of exceeding some pre-determined state critical to the functional performance of the engineered structure. For example, it might be the probability of a load exceeding the structure’s (e.g. a bridge’s) strength, or the probability of a load exceeding a certain level of deformation in the structure, or the probability of environmental factors causing a certain level of material damage (e.g. component fatigue damage, irradiation damage, or corrosion damage). Reliability can be defined as one minus the probability of failure. In the context of loading a structure, the probability of failure can be defined as the overlap between the probability density function of a ‘generalized loading’ applied on the structure and probability density function of the structure ‘generalized resistance’, as shown in Fig. 6.5.

Recently, we have used this approach to predict the likelihood of knee osteoarthritis [9]. This was done on the basis of a simple model of chondrocyte ECM synthesis in response to loading and the possibility for chondrocyte apoptosis under that load. Failure was defined by the ability to resist a test load (i.e. not exceed a maximum strain threshold). The model predicted that low activity leads to low ECM synthesis and so a gradual softening of the tissue. High activity increases ECM synthesis but also exposure to excessive loads. The probabilistic predictions had the median time to onset of failure occurred earlier in the low activity model, and with a relatively narrow uncertainty in onset time. The high activity level had a delayed median onset, but had

Fig. 6.5 The probability of failure of a structure can be estimated by finding the overlapping area under the probability density functions of generalized load and generalized resistance. (Figure adapted with permission from Miramini and Yang [47])



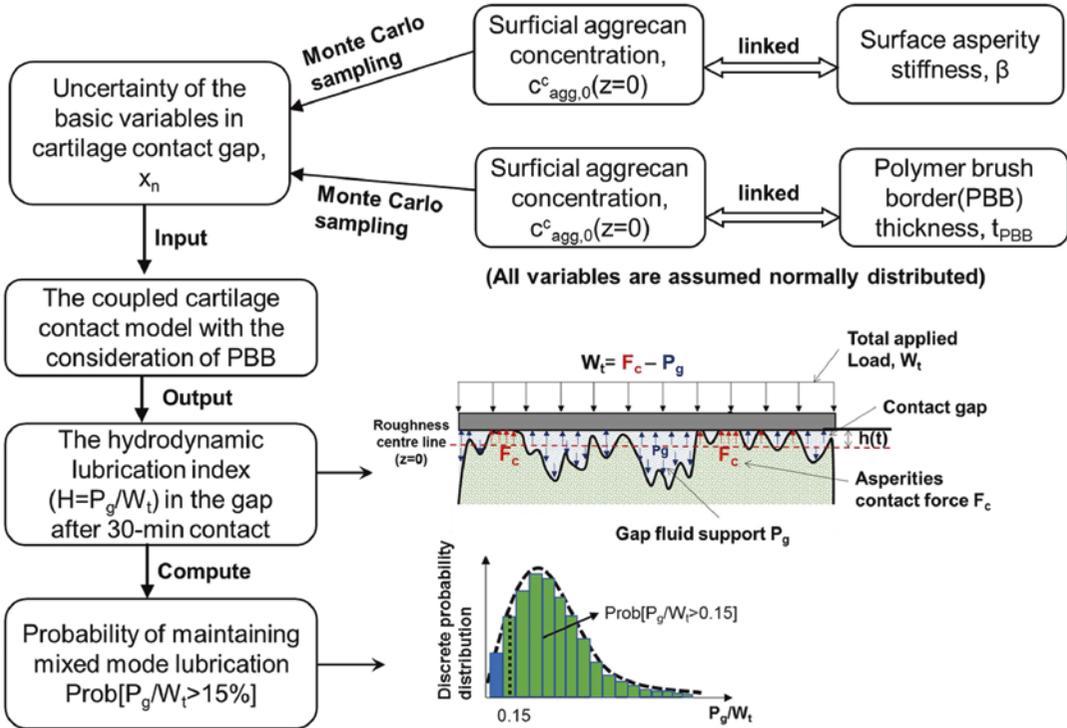


Fig. 6.6 Probabilistic computational model of cartilage lubrication. (Figure adapted with permission from Liao et al. [48])

much wider distribution of failure onset, relative to the low activity predictions [9].

In addition, we have recently developed a multi-scale probabilistic computational model (Fig. 6.6) to simulate the cartilage lubrication behaviour by incorporating the uncertainties associated with the key variables governing cartilage contact gap mechanics [48–50]. The model takes into account the internal relation between different variables and their correlated influence on cartilage lubrication. The simulation results show that an increase of polymer brush border thickness at the cartilage surface improves the hydrodynamic lubrication of cartilage, while the increasing surficial GAG content of the cartilage and increasing asperity stiffness could negatively affect hydrodynamic lubrication. Finally, we note that this probabilistic

approach has also been adopted to estimate the probability of delayed bone fracture healing [47, 51].

6.7 Conclusion

To conclude, we are reaching a stage where it is now possible to connect all the pieces together into a whole picture of articular cartilage homeostasis and to identify pathways to disease. Computational modeling seems to be the natural platform upon which to integrate, into their proper context, the many interacting processes involved. Here we presented various mechanistic sub-models describing aspects of articular cartilage health. However we have also advocated for the merging of these mechanistic sub-models

with the statistical-based models or approaches from (structural) reliability engineering. This then can provide a ‘bridge’ between the molecular and cell biology, biomechanics and epidemiology of osteoarthritis to give a rational basis for patient specific treatments. Although all the computational approaches are present to make this approach possible, the barriers to its adoption depends, not the least, on the adoption by clinicians.

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