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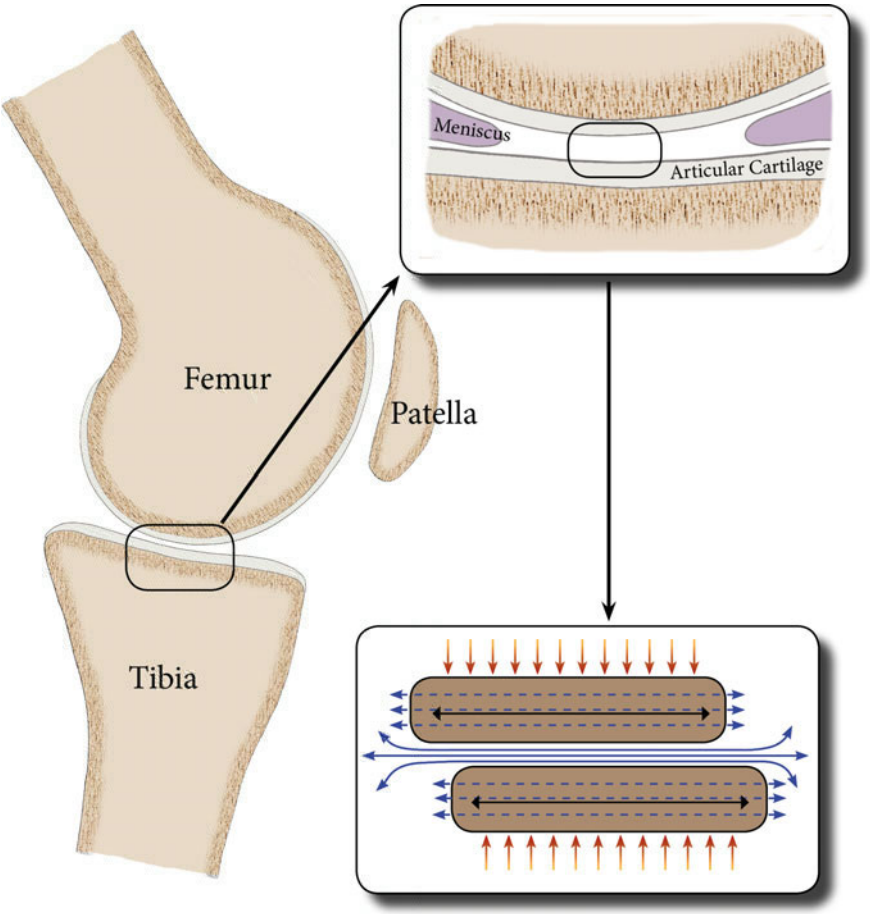
Meniscus
Articular Cartilage
Femur
Patella
Tibia

Foreword

Articular cartilage is found within diarthrodial joints covering the ends of long bones. The two primary mechanical functions of articular cartilage are to reduce the magnitude of contact stresses (the contact area of cartilage on cartilage is much larger than if bone directly contacts bone) and provide a low-friction bearing surface during motion (cartilage on cartilage has a much lower friction coefficient than if bone rubs directly on bone). The reduced contact stress and low friction at the contact interface together minimize internal damage to the cartilage extracellular matrix and resident chondrocytes, as well as minimizing wear damage at the cartilage surface. Fulfillment of these two primary mechanical functions provides the mechanical basis for the cartilage tissue to survive an extremely challenging mechanical environment.

Yet despite the best efforts by joint tissues to maintain themselves, many people develop disease states known collectively as osteoarthritis (OA). OA is a progressive and often disabling disease of the whole joint, involving multiple joint tissues. Over a period of years, the articular cartilage softens and degenerates—the hallmark of OA—leaving bare bone to rub painfully on bare bone. This results in substantial morbidity and much suffering in the general community, as well as generating substantial economic loss due to ill health and/or early retirement. To date, most drug treatments for OA are directed at symptomatic pain relief. It is unfortunate that current drug treatments have no demonstrable impact on altering the rate of structural change within osteoarthritic cartilage.

