Modeling Approaches to Cell and Tissue Engineering

Modeling the Bone Fracture Healing: Taking into Account Vascularization 1

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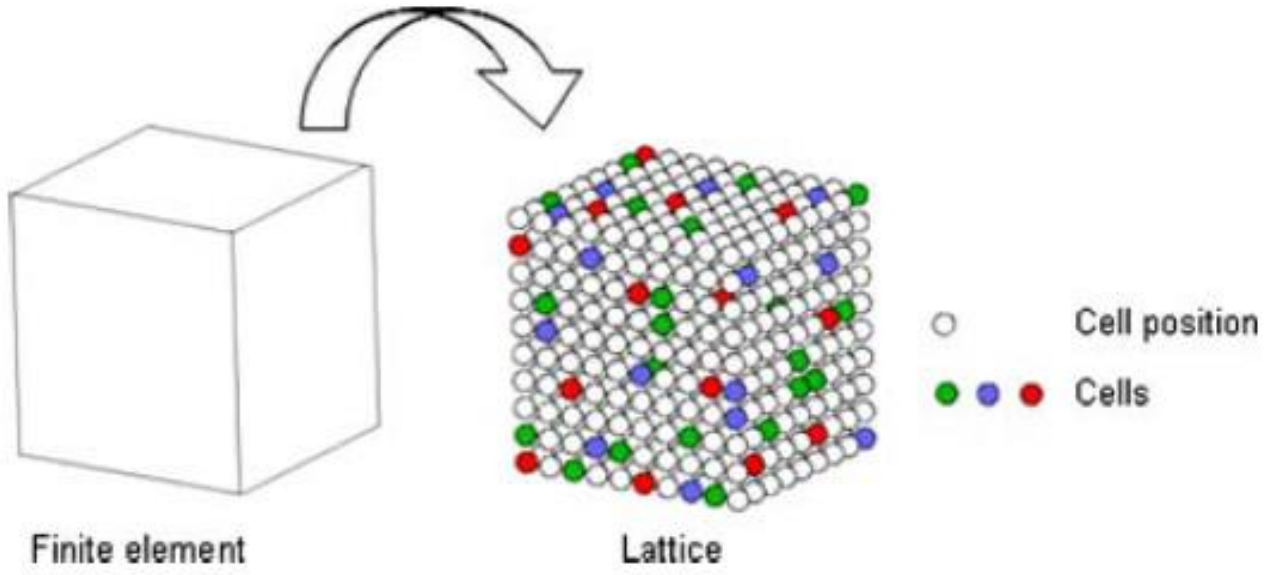
Alexander A. Spector (From Checa and Prendergast, 2009)

1. The lattice model of bone regeneration
2. Cell migration
3. Schematic of computational algorithm of the modeling of bone regeneration
4. Modeling of sprouting
5. Modeling of vessel growth
6. General flowchart of angiogenesis

