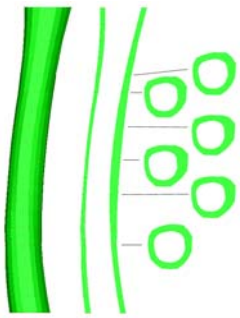
GEMM
Group of Structural Mechanics and Material Modelling

MODELADO MATEMÁTICO DE LA MECANOBIOLOGÍA ÓSEA



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instituto de investigación en ingeniería de Aragón
Universidad de Zaragoza

Santiago de Compostela, Julio 2010

I3A - Definition

WHAT IS THE I3A?

- An Interdisciplinary University Research Institute with wide-ranging activities in various branches of engineering.
- We cover the complete research cycle from the basics to prototype design.
- The generation of new knowledge is one of our essential activities.

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I3A - Definition

What is our purpose?

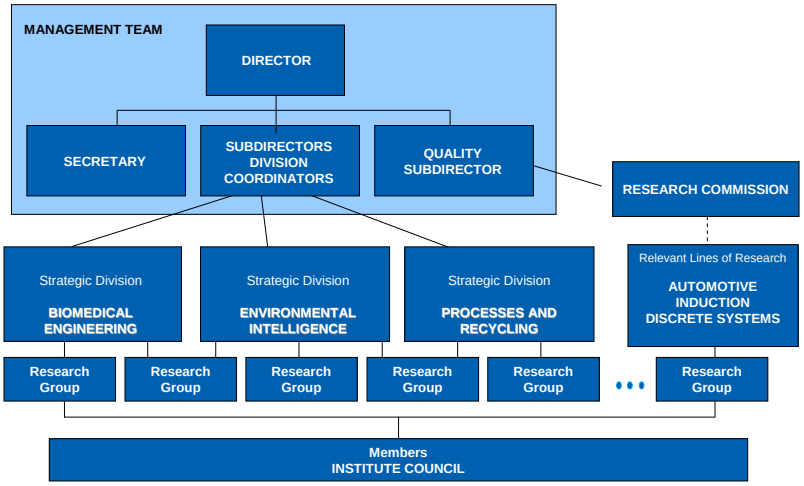
- Promoting and improving scientific research in the continuing search for excellence.
- Supporting economic development through technology transfer to the industrial sector.
- High quality training at postgraduate and doctoral level.
- Promoting science and technology in society.

I3A - Composition

RESEARCH PERSONNEL

- 287 PhD members
- 300 associate members (research fellows, hired staff and graduate lectures)
- 28 research groups recognised by the Government of Aragon
  - 6 excellence level
  - 13 consolidated level
  - 7 consolidated for applied research
  - 2 emergent level

I3A – Structure



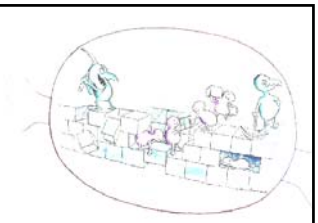
I3A – DIVISIONS IB

BIOMEDICAL ENGINEERING DIVISION

Technology applications for health management and improvement

1. Tissue engineering and biomaterials
2. Biological modelling and biomechanics
3. Imaging, signal and biomedical instruments
4. Healthcare and prevention technologies

OVERVIEW



- ***Bone properties***
- Role of mechanical factors: bone mechanobiology
- Methods of Science: computer simulation
- Modelling Bone Mechanobiology:
  - Bone Remodelling
  - Bone Healing
  - Bone Distraction
  - Bone Tissue Engineering
- Final conclusions

BONE PROPERTIES

- Different functions

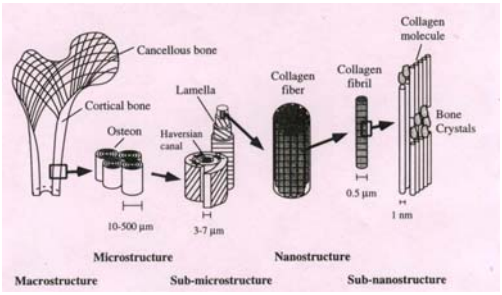
FUNCTIONS OF BONE

- ***Structural support***
- ***Protection*** (e.g. skull encloses brain)
- ***Movement*** (transmission of forces, in fact, muscles use bones as levers)
- ***Mineral storage*** (calcium, phospate)
- ***Blood cell production*** (in bone marrow)

BONE PROPERTIES

- Different functions
- Bone is a ***hierarchical structural composite*** material:

