34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Integrating Degenerative Mechanisms in Bone and Cartilage: a Multiscale Approach

Justin W. Fernandez, Vickie B. Shim, and Peter J. Hunter

Abstract—**At the whole organ level, degenerative mechanisms in bone and cartilage are primarily attributed to modifications in loading pattern. Either a change in magnitude or location can initiate a degenerative path. At the micro scale we often see changes in structure such as porosity increase in bone and fibrillation in cartilage. These changes contribute to a reduced structural integrity that weakens the bulk strength of tissue. Finally, at the cell level we have modeling and remodeling pathways that may be disrupted through disease, drugs and altered stimulus from the micro and macro scales. In order to understand this entire process and the roles each level plays a multiscale modeling framework is necessary. This framework can take whole body loadings and pass information through finer spatial scales in order to understand how everyday dynamic movements influence micro and cellular response. In a similar manner, cellular and microstructural processes regulate whole bulk properties and modify whole organ strength. In this study we highlight the multiscale links developed as part of the open-source ontologies for the Physiome Project using the lower limb as an example. We consider the influence of remodeling in (i) anabolic treatments in cortical bone; and (ii) subchondral bone and cartilage degeneration.**

I. Introduction

Numerous computational models have explored musculoskeletal remodeling mechanisms at either the cell level, micro level or macro level (whole organ). There have been limited attempts to link information across these scales. A holistic view is necessary in order to understand the links between these spatial levels. For example, the influence of disease or therapies on musculoskeletal health is best introduced at the cell level. Disease and therapeutic treatments operate by directly or indirectly influencing the bone absorbing cells (osteoclasts) and bone forming cells (osteoblasts). This, in turn, changes the micro bone architecture and the overall continuum strength observed at the whole bone level. In a similar manner, cartilage is comprised of a fluid filled solid matrix with a fibrillated structure that can exhibit different bulk properties based on the health of the fibril organization. Cartilage can vary from a fairly incompressible response over short time loadings to a compressible solid when injury or disease disrupts the architecture that traps fluid. On the other hand, considering the problem in reverse, understanding how whole body biomechanics influences stimulation of mechanosensitive cells can highlight the links between a particular exercise or walking pattern and musculoskeletal maintenance.

The international bone community has identified the web-based open-source computational tools developed for the Physiome Project at the Auckland Bioengineering Institute as "*not currently being exploited by researchers in the bone field, in spite of their immediate opportunities*" [1]. The multiscale modeling framework developed as part of the International Union of Physiological Sciences (IUPS) Physiome Project is used in this study to link the spatial scales of bone and cartilage. We have applied this framework to two musculoskeletal diseases, (i) osteoarthritis and (ii) osteoporosis. In the first application we integrate a particulate method known as 'smooth particle hydrodynamics' (SPH) [3] into the framework to consider the influence of the natural anabolic Lactoferrin [4] on remodeling in cortical bone. In the second application we examine the initiation of osteoarthritis at the cartilage bone interface, which has been suggested as a pathological mechanism [2]. This is linked to a common knee injury, Anterior Cruciate Ligament (ACL) deficiency, which initiates proinflammatory mediators as a possible pathway to osteoarthritis at the bone-cartilage junction.

II. Methods

The whole organ (macro) level is the starting point for this work with a subset of geometries (lower limb and knee model) adapted from the AnatML database of the Physiome project [5] and highlighted in figure 1. We have developed methods to scale these anatomically-based models to subject-specific anthropometry using free-form deformation techniques [6]. A spatially varying density and young's modulus is fitted from CT images using the CT number and a grey-scale mapping. These models contain supporting soft tissues, muscles, ligaments, tendons and articular cartilage. In particular the muscles have a 3D fibre orientation that has been derived from Diffusion Tensor Imaging (DTI). DTI is a Magnetic Resonance Imaging (MRI) modality used to track the diffusion of water in tissue. It is typically used to perform tractography of neuronal pathways and cardiac tissue fibers. In this study we have performed DTI of lower limb human skeletal muscle to characterize the 3D fibrous architecture. This information was then used to map the 3D spatially varying fiber information as a field onto anatomically-based muscle models. The individual muscles were fitted to a

J. Fernandez is a Research Fellow at the Auckland Bioengineering Institute, The University of Auckland, New Zealand, 1010. (e-mail: j.fernandez@ auckland.ac.nz).

