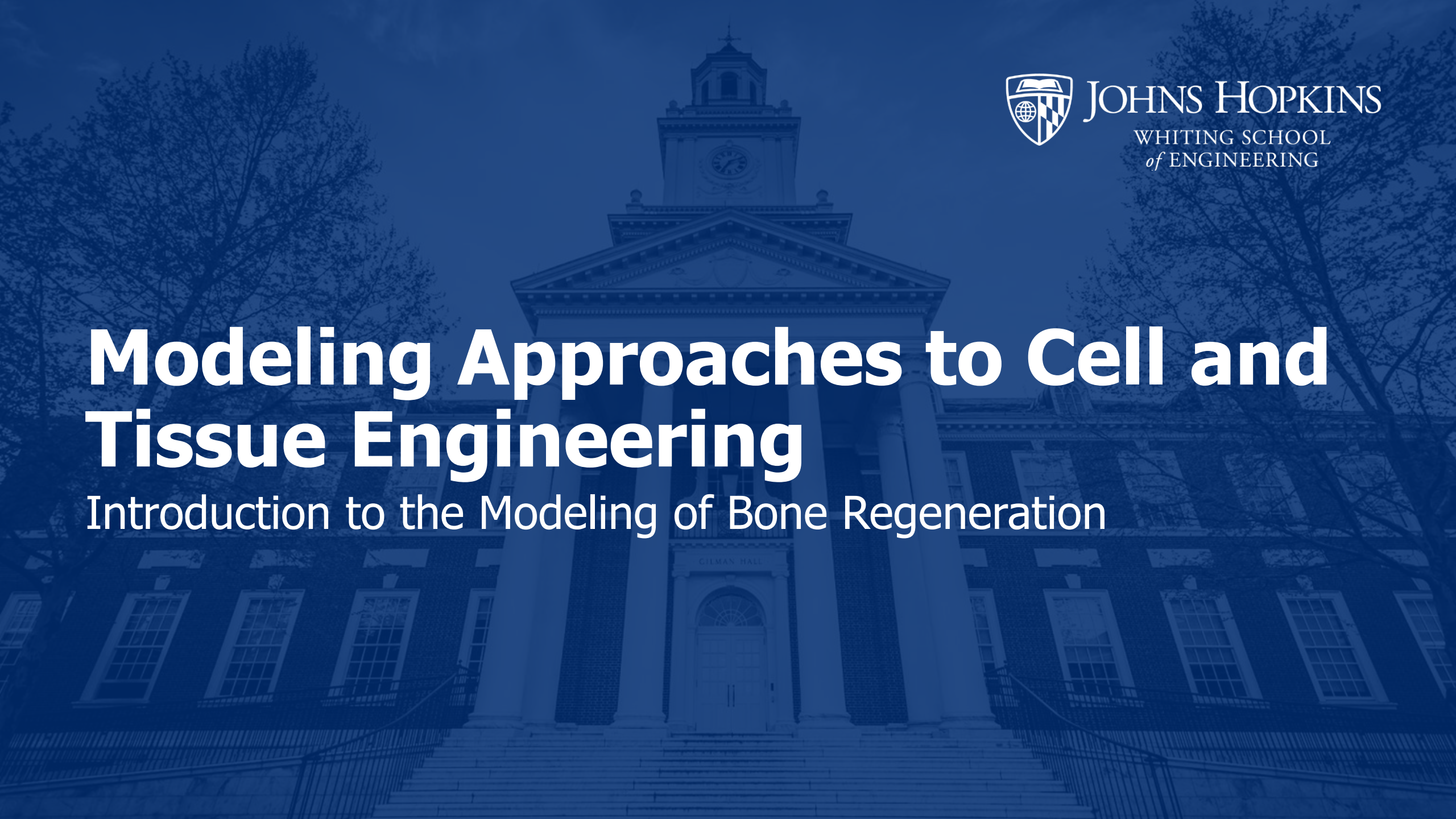


Modeling Approaches to Cell and Tissue Engineering

Introduction to the Modeling of Bone Regeneration

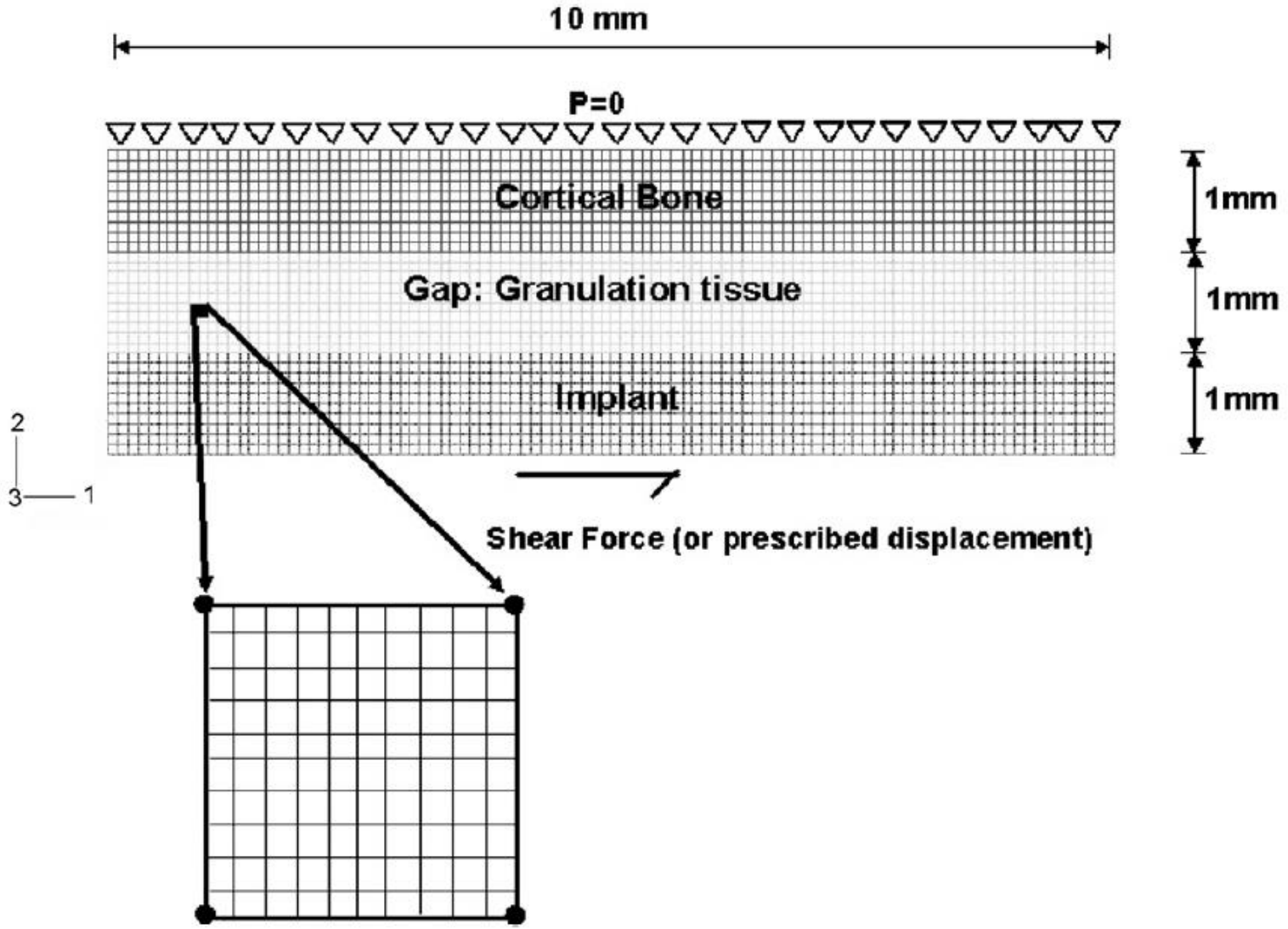
Introduction to the Modeling of Bone Regeneration

Alexander A. Spector (From Perez and Prendergast, 2007)

1. Bone regeneration after fracture, including bone, implant, and a gap between them.
2. The gap is originally with granulation tissue and later is penetrated by MSCs. The bone has originally properties of a cortical bone. The MSCs differentiate into fiberblasts, chondrocytes, and osteoblasts
3. The MSCs differentiation in the bone/implant gap is a result of mechanoregulation which is a function of two poroelastic characteristics, octahedral strain and relative fluid/solid shear velocity.
4. The bone/implant gap is discretized into 2-d poroelastuc finite elements.
5. Inside these elements, a mesh is used.
6. Cells in the bone/implant gap, can divide (proliferate) and occupy vacant locations with certain probabilities. Such division called isotropic (anisotropic) if there is no (there is) preferred direction.
7. Result 1. Predicted displacement at bone/implant gap for its initial values of 150μm and 500μm.
8. Result 2. Predicted shear force at bone/implant gap for two different relative displacement values.
9. Result 3. Predicted cell distributions at bone/implant gap for two relative displacement values 150 μm (a) and 500 μm (b)

Finite Element Model

Figure 1. Finite element model of the bone ingrowth simulation and the lattice where the cell proliferation/migration is performed



