An innovative approach to computational simulation of the functional characteristics of poroelastic materials illustrated with diffusion into articular cartilage

***†Jamal Kashani[1], Lihai Zhang[2], Yuantong Gu[1], and Adekunle Oloyede[1,3]**

[1]School of Chemistry, Physics and Mechanical Engineering, Science and Engineering Faculty, Queensland University of Technology, Brisbane, QLD, Australia.
[2]Department of Infrastructure Engineering, The University of Melbourne, Melbourne, VIC, Australia.
[3]Department of Mechanical Engineering, Elizade University, Ondo State, Nigeria.

*Presenting author: jamalkashani@gmail.com
†Corresponding author: jamalkashani@gmail.com

Abstract

Collecting functional quantitative intra matrix data in experimental samples of articular cartilage is still challenging due to its delicate complex heterogeneous structure in which constituents are intermingled right up to the ultramicroscopic level. Any attempt to insert a transducer inside this material via piercing would damage the structure leading to unrepresentative data. Traditional non-invasive methods are technically difficult for obtaining precise functional data. This paper presents a novel computational approach, using the agent-based concept, to create a 'virtual microscope' that can be used to provide functional information throughout a heterogeneous complex medium, such as articular cartilage, in silico. The method involves two-dimensional cellular automata, a hybrid agent, new local agent rule and a traditional neighbourhood rule. The hybrid agent combines constituents of the system (solid and fluid) where the local rule determines intra-agent evolution. The proposed approach was validated by simulating diffusion into a model of cartilage matrix that was characterized with anisotropic permeability. The simulated results were then compared to magnetic resonance imaging (MRI) data. Spatial map of diffusion at different times and depth-dependent diffusion profiles were provided in colour-coded pictures. Qualitative and quantitative comparison of results with experimental data shows that this novel approach can accurately and efficiently represent diffusion of fluid into the cartilage matrix. It demonstrates the potential of hybrid agent and local rule to enhance agent-based techniques for porous materials and other areas of research. We conclude that the ability to establish a "virtual microscope" offers a viable opportunity for in-silico experiments that can extend our knowledge beyond the capability of traditional laboratory experiments, while also facilitating information for creating models for numerical methods such as finite element analysis, meshless and smoothed particle hydrodynamics. The combination of the approach presented here with conventional simulation methods can provide a framework for modelling and analysis of complex porous materials. We concluded that the hybrid agent and local rule concept introduced in this paper can also be potentially exploited to enhance many of the existing agent-based techniques.

Keywords: Articular cartilage, hybrid agent, local and global rules, porous materials, agent-based method

Introduction

Articular cartilage is a semipermeable porous biomechanically functional material that is saturated with an osmotically active fluid which occupies between 65 and 80 %, proteoglycans and collagen components that constitute its solid skeleton occupying 5-10% and 15-22% respectively of its matrix [2]. These components are intermixed right up to the molecular level [3] such that the tissue is highly heterogeneous and anisotropic in nature [4]. Quantitative observation and understanding of the underlying mechanisms of articular cartilage's functional characteristics at the microscopic and submicroscopic scales is still a major challenge due to the non-phasic nature of the tissue and the complex interactions between its components. Any physical interference, such as probing the matrix with a transducer via piercing can destroy the articular cartilage structure and lead to an unrepresentative tissue in experimental analysis. As a result, classical laboratory experiments are arguably deficient in their ability to provide functional information such as fluid dynamics with simultaneous osmotic activities which plays a significant role in the mechanical function of the tissue [5, 6].

The ability to probe the real time response of articular cartilage during function can provide a view beyond experimental curve-fitting that can only provide an estimated range of physical properties of the tissue [7]. Non-invasive methods, i.e. magnetic resonance imaging (MRI) and computed tomography (CT) scan, have been successfully used to obtain intra-matrix data from the tissue without disturbing its structure, where different components are distinguished based on their radio-densities or radio frequency signals contrast [8-11]. External contrast agents have been applied with MRI techniques to observe function-related properties of articular cartilage such as diffusion [1, 12, 13], however, it is still difficult and technically challenging to obtain accurate data such as time-varying diffusion and fluid percolation characteristics during deformation [14].

