## Bone Ingrowth and Tissue Differentiation

### 1.7.4 Bone ingrowth

Bone ingrowth is a complex biological phenomenon that follows the similar process of primary bone fracture healing (Davies, 1996, 2003), which is a sequential process of different cellular activities and tissue differentiation. Mesenchymal stem cells or MSCs play an important role in primary bone fracture healing. Depending on the appropriate signal, the undifferentiated progenitor MSCs differentiate into different connective tissue cells, which subsequently lead to neo-tissue formation (Barry *et al.*, 2003). Since bone marrow is an MSC-rich region, it is assumed that MSCs migrate towards a bone defect to repair it through this complex tissue differentiation mechanism. MSCs could differentiate into a number of different cellular phenotypes like fibroblasts, chondrocytes, myoblasts, stromal cells and osteoblasts (Fig. 1.16). Subsequently, these cells could generate different tissues like fibrous tissue, cartilage, muscle, marrow and bone, respectively (Fig. 1.16). It has been found that several stimuli including growth factors, changes in oxygen tension (hypoxia) and mechanical loading could influence the connective tissue differentiation. Thus, a balance between different stimuli is necessary for facilitating a particular connective tissue differentiation and growth (Matsuda *et al.*, 1998).

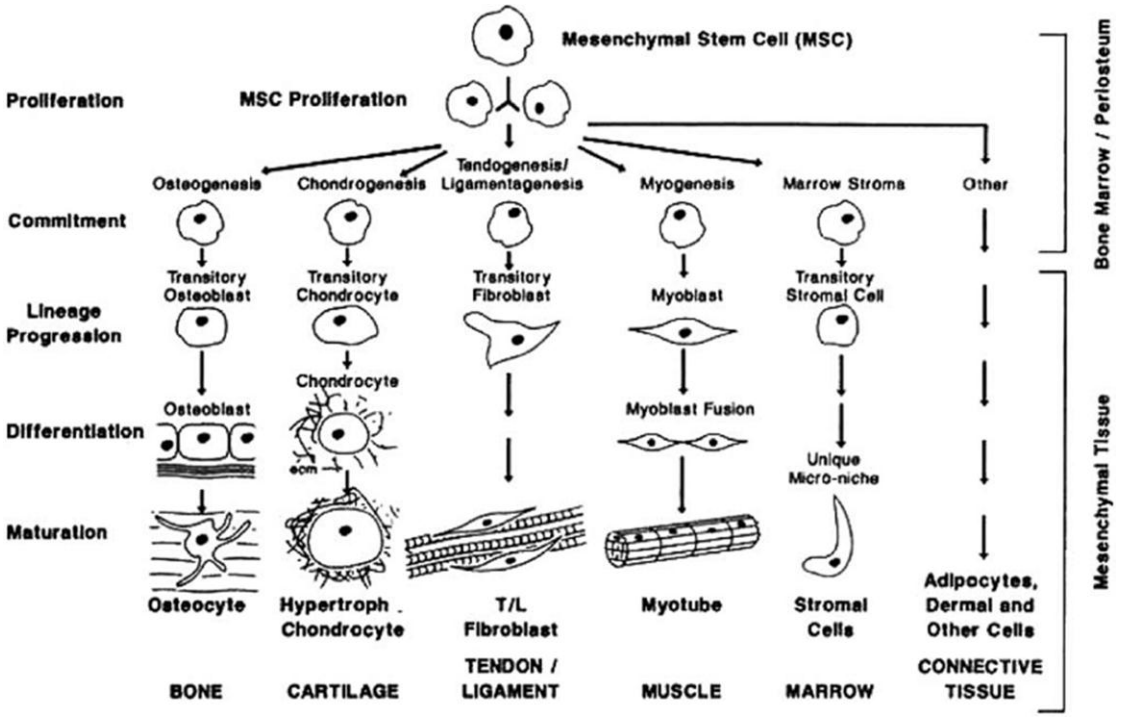


**Fig 1.16:** The mesengenic process: tissue differentiation from Mesenchymal stem cells (Caplan 1994).

The influence of mechanical stimulus on tissue differentiation is of particular interest from the perspective of implant design. Studies indicated that in a chondrogenic medium and in the absence of any growth factor, the progressive tissue differentiation could be regulated by mechanical stimuli alone (Angele *et al.*, 2003; Altman *et al.*, 2002). Usually, sufficient supply of growth factors to stimulate osteoblast proliferation is assumed in a well vascularized orthopaedic surgery. Under such condition, the pathway of MSC differentiation is suggested to be particularly influenced by local mechanical stimuli, namely deviatoric and hydrostatic stresses (Pauwels, 1980; Carter *et al.*, 1988). The cellular transduction mechanism includes strain reception, changes to nutrient and metabolic transfer rates through hydrostatic pressure and cell binding **(**Altman *et al.*, 2002**)**. Both these stimuli are, however, largely influenced by relative interfacial 'micromotion' between the two fragments of the bone fracture (Speirs *et al.*, 2000).

The consideration of the shear and hydrostatic stress approach facilitates accounting for two forms of mechanical deformations: hydrostatic or 'dilatational' stresses representing the volumetric changes without geometric distortion and shear or 'deviatoric' stresses representing geometric distortion without volumetric change. There have been several