Sketch of Isotropic Proliferation

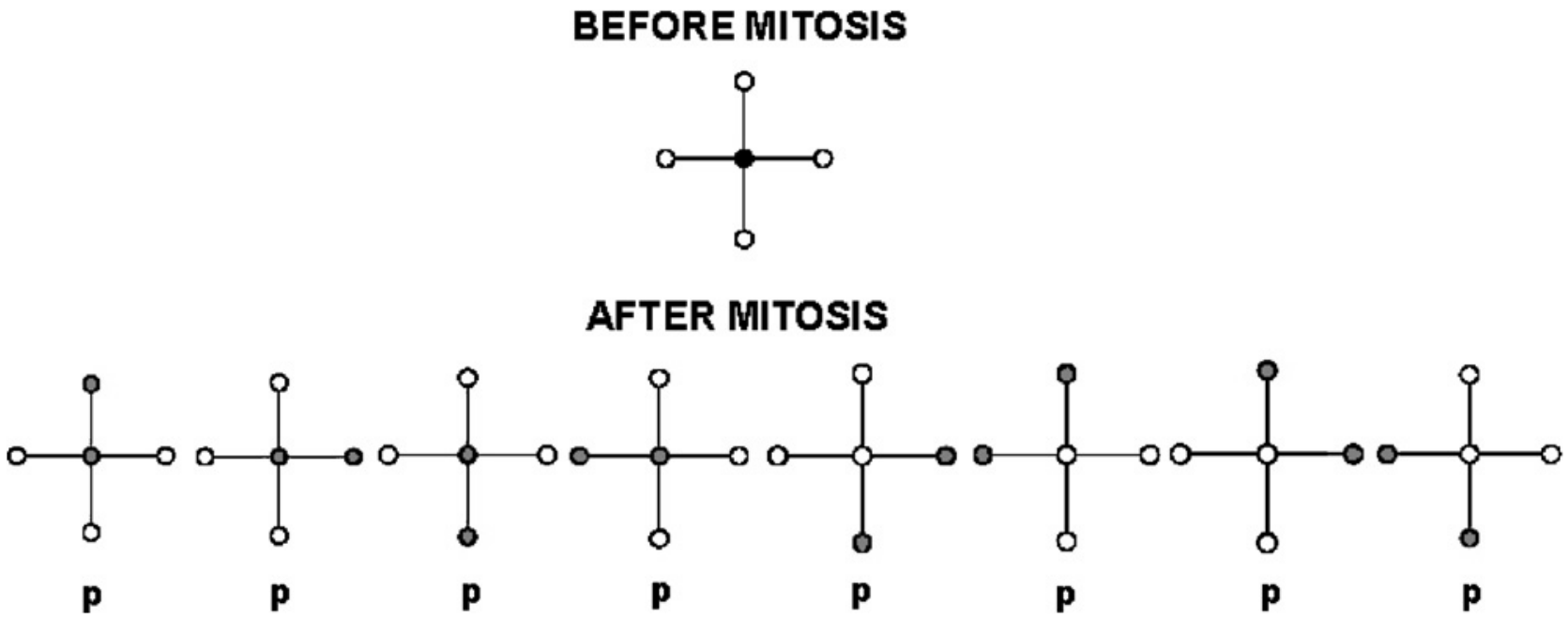


Figure 2. If all the surrounded positions are free, the probability p given in Fig. 1 will be equal to 1/8., If there is only one vacant position, the probability that it will be filled is equal to one. If all neighboring positions are occupied, mitosis will not occur.