Methods based on continuum mechanics and physical laws have been developed to describe the behaviour of porous materials with respect to their phenomenological characteristics under known imposed external conditions [15, 16], while mechanical theories have also been employed to establish governing equations for cartilage behaviour where the tissue was described as a porous media or mixture [17-20]. These are usually represented as differential equations that determine characteristics of the medium as a function of parameters [21] and physical laws, e.g. Darcy's law. However, the solid skeleton and fluid components intermingle right up to the ultramicroscopic molecular level [3], leading to extremely complex responses that require a different approach beyond those available with current mathematical models and traditional experimental techniques. A close scrutiny of the results of such theoretical models demonstrates that they are inadequate for explaining the mechanisms behind observed material or system responses of this important tissue [22-24].

Agent-based methods (ABM) have recently improved capacity to simulate complex systems' behaviours [25, 26]. ABM is suitable for capturing complex emergent phenomena in which the "whole" seems to be more than the sum of its components because of the intricate interactions between the components [27, 28]. In our opinion further elucidation of the behavior of articular cartilage requires agent-based computational simulation, especially if we were to obtain critical insight into the micro-mechanisms underlying its complex responses under external stimuli. In this paper, we present a novel agent-based approach using an enhanced agent (hybrid agent) with local and global rules [29] that can be used to develop representative structural model of this tissue where the interactivities of the hybrid agent and

the neighbourhood rules provide a "virtual microscope" into the internal working of the system to provide critical knowledge in the area of cartilage biomechanics. This methodology would provide spatial and temporal functional data that could then facilitate other models such as finite element, mesh free, course-grained particle and smooth particle hydrodynamics. The method described below is a preliminary examination of the concept of the hybrid agent and use of a combination of local and global neighbourhood rules.

Material and methods

Adaptation of the hybrid agent for the articular cartilage

Hybrid agent contains within it the system's elements. It was adopted for articular cartilage in this study where fluid and solid skeleton are considered to be two major constituent components of the tissue. Hybrid agent (cell) consists of both solid and fluid within it, such that it is neither fully solid nor fluid while it can simultaneously exhibit the characteristics of both solid and fluid in time. Evolution of the hybrid agent occurs by changing and updating its solid and fluid proportion. Hybrid agent is also characterised by poroelastic material properties such as porosity and semi-permeability.

The matrix model

A two dimensional (2D) cellular automata (CA) lattice of hybrid cells, consisting of 29 x 46 cells, was employed to represent the extracellular matrix of the cartilage where all the hybrid cells in the lattice are equal and constant size since diffusion does not cause tissue deformation. Therefore a cell can be identified and characterized by the relevant fluid to solid ratio it contains (fs).

The distribution of fs in the lattice was determined based on known layered weight distribution of fluid and solid [30]. In this simulation diffusion was allowed from every direction except at the bottom of the lattice because of the assumed effect of the subchondral bone that results this region impervious. One layer of pseudo cells filled by marked fluid was added to the lattice at the left, right and top sides (figure. 1). This marked fluid penetrates into the lattice via fluid exchange between the pseudo and hybrid cells that represent the boundary of the cartilage matrix. The progression of the time-dependent flow (diffusion) within the matrix was followed by tracking marked fluid. The simulation ends when all initial fluid (unmarked) in hybrid cells has been replaced by marked fluid. A program in Matlab (Mathworks Inc, MA, USA) was developed to simulate the diffusion process over the time steps.

