An Agent-based Model of Cortical Bone to Explore Cellular Interaction with their Microenvironment

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Statement of Purpose: Agent-based models offer a very different approach to simulating the interactions between a patient's physiology and an implanted biomaterial or medical treatment. In this type of model, the characteristics of agents, in this case cells, are inputted as a series of algebraic rule sets which interact in a locally in a way that mimics the biology occurring in a patient. This approach directly harnesses the knowledge that is found in basic science and gives it a logical framework that allows for tissue and patient-level predictions of biological responses. Since the simulation relies on a systemic approach to biology rather than a reductionist approach, multiple possible outcomes can be predicted from the same model either through varying the inputs or by calibrating the simulation to incorporate the different types of outcomes that are seen in medicine. Also, once this model is created, its initial values can be easily tuned to specific patient physiology in order to logically facilitate the design of a therapeutic for that specific patient.

Methods: The agent-based model was created in the NetLogo programming language. The agents in the model are comprised of both the cells and the extra-cellular matrix (ECM). Each agent is individually able to respond to the agents within a very small area around them and have the capability to change their internal state or various variables in their neighboring agents. During one generation, each agent makes changes and by simulating multiple generations, incremental changes form emergent behaviors and patterns in the overall system. This predicatively mirrors the behavior of the tissue system. The ECM agents composed a continuous grid while the cells' agents are free to move over the grid created by the ECM, given the restriction that cells could not pass through matrix agents that would normally be impenetrable, e.g. mineralized bone matrix.

The three categories of cell agents in the initial time-points of the model are blood cells, pre-osteoclasts, and pre-osteoblasts. The pre-osteoclasts are initially located with the blood cells since they are from the hematopoietic stem cell lineage and have the ability to differentiate into osteoclasts that can demineralize and resorb bone matrix by interacting with ECM agents they are in contact with and altering their states appropriately. The pre-osteoblasts have the ability differentiate into osteoblasts and mineralize the ECM agents they are in direct contact with. In addition, the osteoblasts also have the ability to differentiate into osteocytes if the ECM agents surrounding them become 'mineralized', which correlates directly with the osteoblasts/osteocytes being trapped within mineralizing bone matrix. In order to simulate cortical bone remodeling, and specifically the generation of osteons, osteoclasts were placed randomly on a field of mineralized bone matrix, effectively forming the tips of cutting cones.

Results: The model was able to correct simulate the remodeling of cortical bone, even with a very basic rule set. After osteoclasts forming the tips of the cutting cone were placed randomly on the ECM agents, over the next generations of the simulation these correctly hollowed out the leading cone seen in cutting cones. The osteoblasts were able to correctly orient on the demineralized bone and remodel in the shape of an osteon. One result of particular importance is the ability of the model to differentiate and position the osteocytes in a manner consistent with both the biological mechanisms and in the patterns observed in the lacunae of cortical bone. The number of each cell population left after the formation of an osteon also correlate to those seen in histological analysis of cortical bone.

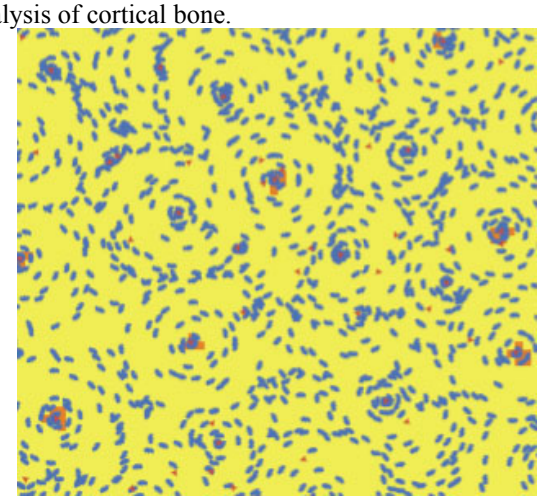

Figure 1. A section of the field of agents forming a field of osteons as seen from a transverse anatomical plane. The blue dots represent osteocytes, the yellow grid squares represent mineralized matrix, and clusters of red mark the location of haversian canals.

Conclusions: These results show that an agent-based model can simulate bone cells responding correctly to changes in their microenvironment, particularly the substrate on which they are located, in a biomimetic fashion while based solely on basic biological mechanisms. This agent-based model also generates full spatio-temporal data, which is key in tracking biological outcomes found in multi-dimensional systems with complex, emergent behaviors.