V. Shim is a Research Fellow at the Auckland Bioengineering Institute, The University of Auckland, New Zealand, 1010. (phone: +64 9 373 7499 ext 86932; fax: +64 9 367 7157 ext 82657; (e-mail: v.shim@ auckland.ac.nz).

P. Hunter is a Professor and Director of the Auckland Bioengineering Institute, The University of Auckland, New Zealand, 1010. (e-mail: p.hunter@ auckland.ac.nz).

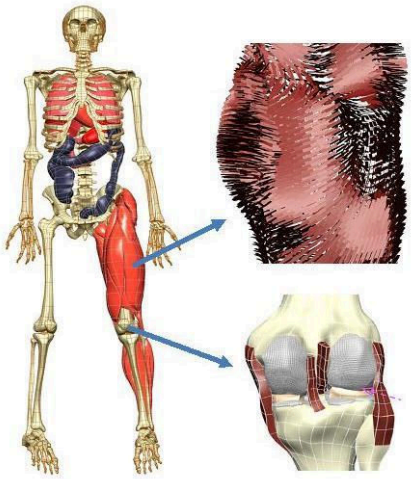

Figure 1: Complete human musculoskeletal model showing quadriceps fibre information from diffusion tensor imaging and detailed knee joint model.

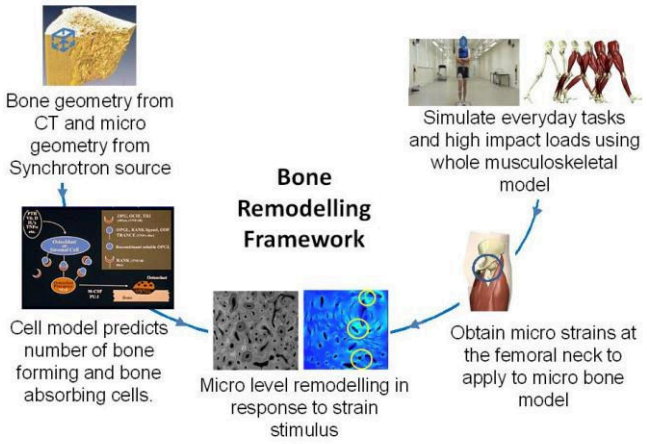

Figure 2: Multiscale musculoskeletal modelling framework linking muscle loads from gait to micro loads and cell models.

single continuum for computational efficiency, where a single field captured the fiber directions of individual muscles in the lower limb. The whole organ models are described using high-order cubic Hermite elements suitable for capturing the topology of complex musculoskeletal structures accurately. These geometries are continuous in their first derivatives so can describe fields across nodes smoothly and the continuity of the surface normal makes the models highly suitable to frictionless contact mechanics and sliding muscles. The deformation of soft tissues are referred to a microstructural curvilinear coordinate system and the constitutive laws that describe the stress-strain behavior of soft tissue are also referred to this anatomically based material coordinate system, adapted from the DTI information. Muscle contraction is described in 3D along the length of these spatially varying fibers using a calcium-tension relation adapted from a Hill model [7].

At the micro level the models were generated from imaging data of a cadaveric human femur using a synchrotron source. The averaged strains at integration points from the whole body model are used as boundary conditions for the micro model. The sample size was $1mm^3$ with a voxel size of 2 microns. The geometry captured the micro-architecture and bone mineral density. We built two models; (i) a cube of bone from the femoral neck modeling the Haversian canals using the SPH framework suited to handling highly evolving geometry; and (ii) a cube of bone representing the subchondral bone, zone of calcified cartilage (ZCC) and cartilage modeled using micro finite elements.

The cell models were adapted from the CellML repository [8]. These are coupled to the micro-level model to drive the amount of growth, resorption or damage in response to strain stimuli. This, in turn, drives tissue adaptation and modified micro architecture. The bone cell model based on the RANK-RANKL-OPG pathway [9] predicts the number of osteoblasts (to deposit bone) and osteoclasts (to absorb bone). The cartilage cell model predicts damage [10] and gives a quantitative description of the nuclear factor-kappa B signaling cascade from micro mechanical stimulus. Peak cartilage strains were used as excitation of the protein complex IκB kinase, which activates the nuclear factor-kappa B pathway, leading to induction of a series of proinflammatory gene expressions.