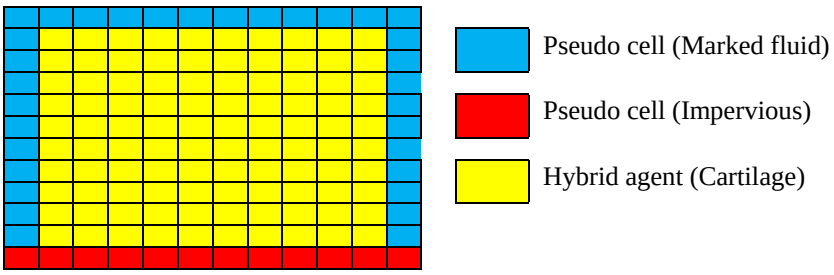

Figure 1: Schematic illustration of the lattice.

Rules

This simulation also incorporates a novel concept of simultaneous combination of local (intra-element) and global (inter-element) responses where intra-agent (local) and neighbourhood (global) rules apply. The local rule determines change within the hybrid cell (intra-agent change) in which the fluid-solid ratio (fs) of the agent changes and the global rule determines inter-agent interactions, e.g. interaction of a cell with its neighbours in the lattice.

Global rule: 2D van Neumann neighbourhood was implemented for interaction between neighbours in which each cell interacts with its orthogonally-adjacent neighbours as demonstrated in Figure 2. Van Neumann neighborhood defines a regular lattice that enables very efficient visualizations of diffusion processes [31].

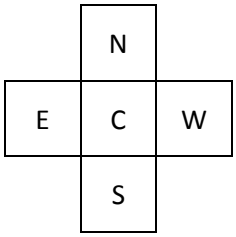

Figure 2. 2D van Neumann neighbourhood. Central cell (cell c) interacts with cells East (E), West (W), North (N) and South (S) at each time step.

Local rule: The following local rules were developed and used in this study:

- Cells are permeable and only fluid, including marked and unmarked, can move in and out of the cell. Since there is no deformation in the matrix, the amounts of fluid types that move in and out are equal.
- The amount of total fluid, marked and unmarked combined, in a cell is constant and does not change over time. Therefore, the ratio of total fluid to contained solid (fs) does not change in a cell. However, the proportion of marked and unmarked fluid may change as a result of fluid exchange.
- Only certain proportion of contained fluid in a cell can move out as a consequence of fluid exchange with neighbours at each time step. This proportion of exchangeable fluid depends on fs of the cell and location of the neighbours. The exchangeable fluid of a cell when interacts with another cell (a neighbour) is estimated as:
  Proportion of exchangeable fluid = k * fs , where k is constant.
  The parameter k depends on cell's neighbour location and indicates the direction of fluid movement. It is assumed that k in the horizontal direction is two times greater than in the vertical direction since hydraulic permeability of cartilage in the axial is half of that in radial direction when the tissue is unloaded [32]. In this simulation, k was set to 0.1 in the horizontal direction and 0.05 in the vertical direction. If a cell exchanges with more than one neighbour, the total exchangeable fluid proportion would be equal to the sum of the individual proportions. For example, when cell C in figure 1 interacts with all of its neighbours (W,E,N and S), the total fluid exchanged equals the sum of fluid exchanged with each neighbour:

$$FEP_C = k_N * fs_C + k_S * fs_C + k_W * fs_C + k_E * fs_C$$

Where, FEP_C is fluid exchange proportion of cell C, fs_C is ratio of fluid to solid content in cell C, and k_N, k_S, k_W and k_E are constant values of k in the N, S, W and E directions which are equal 0.05, 0.05, 0.1 and 0.1 respectively in this simulation.

The results obtained from cellular automata (CA) simulation were compared and validated with experimental data using contrast enhanced cartilage tomography (CECT) and peripheral quantitative computed tomography (pQCT) technique, taken from the literature [1] while 1800 time steps of the CA simulation is equivalent to 12 hours of diffusion. Therefore, each time step corresponds to 2.5 seconds. Width of the experimental samples is 2.5mm while the thickness is 4mm, corresponding to a width to thickness ratio of 0.625 and a simulation lattice dimensional ratio of 29 / 46 (approximately 0.63).