BONE TISSUE: A COMPLEX MATERIAL



(Rho et al., 1998)

- Materials with structural hierarchy
- Porous, heterogeneous and anisotropic material
- Ideal material properties: high stiffness, strength and fracture toughness and low weight
- It has been designed, as all living tissues, by the blind force of natural selection

CORTICAL AND TRABECULAR BONE

- Two different bone tissues: cortical and trabecular
- Both have the same composition and structure
- Cortical bone has lower porosity (10 %) than trabeculae bone (50-90 %)
- Different distribution implies different mechanical properties

Cortical bone

Trabecular bone

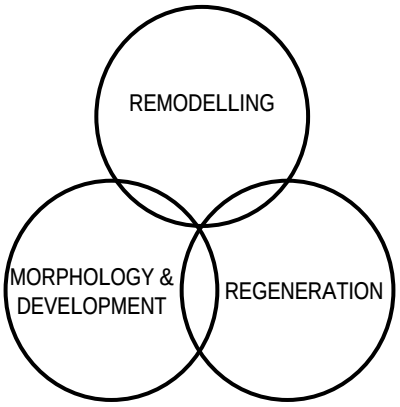
BONE COMPOSITION

- Matrix:
  - It is composed with an organic and inorganic component with water
  - Organic part (mainly collagen) defines the bone shape and tensile strength
  - Inorganic part (mineral) defines the compressive strength
- Cells: responsible of the modification of the structure and properties of tissues (2% of the bone mass)
  - Osteoblasts (surface)
  - Osteoclasts (surface)
  - Bone lining cells (surface)
  - Osteocytes (inside)

BONE PROPERTIES

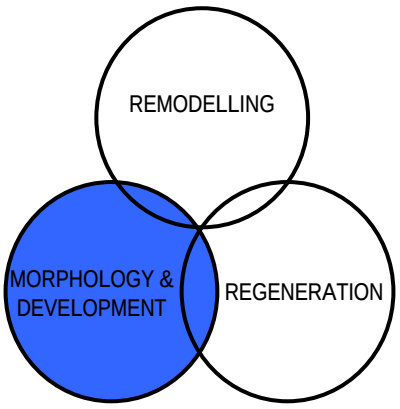
- Different functions
- Bone is a ***hierarchical structural composite*** material:
- It is an ***evolutive (adaptative)*** material able to modify its internal properties, size and shape in function of the environment that is supporting.

EVOLUTIVE BEHAVIOUR OF BONE



BONE PROPERTIES

EVOLUTIVE BEHAVIOUR OF BONE



IN THE
BEGINNING OF LIFE

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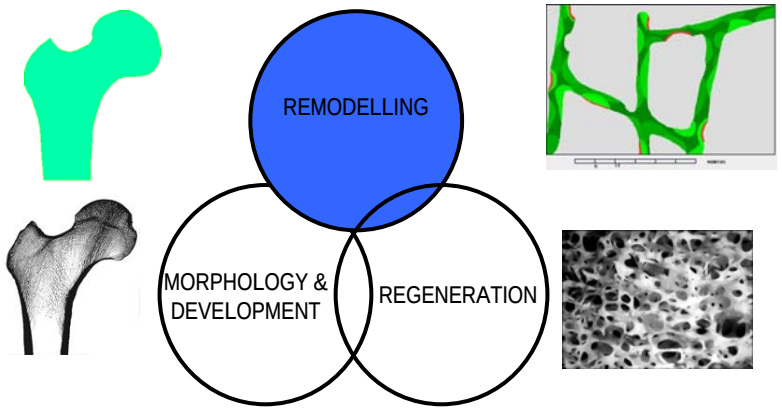
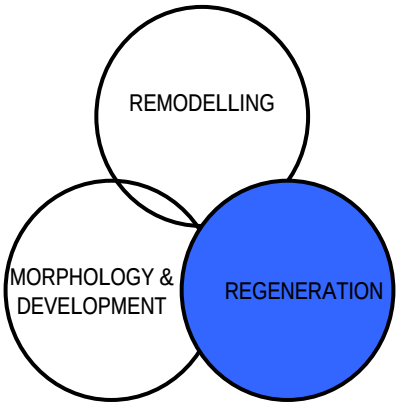
- Construction and reconstruction of tissues is the combined result of two factors: phylogenetic and ontogenetic processes.
- Phylogenetic processes (species evolution) involve random genetic variation and natural selection of the best fitted.
- Ontogenetic (individual) adaptation is accomplished by appropriate mechano-regulatory rules.
- The mechano-regulatory process can be evolved themselves, so epigenetic (environmental) factors can have also important influence in long-term evolution of species. (Carter, D.R., Mikic, B. and Padian, K. "Epigenetic mechanical factors in the evolution of long bone epiphyses". *Zool. J. Linnean Soc.* 123 (1998) 163-178)
- These processes are controlled by a combination of genetic and epigenetic factors (Edelman, *Topobiology. An Introduction to Molecular Embriology*. Basic Books, 1988).
- Genes direct the formation of the basic building blocks, including proteins, extracellular matrix and adhesion molecules.
- Epigenetic factors, including chemical agents, and mechanical strain influence which genes are expressed and how these blocks are assembled into tissues.