Sketch of Anisotropic Proliferation

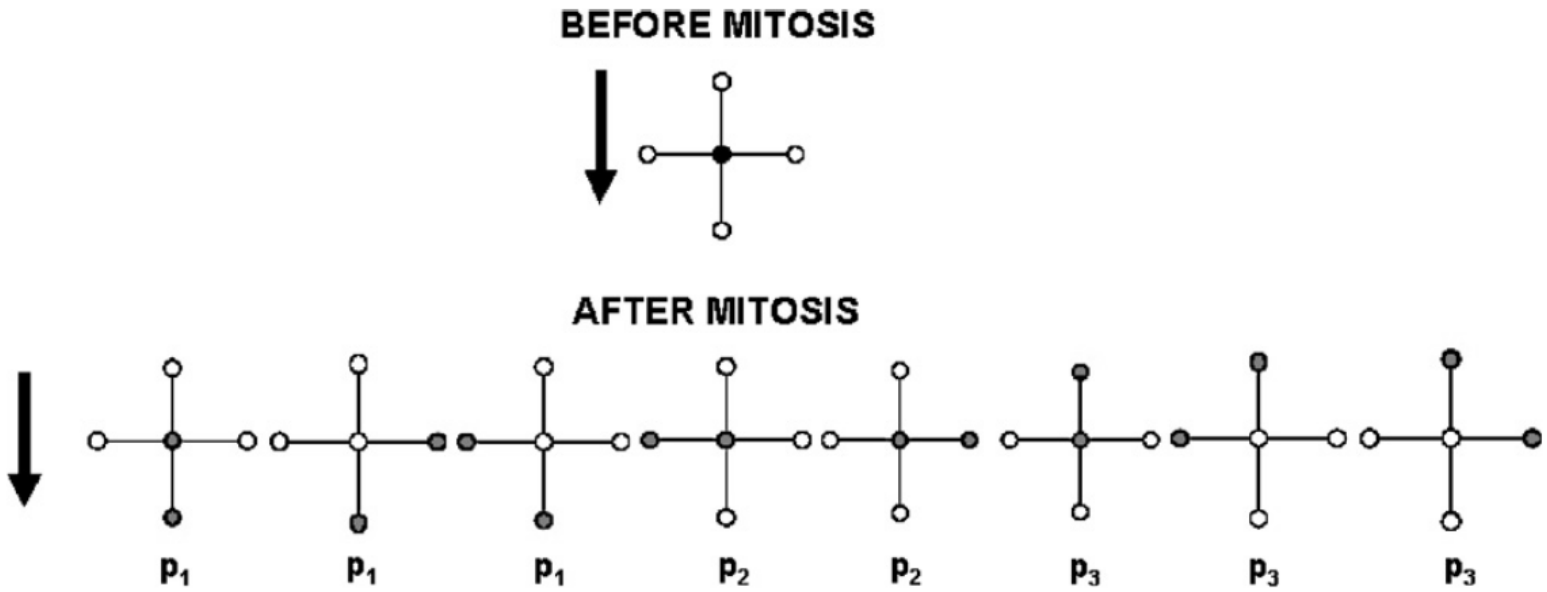


Figure 3. In this study, a strong preferred direction (arrow} was assumed as p1=10p2=60p3=p, and p can be calculated to be as p= 4/13