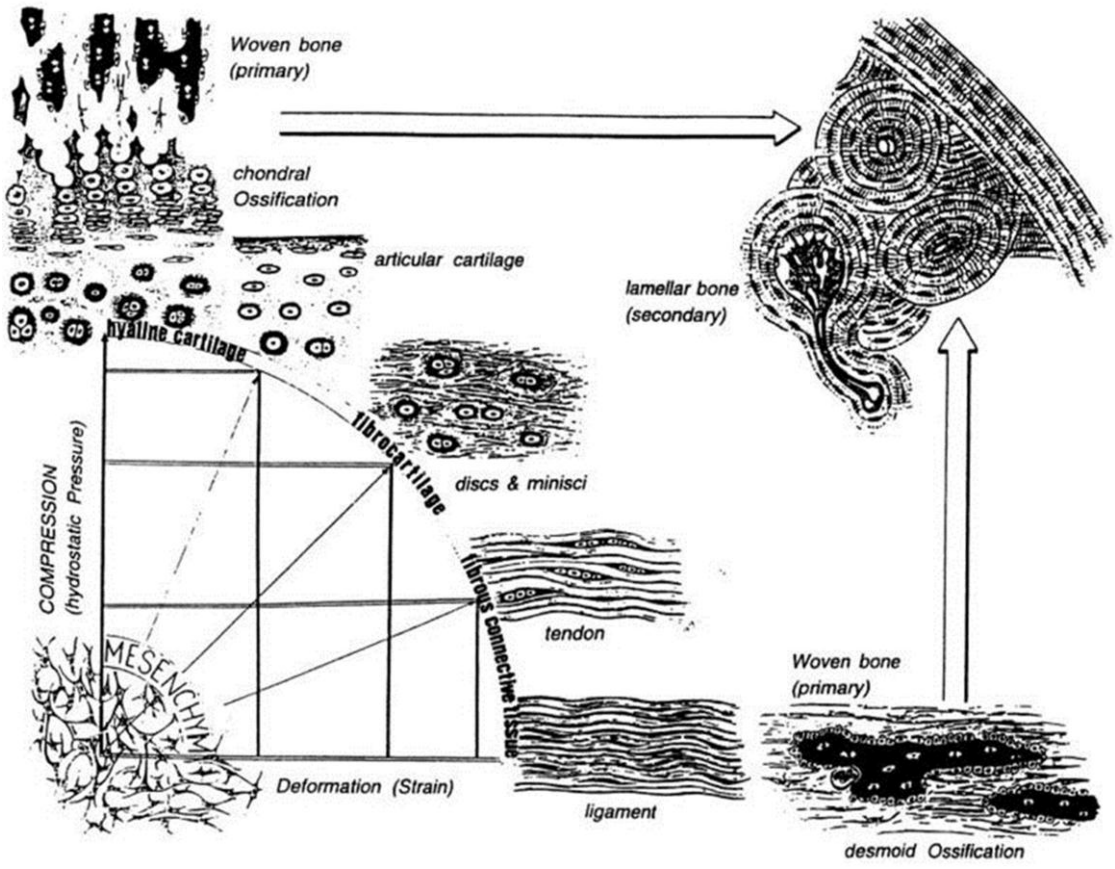


**Fig. 1.17:** Principles of mechanoregulatory tissue differentiation (Weinans and Prendergast 1996).

attempts to quantify the influence of such mechanical stimuli on tissue differentiation (Carter *et al.*, 1988; Claes and Heigele, 1999; Prendergast and Huiskes, 1996; Prendergast *et al.*, 1997; Huiskes *et al.*, 1997). Most of these models predicted fibrous tissue formation for the high magnitude of shear or tensile stresses (Fig. 1.17). However, osteogenesis was predicted in most of the models having good vascularity and lower magnitudes of stresses.

### 1.7.4.1 Mathematical formulation of evolutionary bone ingrowth

Several mechanoregulatory algorithms have been proposed to quantify the tissue differentiation process (Carter *et al.*, 1988; Claes and Heigele, 1999; Prendergast and Huiskes, 1996; Prendergast *et al.*, 1997; Huiskes *et al.*, 1997). Mostly all these algorithms implemented a two-stimuli approach: octahedral shear (*S*) and dilatational hydrostatic (*D*) stresses. Carter *et al.