Results

The diffusion patterns of marked agents into the lattice at T=300, 600, 900 and 1800 are presented in figure 3A. The colour-coded map shows the spatial distribution of the ratio of marked fluid to total fluid content within the matrix based on percentage at a given time step. Each colour represents a certain percentage of concentration according to the legend attached to the pictures. Red colour illustrates regions where the initial fluid has almost been replaced by the marked fluid while blue represents areas with very little proportion of marked fluid. Initially (at T=0) concentration of the marked fluid in the lattice was zero (not shown in the figure). Then the marked fluid percolated into the lattice resulting in increased proportion of marked fluid over time (T=300, 600 and 900). The process of diffusion reaches equilibrium after about 1800 time steps, when all initial fluid was replaced by marked fluid.

Figure 3B presents experimental results [1] at time points 2, 4, 6 and 12 hours (left to right), corresponding to time steps in figure 3A. The legend on the right shows contrast agent concentration based on mM in which red illustrate maximum concentration (15 mM) that can be reached at equilibrium state (after 12 hours) and light blue demonstrate zero concentration. In order to compare the experimental with the simulated data, percentage of contrast agent concentration (left legend) was calculated based on ratio of contrast agent concentration to maximum concentration.

Comparison between CA and experimental data (micrographs) demonstrate similar patterns of diffusion into the cartilage. At T=300 and its experimental corresponding time (2 hours), the concentration at area near surface is high and fluid could not penetrate deep during this time. At T=600 (4 hours) concentration of marked fluid (or contrast agent) has been increased significantly up to the centre of the tissue along its thickness while at T=900 which is equal to 6 hours, only the region close to the bone did not undergo a significant concentration change. Both CA simulation and experimental test reached steady state condition at the same time (T=1800, T=12 hours).

The depth-dependent bulk concentration of marked fluid after 600 time steps and corresponding four-hour diffusion of contrast agents [1] (in percentage) are plotted in figure

4. The concentration is maximum at the surface and then drops gradually to about 40% near the bone with almost the same trend for both experimental and CA simulation results. The discrepancy between results in the middle region can be attributed by biological variation of tissue samples. The CA results compare resonably well with experimental data which substantiates the validity of the results of our CA simulation.