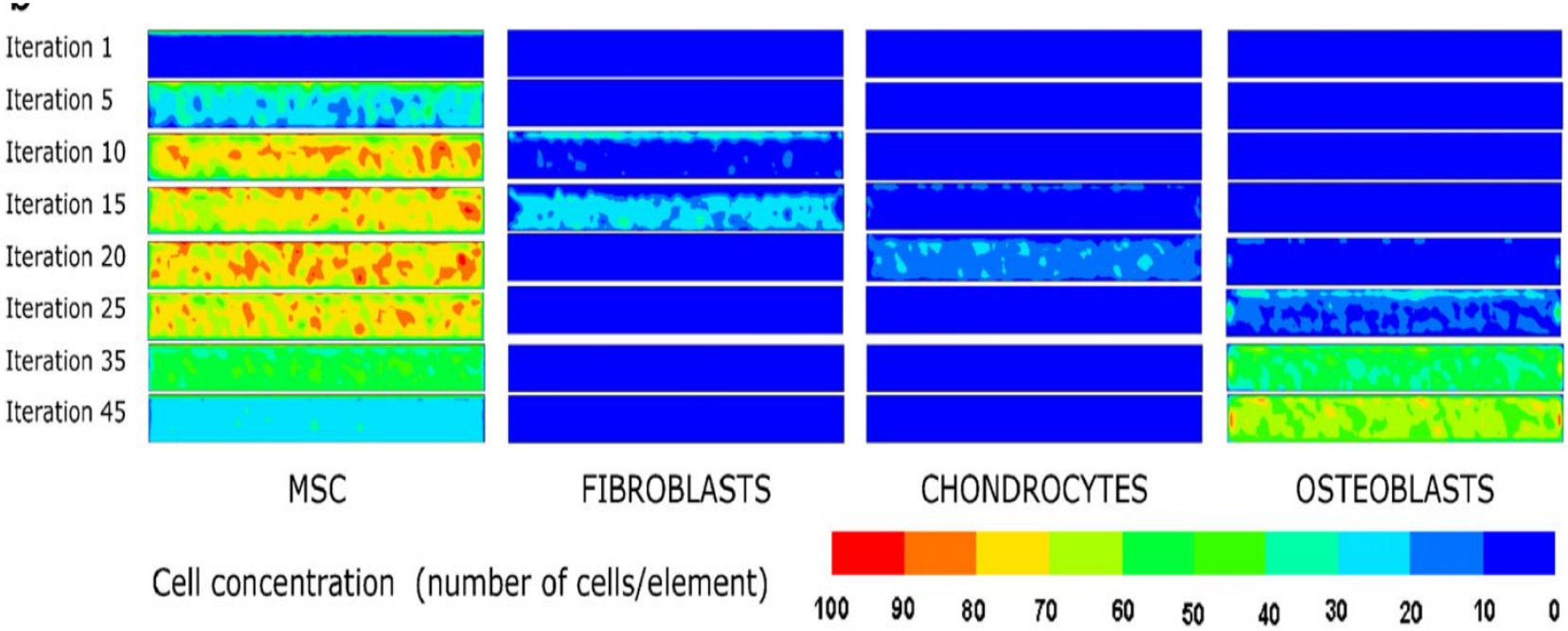
Cell Migration

Cell migration was also based on the stochastic random-walk approach. Recognizing that migration is a more rapid process, a new location for a migrating cell is chosen several times during one iteration of the proliferation process. In the simulations presented here, five random jumps are performed for each cell for each iteration of the simulation. At the end of the migration if that position is free is checked. In the event that the location has already been occupied by another cell, a neighboring location is chosen again randomly, except if the cell population is large enough to prevent the migration of cells. In that case, cells remain in their initial position without migrating.