* (1988) first combined these two stimuli in a single parameter known as Osteogenic Index (Fig. 1.18). Although this osteogenic index approach was developed based on two-dimensional (2-D) FE-models, the method was successful in predicting early trends of tissue differentiation for initial fracture fixation (Carter *et al.*, 1988), foetal metaphyseal development (Carter and Wong, 1988) and around implant-bone interfaces (Prendergast and

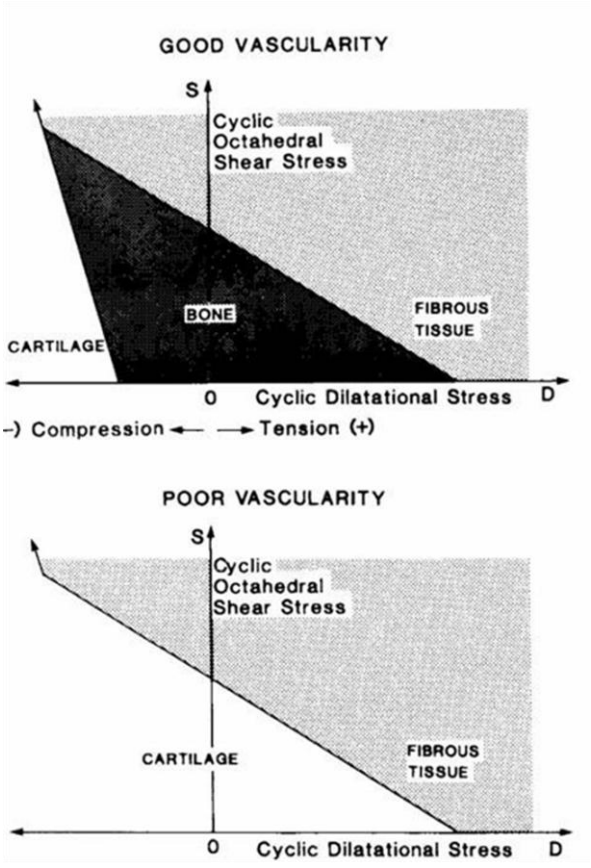


**Fig. 1.18:** Mechanoregulatory hypotheses of Carter *et al.* (1988).

Huiskes, 1996; Giori *et al.*, 1995). However, further advancement in the quantitative basis of tissue differentiation suggested that osteogenic index-based approach becomes less valid with progressive tissue differentiation (Gardner *et al.*, 2004).

A slightly different mechanoregulatory algorithm was developed by Claes and Heigele (1999), wherein the deviatoric strains and hydrostatic stresses were considered as two mechanical stimuli governing the tissue differentiation process (Fig. 1.19). The quantitative limits of both the stimuli were based on the values obtained from a fracture healing study on an ovine model (Claes and Heigele, 1999). This model was also found to predict satisfactory tissue differentiation patterns for drilled hole defects (Heigele and Claes, 1998).