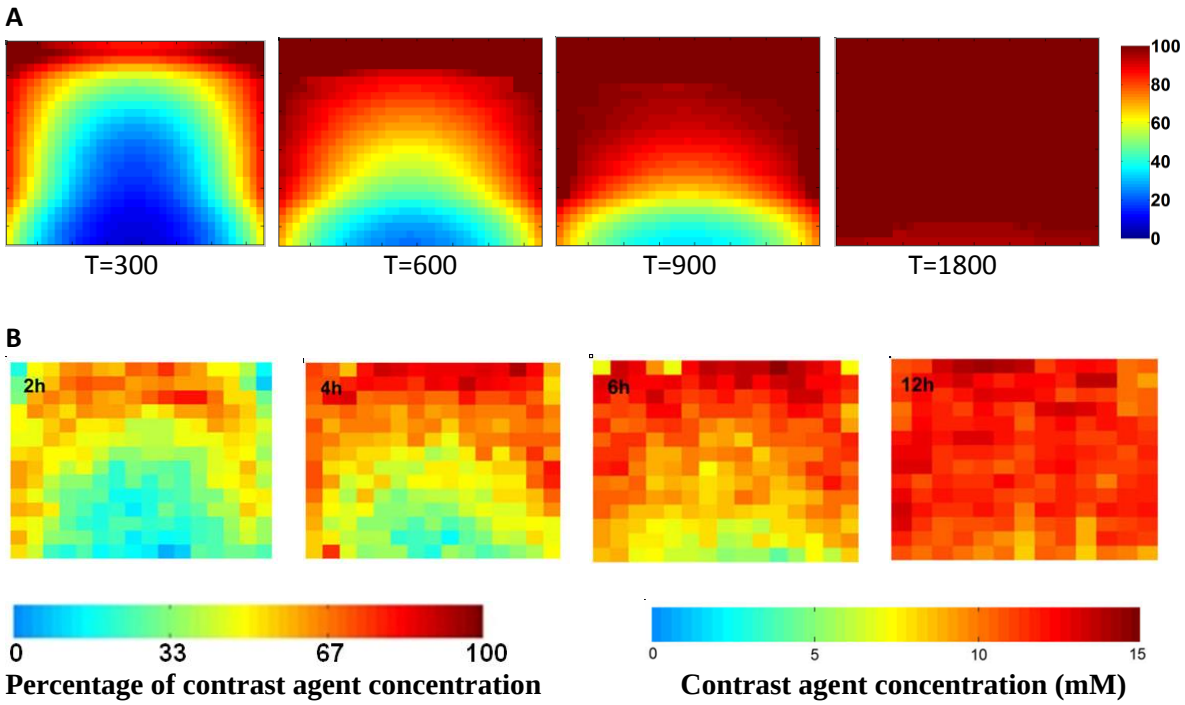

Figure 3. Diffusion into human articular cartilage at different times. A: Percentage of marked fluid in the lattice at time steps 300, 600, 900 and 1800. B: Contrast agent diffusion after 2, 4, 6 and 12 hours immersion [1].

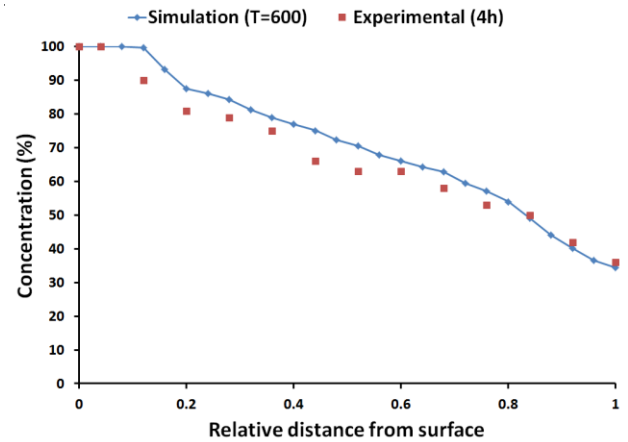

Figure 4. Percentage of depth concentration of marked agent (at T=600) and contrast agent in the human cartilage after 4 hours of immersion [1].

Figure 5 shows depth-dependent bulk concentration percentage of marked fluid collected at various areas in depth including surface, middle (½ thickness depth), ¾ thickness depth and bottom. Overall, the concentrations are lower towards the bottom regions (close to the bone) in time. The curve representing concentration at the surface illustrates that unmarked fluid is replaced by marked fluid rapidly and after about 400 time steps all of unmarked fluid move out of this region. The profile of concentration at the bottom layer follows different trends over time and takes significantly longer time to replace all initial fluid with marked fluid. All curves demonstrate growth of marked fluid over time while the rate of increase over time drops with depth.

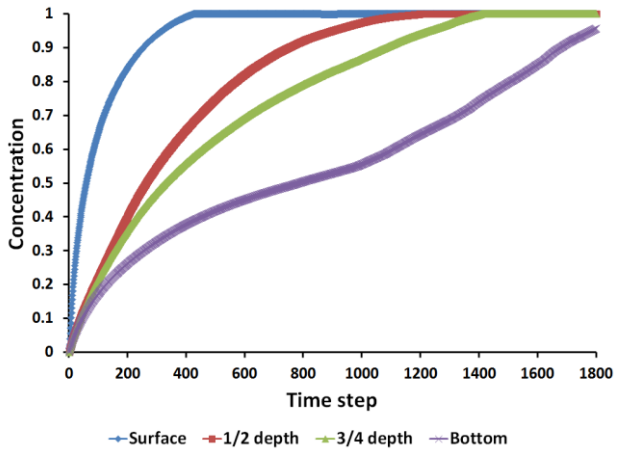

Figure 5. Depth- and time-dependent profiles of marked fluid concentration for surface, bottom, ½ and ¾ thickness depths.