Even after an enormous research effort around the world over many decades, involving the expenditure of many billions of dollars, no single cause of osteoarthritis has been found. Both fundamental and clinical researchers have concluded that there is in fact no single cause and that OA disease states arise through a variety of pathways. Some osteoarthritic disease pathways to OA involve inflammatory initiators, while other pathways clearly involve mechanical initiators (e.g. joint trauma and overuse syndromes). A common view is that the onset of osteoarthrosis occurs when the recuperative processes within the cartilage and the surrounding tissues are pushed beyond their capacity to maintain tissue homeostasis, due to a patient-specific combination of genetic and environmental factors.

The evidence to date suggests that there are no easy answers and there will be no 'silver bullet' that eliminates OA. A more plausible scenario is that avoiding or managing established OA requires advice and treatment on a case-by-case basis—first identifying the specific combination of factors at work in any one individual and then instituting a patient-specific treatment regime. Undoubtedly, the most accurate assessment of disease potential and its management require an evaluation of patient-specific data in the context of a 'system-level' understanding of both normal cartilage physiology and OA cartilage physiology, gained from a deep and sustained integration of knowledge grounded in facts gathered over decades of basic biomedical science and clinical research.

It is our view that despite the intensive research efforts over decades, such a system-level understanding of cartilage is largely missing from the current cartilage literature. The focus of much basic research today remains on discovering the components in cartilage (e.g. signaling molecules, genes or protein expression profiles, or discovering the effect of 'gene silencing' or disabling protein activity). At a clinical level, there is a focus on high-level statistical correlations between system 'perturbations' and system outcomes (e.g. partial meniscectomy and incidence of OA, BMI and the incidence of OA, diabetes and the incidence of OA). Such 'discovery' approaches become problematic only because they completely dominate the current research landscape and, like all activities, are subject to the law of diminishing returns (i.e. successive studies yield diminishing increments to our knowledge). Practiced to excess, discovery, epidemiological and clinical research approaches deflect both attention and research funding from the development of integrated understandings of cartilage, which only serve to limit the potential benefits of the hard-won knowledge obtained from the previous discovery and clinical approaches. In short, our contention is there is currently a deficit of knowledge integration in cartilage research. An aim of this book is to help change this situation.

When integrative models of cartilage are employed, too often such models are far too simple. For example, articular cartilage is presented as a static tissue with a very limited capacity to repair—if it has any capacity to repair at all? From this simple conceptual model, it follows logically that cartilage inevitably 'wears out,' much like a pair of shoes wear out, and so patients are inevitably in need of joint replacement surgery (usually involving a metal implant of some kind). A large industry has grown up around joint replacement, partly because it is so effective.

But the same conceptual model leads to the conclusion that 'conservative treatment' of osteoarthritis is ineffective, and from this, it is a small step to conclude that conservative treatment is simply not beneficial. In practice, most people experience considerable inconvenience, suffering, and loss of income over one or two decades prior to joint replacement, and there is no effective treatment for OA during this long and debilitating period when inactivity, isolation and depression are all too frequent. So-named 'conservative treatments' may be able to reduce the high personal costs of this disease, but one barrier to the development of

conservative treatments is conceptual. In their review of osteoarthritis, Vincent and Watt (2018) neatly sum up the core issue:

> Many clinicians regard OA as being simply a disease of 'wear and tear,' and by implication one in which disease modification is not possible. Such prejudices have led to significant academic apathy in this disease that is reflected not only in our poor understanding of disease pathogenesis, but also in the failure to classify the disease with greater precision and to develop sensitive tools for diagnosis and prognostic assessment.