Considering bone as a biphasic material, another mechanoregulatory based methodology was proposed (Prendergast and Huiskes, 1996; Prendergast *et al.*, 1997), wherein the combined effects of strain and interstitial fluid velocity were considered (Fig. 1.20). The quantitative limits on the mechanical stimuli of this biphasic mechanoregulatory algorithm were also obtained through an empirical fit to an animal model (Huiskes *et al.*, 1997).

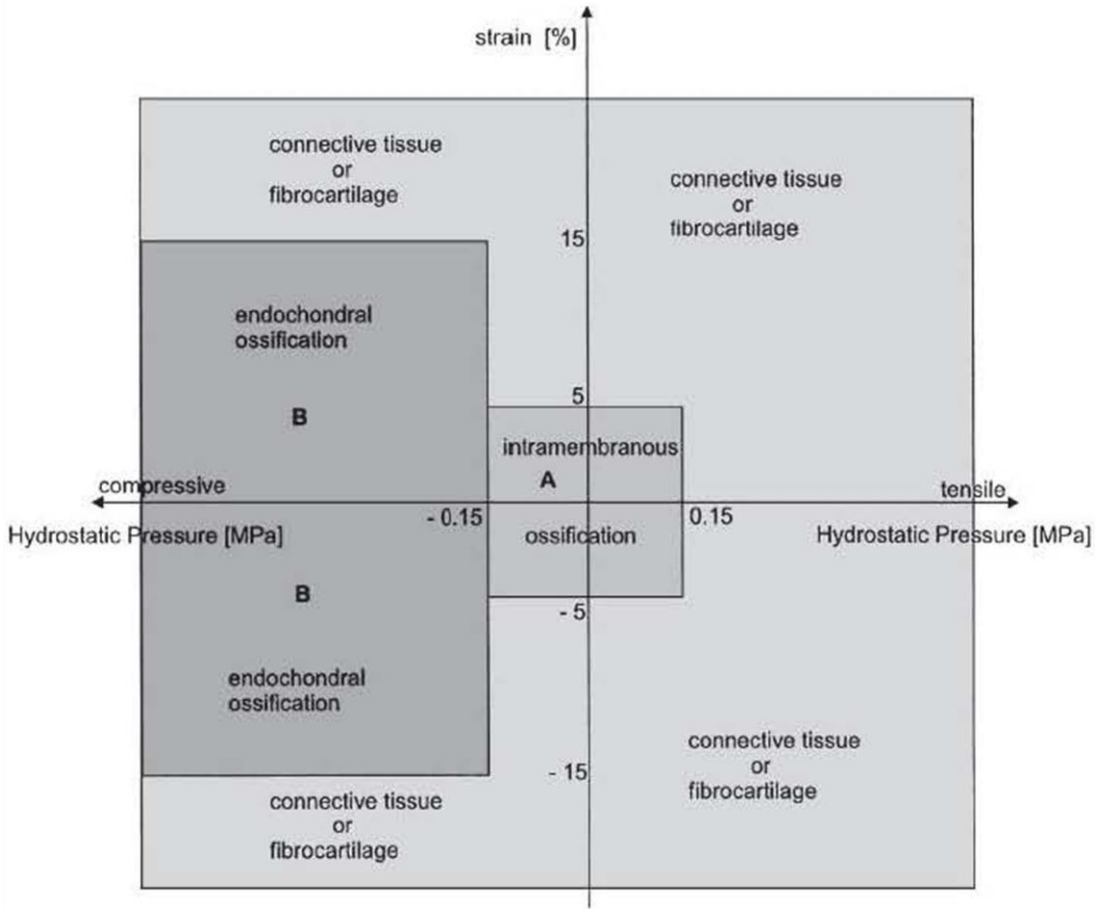


**Fig. 1.19:** Mechanoregulatory principles of Claes and Heigele (1999).

This mechanoregulatory algorithm was further implemented in a numerical framework to simulate fracture healing, following a diffusion based principle (Lacroix *et al.*, 2002; Lacroix and Prendergast, 2000, 2002):