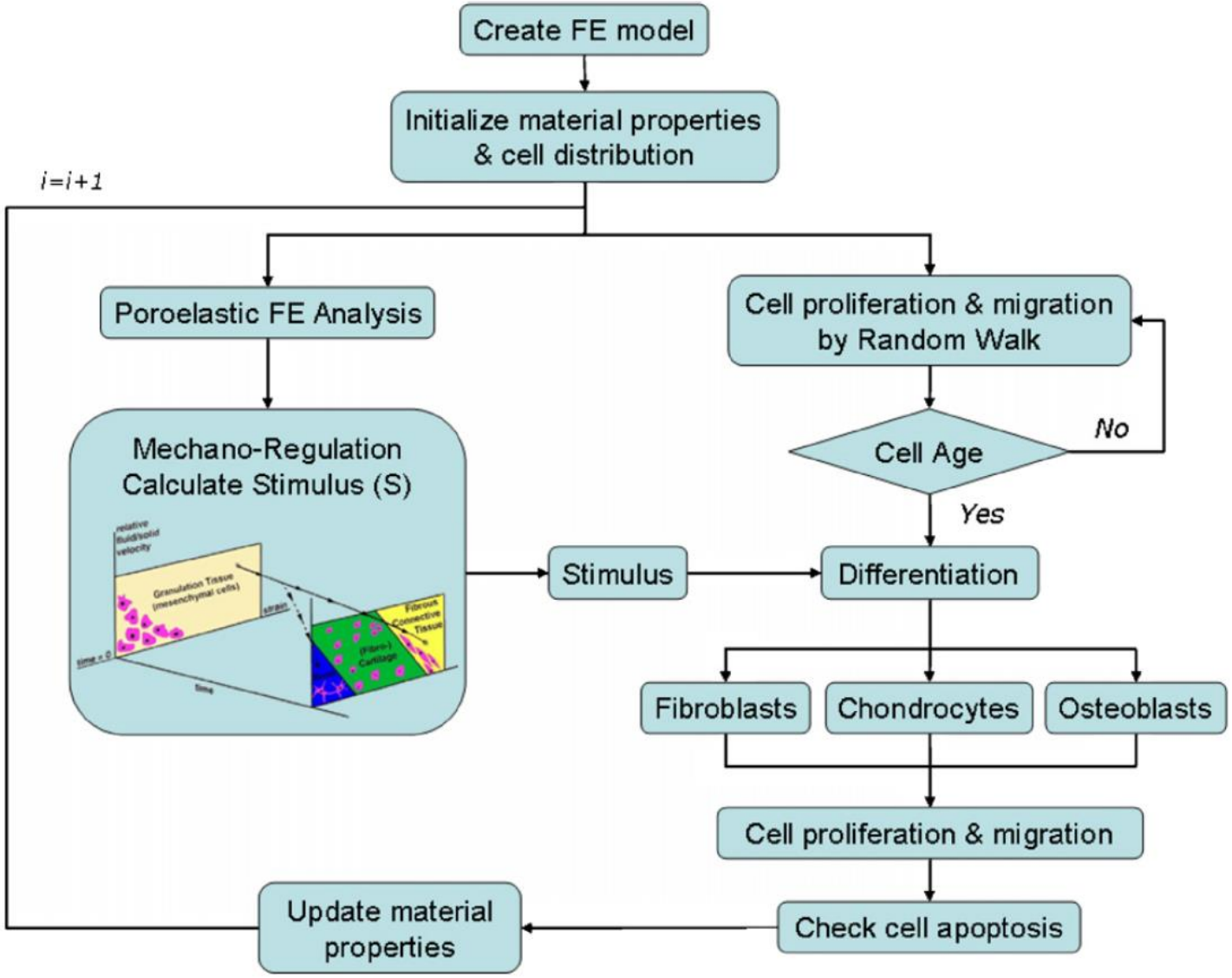
Mechanobiological Regulation

Following Prendergast et al. (1997), two biophysical stimuli (octahedral shear strain γ and relative fluid/solid velocity v) are used to regulate tissue differentiation. The octahedral shear strain is computed by means of the principal strains (ε_{I}, $\varepsilon_{\mathrm{II}}$, $\varepsilon_{\mathrm{III}}$) as $\gamma = 1/3\sqrt{(\varepsilon_{\mathrm{I}} - \varepsilon_{\mathrm{II}})^2 + (\varepsilon_{\mathrm{I}} - \varepsilon_{\mathrm{III}})^2 + (\varepsilon_{\mathrm{II}} - \varepsilon_{\mathrm{III}})^2}$. This theory proposed that the mechanical environment in the tissue has a controlling influence on tissue differentiation