Another barrier to the development of conservative treatments is the type of business model required to support conservative treatments. It is a truism to observe that much of the modern medicine is geared to acute care, rather than geared to disease prevention or chronic care models—but this should not diminish the importance of either prevention or chronic care. With healthcare systems geared to acute care, conservative treatments almost inevitably play a minor role among the therapeutic options in most advanced healthcare systems around the world today. With many vested interests within the healthcare systems, weak consumer knowledge and little bargaining power in their dealings with acute care specialists, potentially health insurers are the most likely vested interest group capable of leading a rebalancing of healthcare systems toward the prevention and conservative management of chronic diseases. Health insurers already reduced the premiums and so reward those who lead certain lifestyles, but if health insurers realized the potential advantages, quite possibly health insurers might in the future offer funding for 'integrative research' of the type presented here.

In this book, we argue for a new, deeper functional understanding of normal cartilage that is offered by the simple 'use and replace' model of cartilage described above. The theme throughout the book is that cartilage is not a static tissue, rather, it is a dynamic tissue that adjusts and remodels itself throughout the life to meet the changing environmental demands placed upon it. Unsurprisingly, articular cartilage is much like all tissues in the body [and yes, even brain tissue remodels, and in some parts of the brain, there is even neural cell proliferation (Boldrini et al. 2018; Sahay et al. 2011; Spalding et al. 2013; Pilz et al. 2018)]. However, articular cartilage tissue remodeling occurs over a longer timescale than many other tissues in the body (and often on a timescale much longer than busy modern lifestyles allow us!). For in the absence of a deeper understanding of cartilage tissue physiology, we are severely constrained in the formulation of strategies for maintaining healthy cartilage and for treating diseased cartilage. Without a deeper understanding, palliative care followed by joint replacement is all but inevitable. And in the absence of an integrated framework that explains how the cartilage 'works' as a tissue, discovery-based science is left to find new therapies through serendipity. But we know that ignorance of basic tissue and cell physiology is demonstrably an inefficient and very costly way to advance clinical science.

For these reasons, we aim to accelerate the process of developing a logical framework for understanding cartilage tissue by attempting to describe how we believe cartilage successfully operates as a tissue over a lifespan. To develop a more complete and hopefully more useful integrated framework for cartilage physiology

we have to extrapolate beyond the limited experimental data currently available. The conceptual frameworks presented here can be interpreted as an extended hypothesis. We adopt a hypothetico-deductive approach, which enables us to formulate a more subtle and complete understanding of cartilage physiology that has been attempted heretofore. The risk in this approach is overreach. But the potential reward of this approach is that it offers new conceptual frameworks that are essential for the development of integrated models of cartilage behavior. By taking this riskier approach, we hope that new ways to rationally modify tissue responses to preserve cartilage tissue or reduce its rate of degradation will suggest themselves naturally to readers. And using this approach, basic biomedical science can be more rapidly and precisely be applied to clinically important questions.

To both interpolate between sparse data sets and extrapolate beyond existing data sets, we use our backgrounds in systems modeling of cartilage and related tissues, guided by our grounding in various fields of engineering, physics, chemistry, materials science, poroelasticity, and reactive transport. We freely apply engineering, physics, and chemical principles in the context of cartilage, gleaned from our experiments and a wide re-reading of the cartilage literature. Such knowledge helps to constrain the 'space' of acceptable solutions. We prefer a 'Bayesian approach' to inference (http://en.wikipedia.org/wiki/Bayesian_inference). In other words, our prior beliefs, developed in the engineering sciences, have strongly shaped our interpretation of the literature in order to identify what we believe is the most appropriate a priori models for cartilage (i.e. those interpretations consistent with established principles in the major fields of endeavor noted above). This book can then be interpreted as an attempt to develop rational a priori models (or 'constructs' as some prefer to call them) to progress our conceptual understanding of cartilage physiology.

For a 'Bayesian approach' to inference, such a priori models are crucial because they provide the basis for the interpretation of new data sets. For a Bayesian approach to science, knowledge is cumulative, with a posteriori models becoming a priori models in the next iteration. This fits nicely with an engineering approach to developing analytic and computational models of systems. This Bayesian approach may be contrasted with a 'frequentist approach' to inference, adopted by many scientists, where either a true or false inference is drawn on the basis of 'statistical tests' on data: see (http://en.wikipedia.org/wiki/Frequentist_inference). In this frequentist approach to science, a priori knowledge often plays no formal role in inference, as the underlying pattern is to be distinguished from 'random events' on the basis of statistical tests that have a pre-determined power and significance levels to control type I and type II errors. But the academic landscape is finally beginning to change, and Bayesian approaches are now becoming well-established, even in Statistics Departments, over the last two decades.