$$k\nabla^2 c = \frac{dc}{dt} \tag{1.8}$$

where, $k$ is a diffusion constant and $c$ is the element-specific cellular concentration. This diffusion based principle was employed to simulate both the cellular migration and proliferation at the fracture site. The tissue adaptation was simulated following the biphasic tissue differentiation algorithm. The effective material properties ($E$) of the neo-tissue layer were computed through a rule of mixture:

$$E_{n+1} = \left(\frac{c_{max} - c_{tissue}}{c_{max}}\right)\Big|_n E_{granulation} + \left(\frac{c_{tissue}}{c_{max}}\right)\Big|_n E_{tissue} \tag{1.9}$$

where, $E_{n+1}$ is the resulting material property of the neo-tissue layer; $E_{granulation}$ and $E_{tissue}$ are the material properties of the granulation tissue and the newly evolved tissue, respectively; $c_{max}$ and $c_{tissue}$ are the maximum cellular concentration and the actual element-specific concentration of cells. In order to avoid numerical instability and artificially fast tissue differentiation, a further temporal smoothing method was implemented while updating these iterative material properties of the newly formed tissue layer (Lacroix and Prendergast, 2000):

$$E_{n+1,smoothed} = \frac{1}{10}\sum_{i=n}^{n-9} E_i \tag{1.10}$$

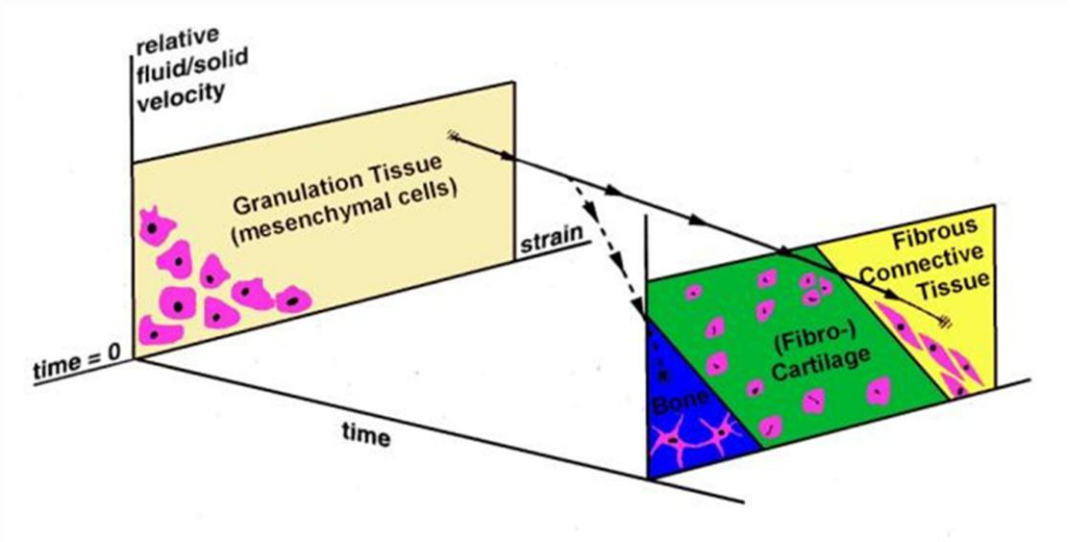


**Fig. 1.20:** Biphasic mechanoregulatory algorithm of Prendergast *et al.* (1997).

The schematic of this approach is shown in Fig. 1.21. A number of studies have employed this approach to investigate fracture healing (Isaksson *et al.*, 2006, 2008a, 2008b, 2009), osteochondral defect healing (Kelly and Prendergast, 2005) and implant-bone interfacial tissue differentiation (Scannel, 2006, Chou and Müftü, 2013, Dickinson *et al.*, 2012). Later, the efficacies of different mechanoregulatory algorithms were also compared and found that all the algorithms were capable of predicting similar trends of tissue adaptation (Isaksson *et al.*, 2006). More recently, a number of cell-phenotype specific algorithms have also been proposed, wherein, the different cellular activities of each of the cells and their influences on tissue differentiation have been explicitly modelled (Isaksson *et al.*, 2008a; Andreykiv *et al.*, 2008). However, these cell-phenotype specific algorithms are computationally far more complex as compared to the diffusion-based phenomenological algorithms.