according to a stimulus S where $S = \gamma/a + v/b$, where $a = 0.0375$; $b = 3\,\mu\mathrm{m/s}$; these constants were derived by Huiskes et al. (1997). High levels of stimuli ($\gamma/a + v/b > 3$) promotes the differentiation of MSCs into fibroblasts, intermediate levels ($\gamma/a + v/b > 1$ and $\gamma/a + v/b < 3$) stimulate the differentiation into chondrocytes and low levels ($\gamma/a + v/b < 1$) favour the differentiation of osteoblasts from the MSC pool. Cells then synthesise the appropriate extracellular matrix leading to tissue formation and new mechanical properties for the tissue.

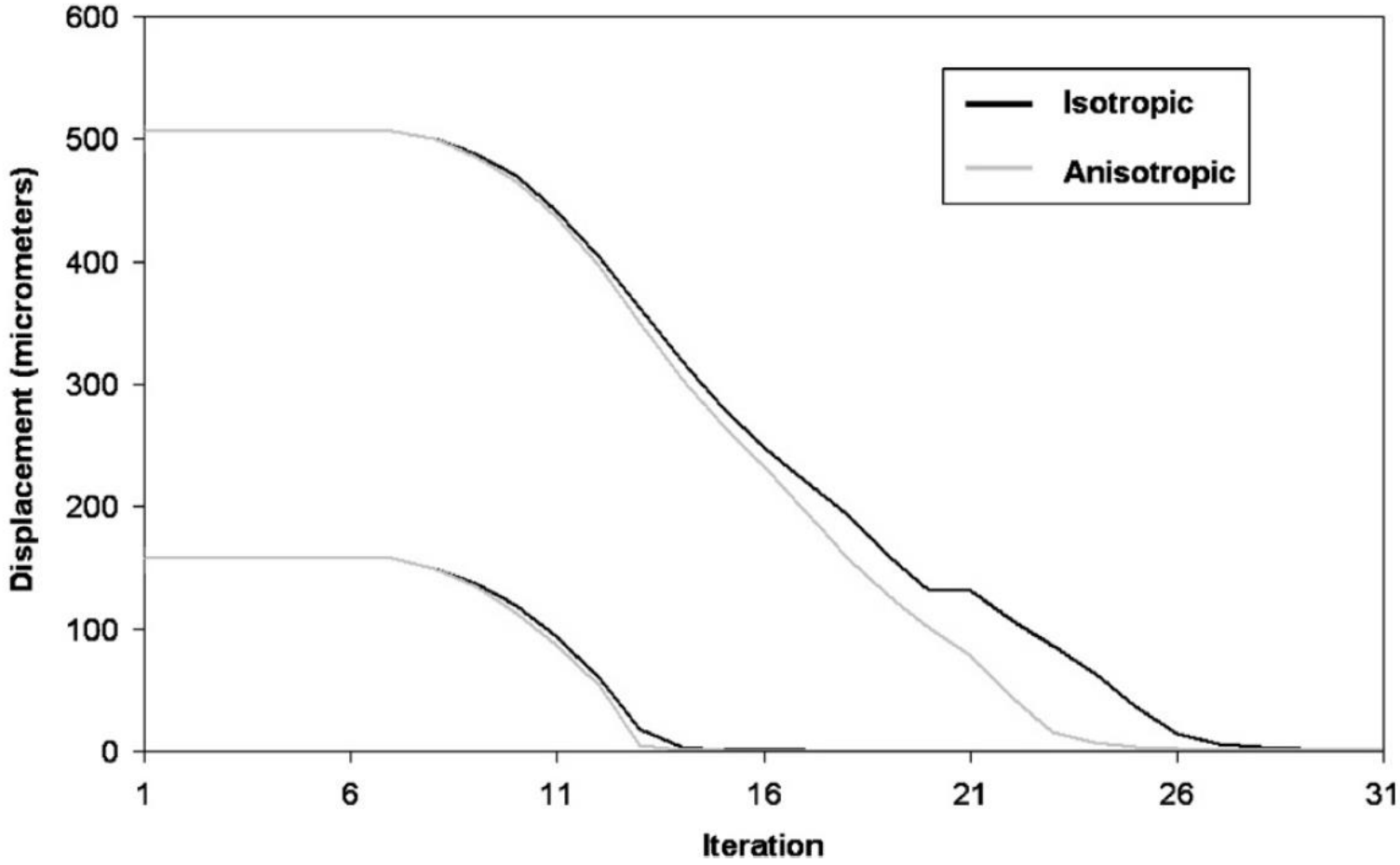
Cell Differentiation at the Bone/Implant Gap