The models are two-way coupled in that they use localized micro stress from a whole knee model as boundary conditions to drive micro bone remodeling (with remodeling rates from the cell model). In return, the modified micro models have their remodeled material properties homogenized where the applied stress to the representative micro model is the average or macro stress. This equivalent macro stress is then mapped back to the whole knee model.

In the first application, we introduced the influence of the natural anabolic agent (Lactoferrin), which has been shown to increase bone growth by increasing the number of osteoblasts (bone building cells) and inhibiting osteoclastogenesis (the precursor to bone resorbing cells). We modified the RANK-RANKL-OPG pathway to account for these changes and did not alter any other pathways. For example, we did not modify the mature osteoclasts, only the precursor cells. Figure 2 outlines the approach used showing gait analysis of the lower limb for computation of muscle force estimates from kinematics and kinetics. Detailed stresses of the joints (highlighted is the femoral neck) are used to provide boundary conditions to a micro model of bone architecture, taken from a synchrotron source. Cell models describing remodeling pathways are used to calculate spatial remodeling rates linked to micro stimulus sensed by osteocytes.

In the second application, we used the same framework but the whole body loadings were taken from around the knee acting on articular cartilage. We simulated both healthy and an ACL deficient (ACLD) case. In the healthy knee a peak contact load of 1.1 Body Weight (BW) was located centrally on the tibial articular cartilage, whereas the load was translated to the thinner posterior region of the tibial

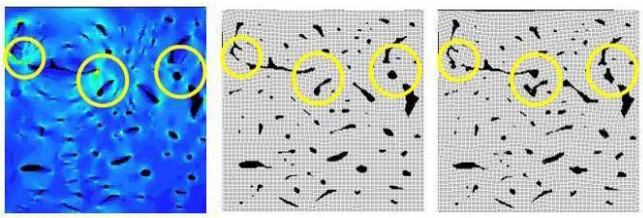

Figure 3: (left) Cortical bone strain pattern in 69 year old subject; (middle) remodeling with Lactoferrin influence showing reduced bone absorption; and (right) remodeling with no Lactoferrin influence showing increased bone absorption and pore merging.

articular cartilage in the ACLD case. This is suggested as a possible cause of osteoarthritis due to loading in the ACLD knee being centered on different regions in the cartilage that do not normally support load. The model consisted of cartilage, calcified cartilage and subchondral bone. To simulate remodeling in subchondral bone we assigned normal gait as the homeostatic equilibrium state. In this condition both bone and cartilage are maintained and no modeling or remodeling occurs. We then simulated the ACLD case to generate altered strains and the difference with the homeostatic case was used to initiate bone remodeling. This, in turn, initiated a pro-inflammation cartilage map in regions of articular cartilage that do not normally cope with high strain.

III. RESULTS

In the first application, remodeling in a 69 year old cadaveric bone is shown in figure 3. The Haversian canals have a state of strain around the pores specific to the subject's configuration leading to zones of low strain (strain shielding) in between the Haversian canals (black pores). This condition has been shown to lead to pore merging, which weakens the integrity of bone. The Von Mises strain pattern in figure 3 (left) is the mechano-stimulus for remodeling to occur. Figure 3 (middle) shows simulated remodeling with Lactoferrin being introduced to increase the proliferation of osteoblast numbers and reduce pre-osteoclast numbers. There is very little change in the osteon pattern showing that remodeling has been stagnated. Figure 3 (right) shows simulated remodeling over the same period of time without Lactoferrin where the rate of bone removal is higher than bone deposition. The Haversian canals start to grow forming long fragmented structures. These structures merge forming larger pores that contribute to the reduction in bone strength. The bone configuration in figure 3 (right) shows signs of buckling under this load.

In the second application, the knee joint micro bone-cartilage model was deformed by ~100 μm in response to whole body loads. Figure 4 shows the modeling setup with whole loads creating deformation in a micro model of the cartilage interface, leading to peak strains in bone, remodeling structures and production of inflammation over the femoral cartilage condyles. The subchondral bone was remodeled with red regions showing bone growth and dark blue regions bone resorption. There was reduction in pore