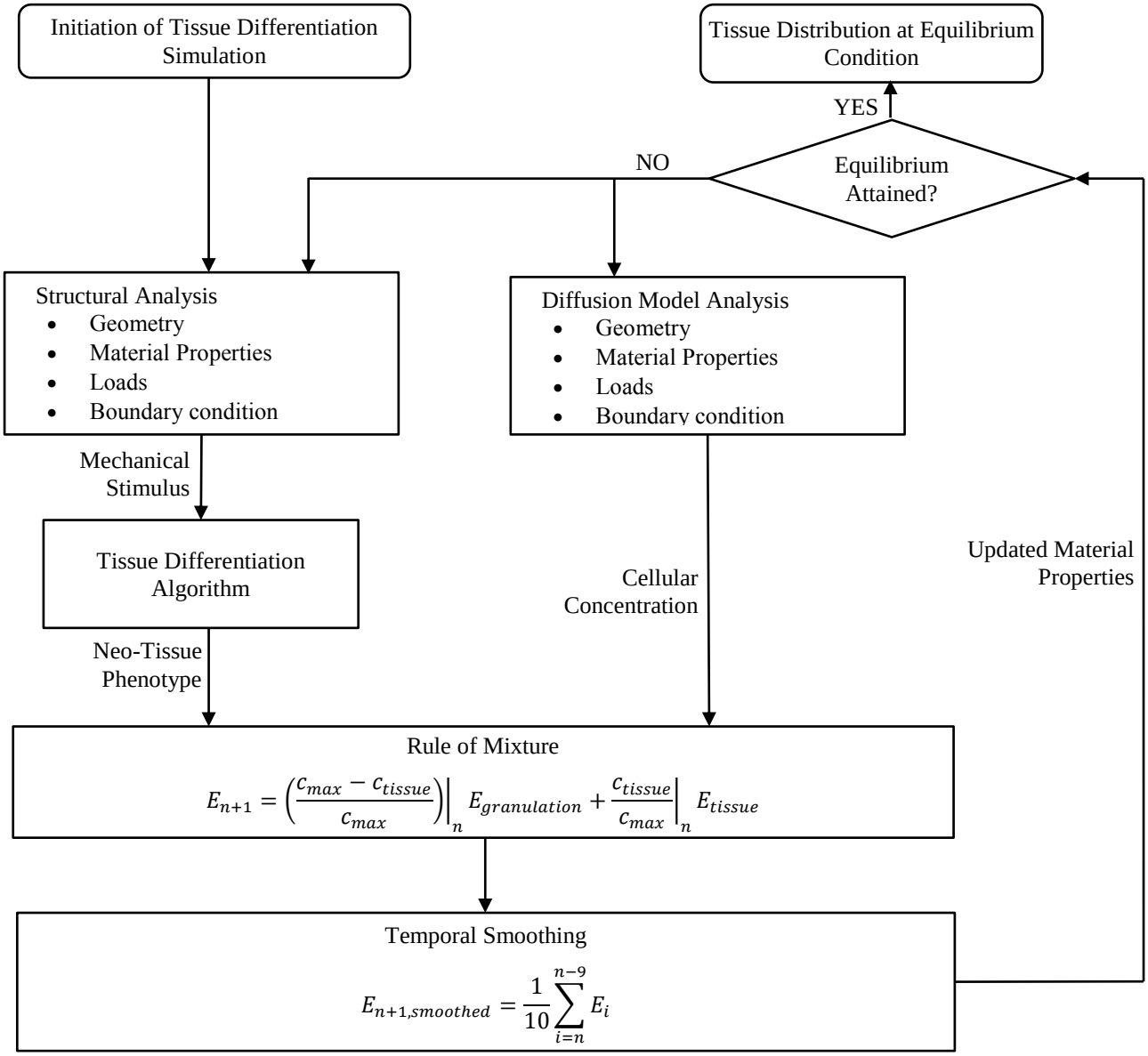


**Fig. 1.21:** Computational scheme for mechanoregulatory tissue differentiation simulation.