General Flow Chart of Cell Proliferation & Migration by Random Walk during Bone Regeneration



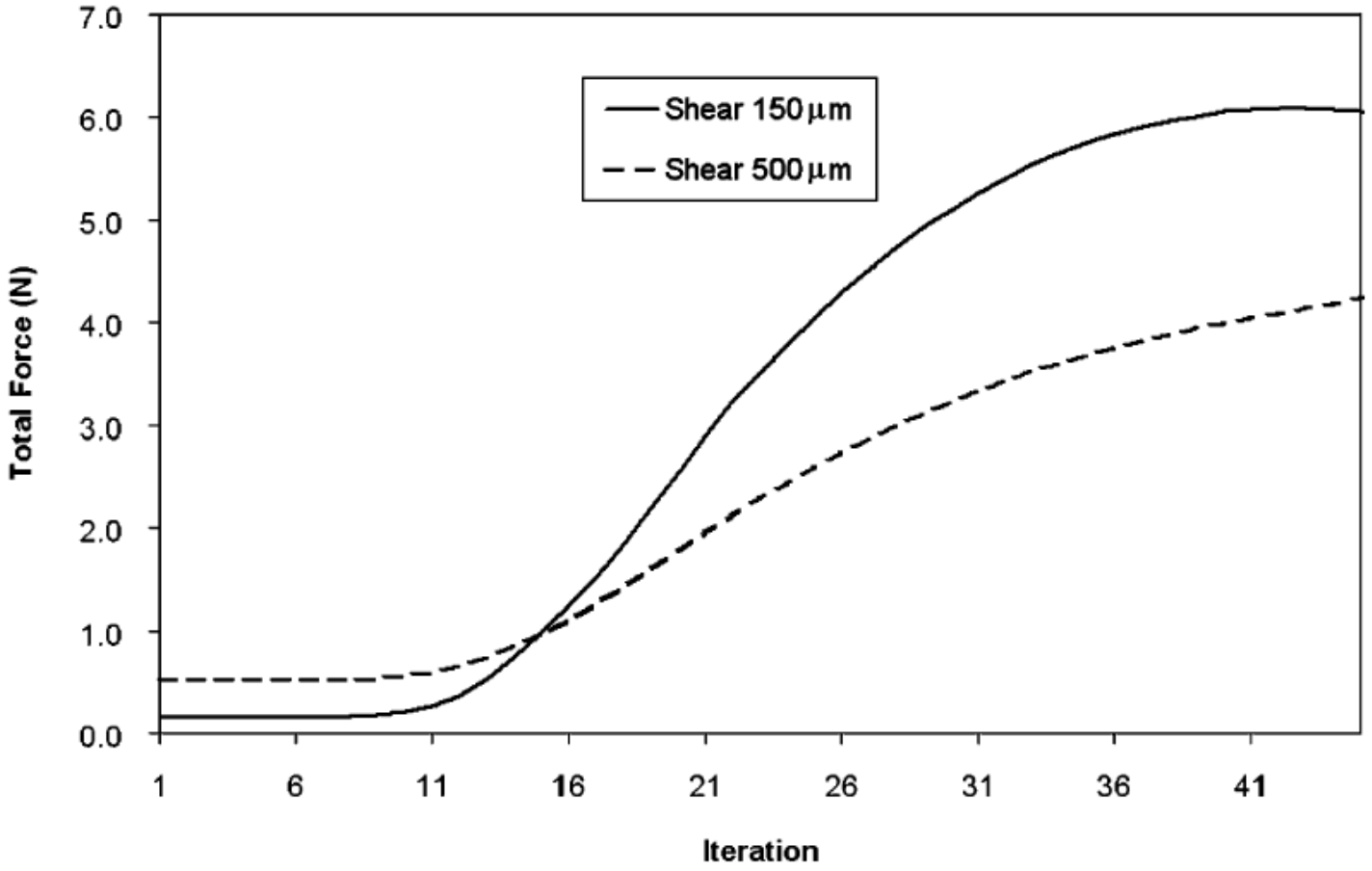
Micromotion of Isotropic and Anisotropic Cell Movement