Of course, this does not mean that the extended hypothesis on cartilage physiology developed here is necessarily right—by definition, a Bayesian approach dynamically weights and updates hypotheses (a priori knowledge) given the new evidence and/or new beliefs. Explaining the scientific process, McIntyre (2017) comments on 'multilevel thinking':

> Similarly, the most powerful, versatile, and innovative scientific thinking uses varieties and hierarchies of models including precise mathematical models and computer codes in partnership with "conceptual" models that are fuzzier, more intuitive, and often not overtly mathematical—perhaps expressed more in words or pictures or even in intuitive feelings. Quite often, the intuitive models are wrong or partly wrong to begin with, until modified as a result of crosschecking against something more precise.

Precisely, the approach we believe is most beneficial and so efficient given our current state of knowledge. Our a priori 'multilevel' conceptual models of cartilage integrate many separate hypotheses (some of which are reasonably well established in the existing research literature), while developing others that are more speculative. This approach leads to some obvious conclusions about cartilage (often with the usual response by biologists being 'of course!'), along with some surprising conclusions and the seemingly inevitable responses from biologists and clinicians: 'do a (frequentist-designed) animal study or clinical trial to test its significance!'. But doing an animal study or clinical trial is not always possible or advisable. While some frequentist inference is clearly necessary (particularly, in the discovery-led phase of science), to rely on it as much as we do today with decades of research behind us leads to an inefficient and very costly way to progress science from our current state (e.g. many experiments duplicate previous work, or identify false leads that are pursued at considerable cost of limited time and resources) (Ioannidis 2005; Ioannidis 2016). Indeed, for complex systems, application of standard statistical tests can lead to unacceptably high rates of false positives and false negatives (e.g. see the NAS publication: *The Irreproducibility Crisis of Modern Science Report* https://www.nas.org/articles/nas_launches_new_report_the_irreproducibility_crisis). On the other hand, concepts and theories can organize and give meaning to large swathes of experimental data and help flag false interpretations, and by these means increase information gain and improve research efficiency.

Hopefully, government-sponsored funding bodies will come to realize and acknowledge these real costs to the research enterprise of 'business as usual' and begin to reduce their reliance on discovery-based biomedical research, rebalancing toward a more appropriate mix of theoretical biology and experimental research that reflects the maturity of biomedical and clinical sciences today. In the future, we expect funding bodies will offer greater support to research that organizes existing knowledge and research that has the goal of embodying the cumulative knowledge of that discipline area, providing a firmer platform for new knowledge creation.

While an essential part of organizing knowledge is about developing reductionist databases (e.g. UniProt), we need to aim higher in our 'knowledge organization' endeavor and improve the fidelity of both conceptual and quantitative models of biological systems. While the politics of negotiating change is tortuous, such a change in scientific methodology is all but inevitable as disciplines advance. Indeed, history shows science practiced in its mature phase is led by theory rather than by discovery (e.g. the Higgs boson was discovered theoretically—by Peter Higgs in the 1960s—as a particle in the Standard Model for particle physics. This theoretical prediction was confirmed experimentally in 2013 using the Large Hadron Collider at CERN). Interestingly, signs of a transition in the practice of

biomedical and clinical sciences can be found at the US FDA, which is beginning collaborative agreements to develop new computational tools to 'virtually test' new drugs and medical devices (e.g. heart pacemakers) as part of their approval process (http://www.3ds.com/products-services/simulia/solutions/life-sciences/the-living-heart-project). Perhaps surprisingly, it is often regulations that most influence the pace of change, rather than rational debate about research funding models.