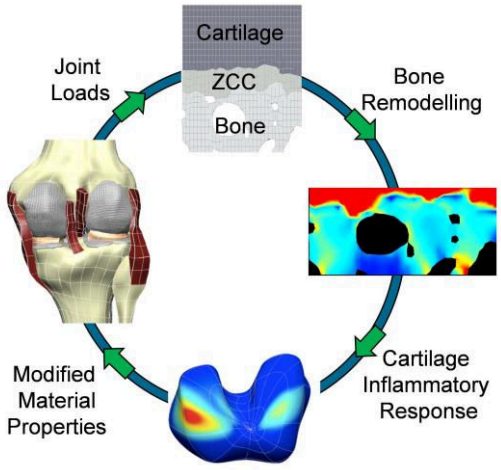

Figure 4: Bone and cartilage remodeling leading to increased cartilage inflammation on the medial femoral condyles.

size and a thickening in the bone tide, which reduced cartilage thickness. The tide was also noted to become more irregular and similar to structures observed in pathologic cartilage. The peak cartilage strains increased giving rise to a prediction of inflammatory cytokines in the ACLD knee, especially on the medial femoral condyles. The medial condyle has the highest loading as most of the load is directed along the medial side of the knee. Even after the knee was returned to a healthy state by simulating an ACL reconstruction, the strains continued to be higher in the ACLD knee due to the remodeled bone.

IV. DISCUSSION

The presented modeling framework is a web-based open-source repository of models, which contributing scientists can easily use and disseminate their findings. Furthermore, this framework can employ different numerical methods at different scales. For example, while the macro and micro models both employed finite elements in this study, the micro model could easily employ a meshless method like smooth particle hydrodynamics, which can easily handle complicated evolving geometries during remodeling. We have demonstrated this framework by (i) showing the possible influence of the anabolic Lacotoferrin on micro architecture and bone integrity; and (ii) showing how changes in loading pattern induced by injury (an ACLD knee) can lead to a degenerative breakdown in cartilage health. These modeling concepts can be used to both explore hypotheses and provide explanations for changes only observed at the whole organ level.

In the case of the Lactoferrin application we showed that the anabolite had a stagnation effect on remodeling. Given that we have chosen an arbitrary dosage level the effect of Lactoferrin may have slowed or even added bone. The main benefit is that with less osteoclasts available bone structure is maintained longer. Secondly, when the average strength was measured the Lactoferrin bone was enough to maintain the shape of the specimen, while the control started to buckle. At the femoral neck, this could potentially lead to catastrophic failure. It may also have implications on bone regeneration

strategies by suggesting likely sites of bone growth to protect the geometrical shape. It appears that bone needs certain architecture to prevent collapse and understanding where bone can best be grown may assist with preventing endocortical expansion in bone also known as trabecularisation. Once this gets to a critical level then degeneration is impossible to prevent.

In the second application the findings in this study may suggest a path from altered subchondral bone loading to a degenerative cycle in the cartilage matrix. Furthermore, the subchondral bone expansion and formation of bony spurs are early signs of osteoarthritis. When altered loads were applied, the subchondral plate adapted. Therefore, loading due to misalignment plays a role in subchondral bone changes. Hence, cartilage thinning or subchondral bone stiffening of the cartilage may not be as significant as site of applied load as in the case of ACLD [11]. The current implementation examines a purely biomechanical link between cartilage and bone, however, vascular channels and the irregular geometry at the interface may facilitate molecular transport. The next step of this work is to directly link feedback of the modeling pathways between the bone and cartilage cell models. This is consistent with the proposal that irregular geometry provides a mechanism of molecular diffusion from bone to cartilage [12].

This framework has a number of limitations as presented here. First, the loads are only driven by motion capture from gait at self-selected speed. Other dynamic tasks may have different effects such as from running, stair climbing or other non-cyclic events, which are known to be more bone forming [13]. Moreover, ACLD subjects may walk with a compensatory-gait, which was not considered here. The current setup has used the same micro model at different spatial locations of the knee but this can easily be adapted to the spatially varying micro-structure with more imaging data. Furthermore, there is no real evidence to say that Lactoferrin operates via the RANK-RANKL-OPG pathway. Our observations are implemented based on osteoblast and osteoclast responses [4]. More experimental data is necessary to validate the predicted structural changes at the micro level. While the results are consistent with imaging studies they require time-lapsed microstructural imaging to validate the predicted remodeling changes in bone. This is turn would require model tuning to the classic ‘mechanostat’ curve on a subset of samples and validation on the remainder.