Discussion

In the present paper, an enhanced agent-based approach involving the combination of a novel hybrid element, local intra agent and neighbourhood inter agent rules was applied to articular cartilage. This methodology provided a unique opportunity for investigating the transient intramatrix diffusion of the cartilage. For the first time, diffusion and percolation of fluid into cartilage as a non-phasic material was successfully investigated quantitatively (fig. 3) and qualitatively (figs 4 and 5) using an agent-based method. The comparison of results of this novel approach with corresponding experimental data shows a reasonably close agreement. The success of this approach suggests that it can be used for further investigation of the functional characteristics of loaded and deforming articular cartilage, and also tissues that are affected by degeneration and disease where current methods are technically or ethically inadequate.

The hybrid agent provides us an opportunity to create multi-component structures without any obligation to distinguish constituent components. This capability makes hybrid agent suitable for non-phasic porous materials such as biological tissues and articular cartilage in particular. In addition, as cells (agents) are micro-scale elements of an agent-based structure, hybrid agent, by means of local rule, is capable of intra-agent evolution that provides the feasibility

of studying system change in time at micro-scale level. Therefore, micro-scale spatial and temporal data can be obtained in a manner describable as using a "virtual microscope" in which tissue can be probed unlimitedly. It proposes a viable opportunity for in-silico experiments that can facilitate provision of input data for numerical methods such as finite element analysis, meshless and smoothed particle hydrodynamics. The combination of the approach presented here with numerical methods can prepare a framework for modelling and analysis of complex porous materials where the constituents of the system may be indistinguishable in the manner of known mixtures.

Acknowledgment
Authors would like to gratefully acknowledge the financial support provided by the Queensland University of Technology Postgraduate Research scholarship.

References

1. Silvast, T.S., et al., *pQCT study on diffusion and equilibrium distribution of iodinated anionic contrast agent in human articular cartilage – associations to matrix composition and integrity.* Osteoarthritis and Cartilage, 2009. **17**(1): p. 26-32.
2. Mow, V.C. and X.E. Guo, *Mechano-electrochemical properties of articular cartilage: their inhomogeneities and anisotropies.* Annual Review of Biomedical Engineering, 2002. **4**(1): p. 175-209.
3. Harrigan, T.P. and R.W. Mann, *State variables for modelling physical aspects of articular cartilage.* International Journal of Solids and Structures, 1987. **23**(9): p. 1205-1218.
4. Fox, A.J.S., A. Bedi, and S.A. Rodeo, *The basic science of articular cartilage: structure, composition, and function.* Sports Health: A Multidisciplinary Approach, 2009. **1**(6): p. 461-468.
5. Torzilli, P.A. and V.C. Mow, *On the fundamental fluid transport mechanisms through normal and pathological articular cartilage during function—I the formulation.* Journal of Biomechanics, 1976. **9**(8): p. 541-552.
6. Freeman, M.A.R., *Adult articular cartilage*. 1973, London: Pitman.
7. Grodzinsky, A.J., et al., *The significance of electromechanical and osmotic forces in the nonequilibrium swelling behavior of articular cartilage in tension.* Journal of biomechanical engineering, 1981. **103**(4): p. 221.
8. Hsieh, J. *Computed tomography: principles, design, artifacts, and recent advances*. 2009. SPIE Bellingham, WA.
9. Brown, M.A. and R.C. Semelka, *MRI: basic principles and applications*. 2011: John Wiley & Sons.
10. Nissi, M.J., et al., *T2 relaxation time mapping reveals age- and species-related diversity of collagen network architecture in articular cartilage.* Osteoarthritis and Cartilage, 2006. **14**(12): p. 1265-1271.
11. Kulmala, K.A.M., et al., *Diffusion coefficients of articular cartilage for different CT and MRI contrast agents.* Medical engineering & physics, 2010. **32**(8): p. 878-882.
12. Winalski, C.S. and P. Rajiah, *The evolution of articular cartilage imaging and its impact on clinical practice.* Skeletal Radiology, 2011. **40**(9): p. 1197-222.
13. Stewart, R.C., et al., *Contrast-enhanced CT with a high-affinity cationic contrast agent for imaging ex vivo bovine, intact ex vivo rabbit, and in vivo rabbit cartilage.* Radiology, 2013. **266**(1): p. 141-150.
14. Binks, D., et al., *Quantitative parametric MRI of articular cartilage: a review of progress and open challenges.* The British journal of radiology, 2013. **86**(1023): p. 20120163.
15. Bowen, R.M., *Incompressible porous media models by use of the theory of mixtures.* International Journal of Engineering Science, 1980. **18**(9): p. 1129-1148.
16. Whitaker, S., *Advances in theory of fluid motion in porous media.* Industrial & engineering chemistry, 1969. **61**(12): p. 14-28.
17. Wang, H., *Theory of linear poroelasticity with applications to geomechanics and hydrogeology*. 2000: Princeton University Press.
18. Biot, M.A., *Mechanics of deformation and acoustic propagation in porous media.* Journal of applied physics, 1962. **33**(4): p. 1482-1498.
19. Mow, V.C., et al., *Biphasic creep and stress relaxation of articular cartilage in compression? Theory and experiments.* Journal of biomechanical engineering, 1980. **102**(1): p. 73.