Despite such cultural differences in the practice of research, we believe the extended hypotheses championed here can provide a useful foundation for thinking about and formulating rational, coherent a priori functional models of cartilage physiology. Adopting this approach can help both wet-laboratory and computational biologists alike and eventually help speed translation into a range of rational therapies employed in the clinical sciences. Where possible, we explain the relevance of our extended hypotheses to clinical science, but in the near term, we expect that the extended hypotheses developed here will be most useful in interpreting new and existing experimental data, in formulating new testable hypotheses, and in helping to direct new experimental and theoretical studies toward the most relevant areas of missing information. We both hope and expect that the approach developed here can be built upon (and of course be modified over time) and that this process will yield additional value from the many billions of research dollars already invested in the cartilage research, as well as yield greater value from the expensive experiments and clinical studies to take place in the future.

This book is organized in the following way:

In Chap. 1, we introduce articular cartilage biology consistent with that found in the literature. It explains what cartilage is, how it works as a biocomposite material, how it deforms, and how cartilage depends on synovial tissue for its nutritional needs.

In Chap. 2, we explain how an aggrecan-collagen network forms in vivo and how they work together to create a functional tissue suited to its in vivo mechanical role. Under repeated cyclic loads, aggrecan, collagen and dozens of extracellular matrix components are continually damaged and so have to be repaired. A key focus is how aggrecan, hyaluronan, the collagen network, and the chondrocyte population together maintain homeostasis of the tissue in vivo. This helps establish a view of articular cartilage as a responsive tissue that can continually adjust to its changing circumstances. While much of this chapter is well supported by the research literature, we touch on some aspects that are more speculative (i.e. meaning there is paucity of direct experimental evidence to support them (e.g.) (i) collagen homeostasis, (ii) radial zonation of the extracellular matrix around chondrocytes, and (iii) ongoing chondrocyte proliferation and migration), but we attempt to make sense of them based on our knowledge of cartilage and in light of our understanding of physical and biological sciences.

In Chap. 3, we propose that articular cartilage is able to adapt to significant changes in its environment. This new view of cartilage is more speculative and really forms an 'extended hypothesis' that attempts to answer some of the key unknown questions about cartilage: (i) From where does the superficial zone in adult articular cartilage originate, (ii) what are the failure modes in articular cartilage, and (iii) is aggrecan and collagen really shed to the synovial fluid and what role does this play in maintaining articular cartilage health?

In Chap. 4, we explain the technical basics of our current understanding of cartilage lubrication. Clearly, lubrication of the joint is very important functionally, for without adequate lubrication, cartilage surfaces roughen, wear rates increase, and the cartilage tissue may progress toward osteoarthritis. We distill a complex set of ideas and principles into something that is coherent using the principle of effective stress and show that that weeping lubrication and a type of boosted lubrication together ensure articular cartilage minimizes wear.

Chapter 5 explains a number of 'systems approaches' for understanding biological tissues. This chapter contains a reasonably detailed account of the cell–cell signaling systems operating in cartilage and a briefer account of the intracellular signaling systems operating inside chondrocytes. It also contains higher-level conceptualisations drawn from other disciplines to aid our understanding of cartilage tissue at a system level.

Chapter 6 explains in detail the meaning of osmotic pressure, Donnan osmotic pressure, and effective stress. We explain the relationships between physical chemistry and articular cartilage mechanics. The chapter begins the process of building a rational, quantitative framework from first principles, which complements biological methods of cartilage investigation.

Chapter 7 presents a large deformation, continuum framework for quantitative modeling of cartilage, using poroelastic modeling as a starting point. This model can be extended as far as a research question might require (e.g. to poro-visco-elasto-plastic models with or without fiber reinforcement with reactive transport).

We hope you enjoy joining us on this demanding but exciting journey, and moreover, we hope that this book forms the basis of ongoing thought-provoking discussions about how cartilage functions as a dynamic tissue.

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VIC, Australia — Lihai Zhang
MA, USA — Alan J. Grodzinsky

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