V. Conclusion

This study has demonstrated how whole body loadings can be used as boundary conditions for exploring different degenerative mechanisms in bone and cartilage. We have chosen osteoporosis in cortical bone and osteoarthritis at the knee to highlight this work. Knee joint loads for the healthy knee can be perturbed to explore slow walking, stair gradients and shuffle gait (in the elderly) as future work. The Physiome Project markup languages were used to link the different spatial scales and provide a platform for model storage and dissemination [14, 15]. We are also able to incorporate different numerical methods together such as finite element methods at the whole organ level, smooth particle hydrodynamics at the micro level and ordinary differential equations at the cell level.

Acknowledgment

The authors acknowledge an Aotearoa Bioengineering Fellowship sponsored by the Robertson Foundation and HRC grant (11/428) awarded to J Fernandez; and HRC grant (11/496) awarded to V Shim.

References

[1] D. Webster and R Müller, "In silico models of bone remodeling from macro to nano-from organ to cell," *WIREs Syst Biol Med* vol. 3, pp. 241–251, 2011.

[2] R. M. Aspden, B. A. Scheven, and J. D. Hutchison, "Osteoarthritis as a systemic disorder including stromal cell differentiation and lipid metabolism," *Lancet,* vol. 357, pp. 1118-20, Apr 7 2001.

[3] P Cleary and R Das, "Computational and Modelling Aspects of Inelastic Media. The Potential for SPH Modelling of Solid Deformation and Fracture," *IUTAM Symposium on Theoretical,* vol. 11(6), pp. 287-296, 2008.

[4] D Naot, A Grey, I Reid et al., " Lactoferrin–a novel bone growth factor," *Clin Med Res.* vol. 3(2), pp. 93-101, 2005.

[5] P. Hunter, N. Smith, J. Fernandez, and M. Tawhai, "Integration from proteins to organs: the IUPS Physiome Project," *Mech Ageing Dev,* vol. 126, pp. 187-92, Jan 2005.

[6] J. W. Fernandez, P. Mithraratne, S. F. Thrupp, M. H. Tawhai, and P. J. Hunter, "Anatomically based geometric modelling of the musculo-skeletal system and other organs," *Biomech Model Mechanobiol,* vol. 2, pp. 139-55, Mar 2004.

[7] J. W. Fernandez and P. J. Hunter, "An anatomically based patient-specific finite element model of patella articulation: towards a diagnostic tool," *Biomech Model Mechanobiol,* vol. 4, pp. 20-38, Aug 2005.

[8] P. J. Hunter and T. K. Borg, "Integration from proteins to organs: the Physiome Project," *Nat Rev Mol Cell Biol,* vol. 4, pp. 237-43, Mar 2003.

[9] P. Pivonka, J. Zimak, D. W. Smith, B. S. Gardiner, C. R. Dunstan, N. A. Sims*, et al.*, "Model structure and control of bone remodeling: a theoretical study," *Bone,* vol. 43, pp. 249-63, Aug 2008.

[10] J. Nam, B. D. Aguda, B. Rath, and S. Agarwal, "Biomechanical thresholds regulate inflammation through the NF-kappaB pathway: experiments and modeling," *PLoS One,* vol. 4, p. e5262, 2009.

[11] T. P. Andriacchi, P. L. Briant, S. L. Bevill, and S. Koo, "Rotational changes at the knee after ACL injury cause cartilage thinning," *Clinical Orthopaedics and Related Research,* pp. 39-44, Jan 2006.

[12] R. J. Lories and F. P. Luyten, "The bone-cartilage unit in osteoarthritis," *Nat Rev Rheumatol,* vol. 7, pp. 43-9, Jan 2011.

[13] T. P. Andriacchi, S. Koo, and S. F. Scanlan, "Gait Mechanics Influence Healthy Cartilage Morphology and Osteoarthritis of the Knee," *Journal of Bone and Joint Surgery-American Volume,* vol. 91A, pp. 95-101, Feb 2009.

[14] G. R. Christie, P. M. Nielsen, S. A. Blackett, C. P. Bradley, and P. J. Hunter, "FieldML: concepts and implementation," *Philos Transact A Math Phys Eng Sci,* vol. 367, pp. 1869-84, May 28 2009.

[15] D. Nickerson and P. Hunter, "Using CellML in computational models of multiscale physiology," *Conf Proc IEEE Eng Med Biol Soc,* vol. 6, pp. 6096-9, 2005.