20. Lai, W.M., J.S. Hou, and V.C. Mow, *A triphasic theory for the swelling and deformation behaviors of articular cartilage.* Journal of biomechanical engineering, 1991. **113**(3): p. 245-258.
21. Wolfram, S., *Cellular automata as models of complexity.* Nature, 1984. **311**(5985): p. 419-424.
22. Brown, T.D. and R.J. Singerman, *Experimental determination of the linear biphasic constitutive coefficients of human fetal proximal femoral chondroepiphysis.* Journal of Biomechanics, 1986. **19**(6): p. 474-474.
23. Chen, A.C., et al., *Depth- and strain-dependent mechanical and electromechanical properties of full-thickness bovine articular cartilage in confined compression.* Journal of Biomechanics, 2001. **34**(1): p. 1-12.
24. Oloyede, A. and N. Broom, *The biomechanics of cartilage load-carriage.* Connective tissue research, 1996. **34**(2): p. 119-143.
25. Darley, V., *Emergent phenomena and complexity.* Artificial Life, 1994. **4**: p. 411-416.
26. Helbing, D., *Agent-based modeling*, in *Social self-organization*. 2012, Springer. p. 25-70.
27. Bonabeau, E., *Agent-Based Modeling: Methods and Techniques for Simulating Human Systems.* Proceedings of the National Academy of Sciences of the United States of America, 2002. **99**(10): p. 7280-7287.
28. Odell, J., *Agents and emergence.* Journal of Object Oriented Programming, 2000. **12**(9): p. 34-36.
29. Kashani, J., et al., *A hybrid agent for simulating porous fluid-saturated structures with complex microscale properties.* Submitted to journal of computational material science, 2016.
30. Rieppo, J., et al., *Spatial determination of water, collagen and proteoglycan contents by Fourier transform infrared imaging and digital densitometry.* Trans Orthop Res Soc, 2004. **29**: p. 1021.
31. Edmonds, B. and R. Meyer, *Simulating Social Complexity*. 2015: Springer.
32. Jurvelin, J.S., M.D. Buschmann, and E.B. Hunziker, *Mechanical anisotropy of the human knee articular cartilage in compression.* Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 2003. **217**(3): p. 215-219.