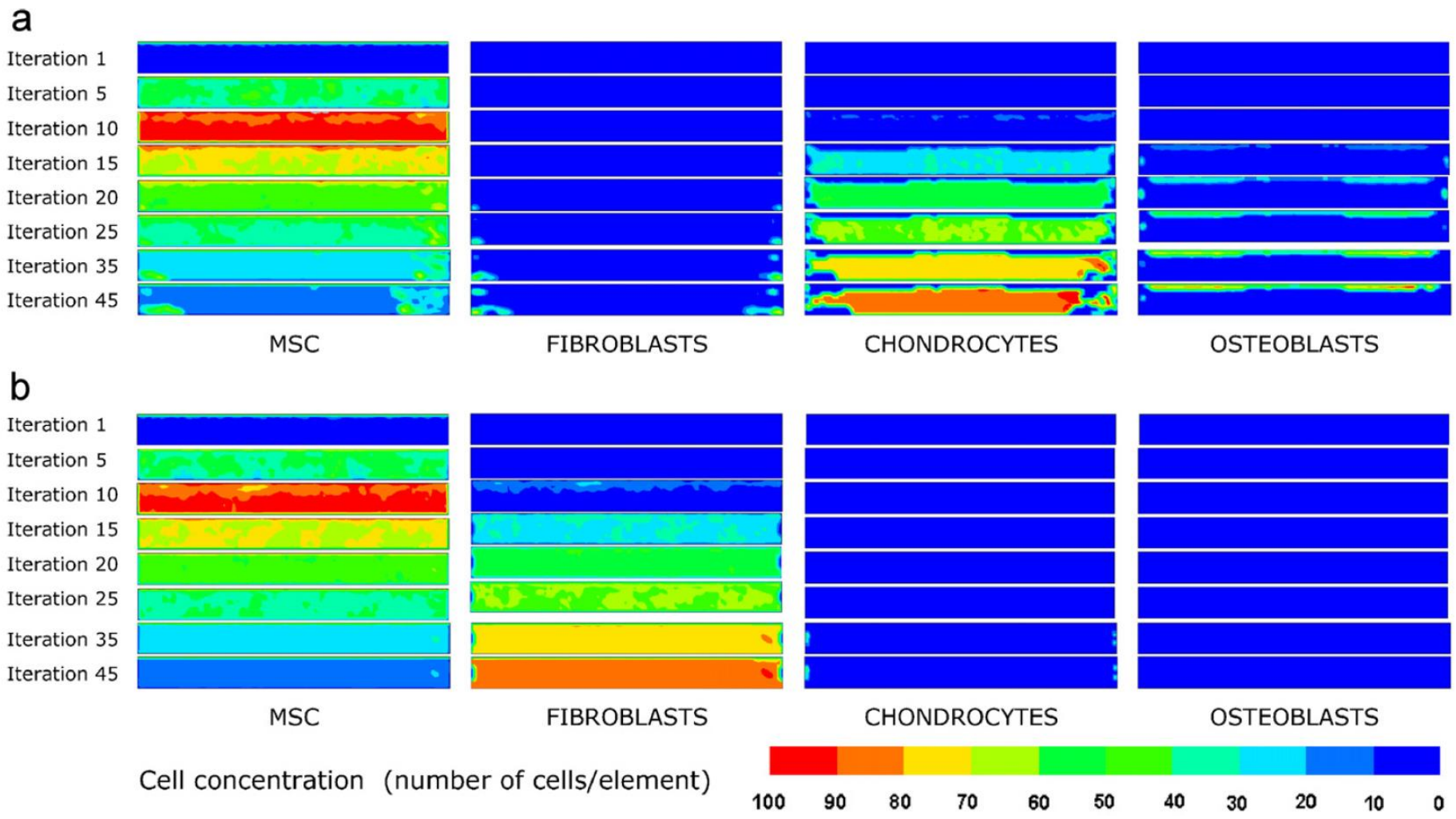
Micromotion predicted at the bone/implant interface with isotropic and anisotropic cell movement and force-control to obtain initial relative displacement (150 or 500 mm).

Force of Anisotropic Cell Movement

Figure 9. Force predicted at the bone/implant interface with anisotropic cell movement under displacement-control for two different relative displacements.



Cellular Composition in the Bone/Implant Gap



Cell distributions at the bone/implant gap for two different initial relative displacements $150\mu m$ (a) and 500 μm (b)