Lattice Model of Bone Regeneration

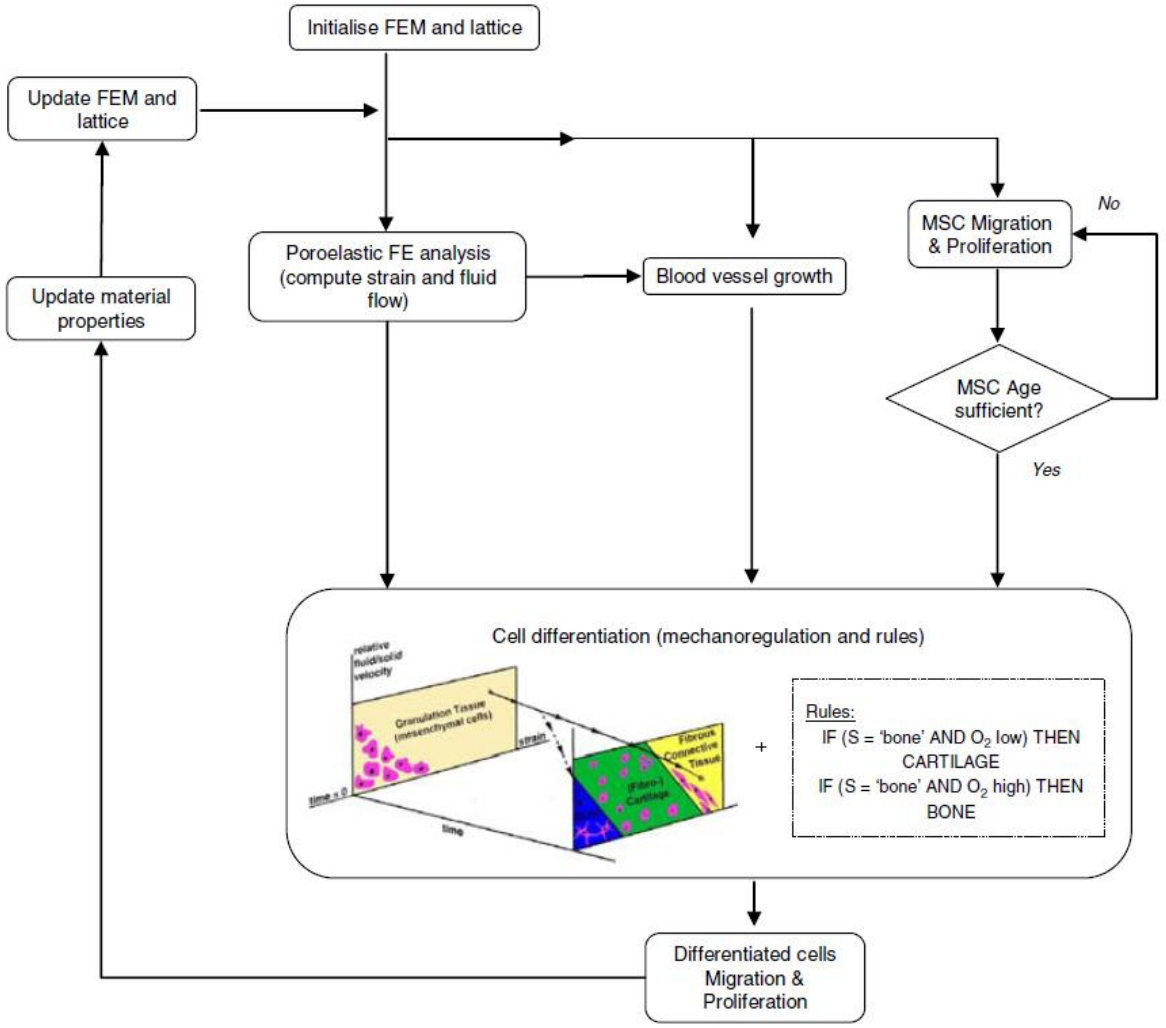


Lattice model for the simulation of cell activity.
Each lattice point represents a possible position for a cell.

Cell Migration

To model cell migration, a new position is chosen randomly from the surrounding locations. If the selected position is already occupied, a new neighboring position is chosen, again randomly. If there are no free neighboring lattice points, then migration ceases. In that case, the cell remains in its original location. Recognizing that cell migration is a more rapid process than cell proliferation, a new location for the migrating cell may be chosen several times during one proliferation cycle.

Model Tissue Regeneration Schematic



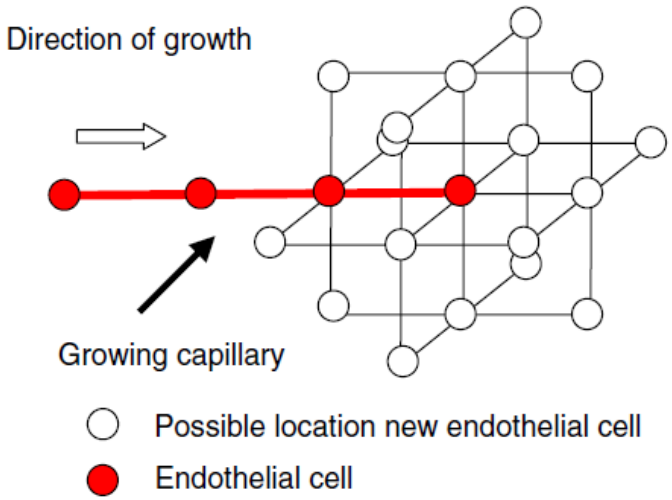
Schematic representation of the computational algorithm to model tissue regeneration. The differentiation process is regulated by the local mechanical environment and the local vascularity

Growth of Vascular Network

The growth of the vascular network was modeled through the following fundamental events:

1. The formation of vessel sprouts from pre-existing sprouts or vessels (branching)
2. The growth of the sprouts
3. The fusion of a sprout tip to another sprout tip or another sprout (anastomosis)

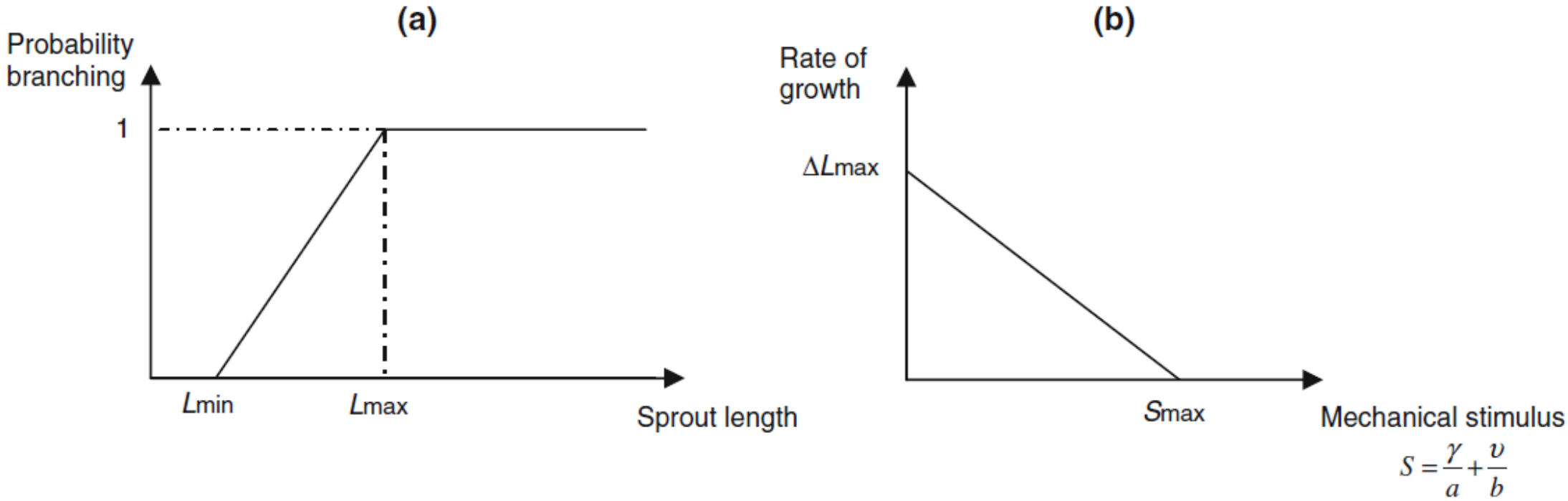
Each capillary was modeled as a sequence of endothelial cells whose path was determined by the path of the endothelial cell at the capillary tip which moved following a random walk with the possibility of directional bias and persistence.



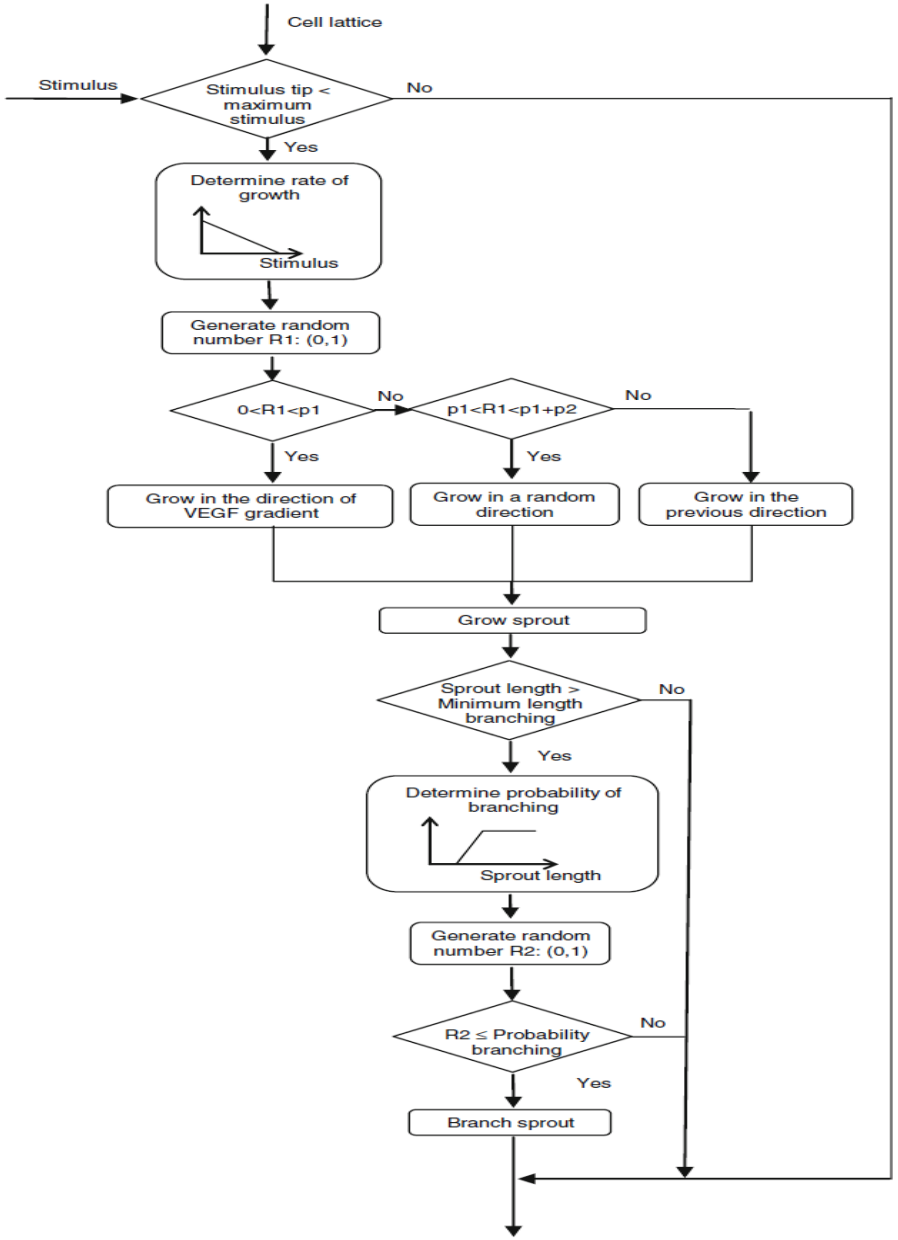
Chemotaxis (directed movement along chemical concentration gradients) was modeled assigning biased probabilities to the 17 possible directions that a tip cell can take (Fig. 3) according to the relative concentration of hypertrophic chondrocytes (mature chondrocytes under a mechanical stimulus favorable for bone formation) in each of the directions, so that the cell is more likely to move toward higher concentrations of hypertrophic chondrocytes. This aims to replicate experimental observations during endochondral ossification where chondrocytes exit their proliferative cycle and mature toward hypertrophic chondrocytes. Hypertrophic chondrocytes in the matrix start producing VEGF, attracting endothelial cells into the mineralized matrix, increasing vascularity and triggering matrix metalloproteinases (MMPs) to degrade the cartilage matrix. The direction of growth is then determined based on assigned probabilities for the cell to follow the chemotactic direction (chemotactic direction ratio: p_{1}), its direction on the previous time step (persistence ratio: p_{2}), or a random direction (random direction ratio: p_{3}), such that p_{1}+p_{2}+p_{3}=1

Sprout Branching

(a) Probability of sprout branching as a function of sprout length. L_{min} represents the minimum length for a sprout to branch, while L_{max} represents the maximum length for a nonbranching sprout and (b) Sprout rate of growth as a function of the mechanical stimulus (combination of fluid flow and shear strain).



Another Model Tissue Regeneration Schematic



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