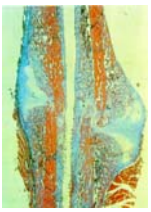
EVOLUTIVE BEHAVIOUR OF BONE



ALL THE LIFETIME

EVOLUTIVE BEHAVIOUR OF BONE



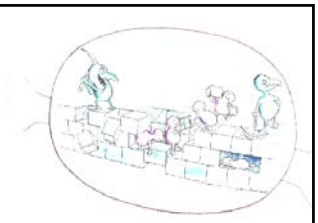


AFTER A FRACTURE

BONE PROPERTIES

- Different functions
- Bone is a ***hierarchical structural composite*** material:
- It is an ***evolutive (adaptative)*** material able to modify the properties and geometry in function of the environment that is supporting.
- Although the ***biology*** of these evolutive processes charactistic of these living tissues is mainly controlled by ***biochemical*** factors, the ***mechanical*** effects can also regulate them.

OVERVIEW



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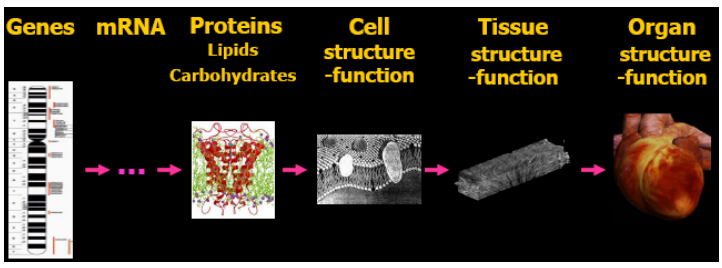
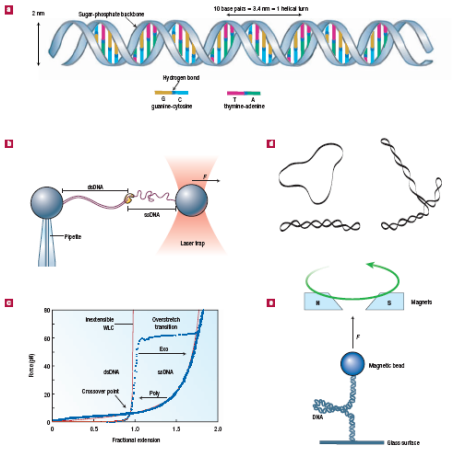
MECHANICAL FACTORS CAN REGULATE BIOLOGY

- Mechanical forces modulate morphological and structural fitness of the skeletal tissues (bone, cartilage, ligament and tendon) (van der Meulen and Huiskes, 2002)
- Mechanical forces may act within tissues to regulate biological processes at different spatial scales



(Hunter and Borg, 2003)

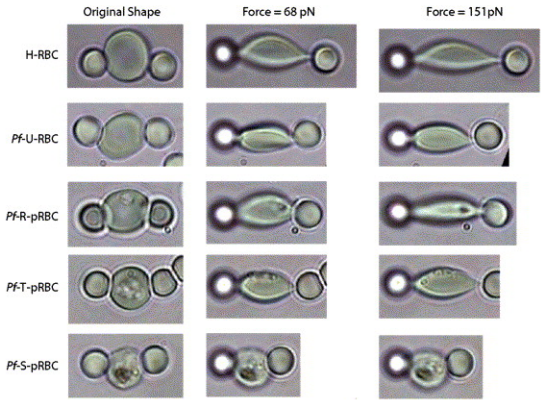
At molecular level, e.g., DNA mechanics



Bao and Suresh, *Nature Materials* 2003

BONE MECHANOBIOLOGY

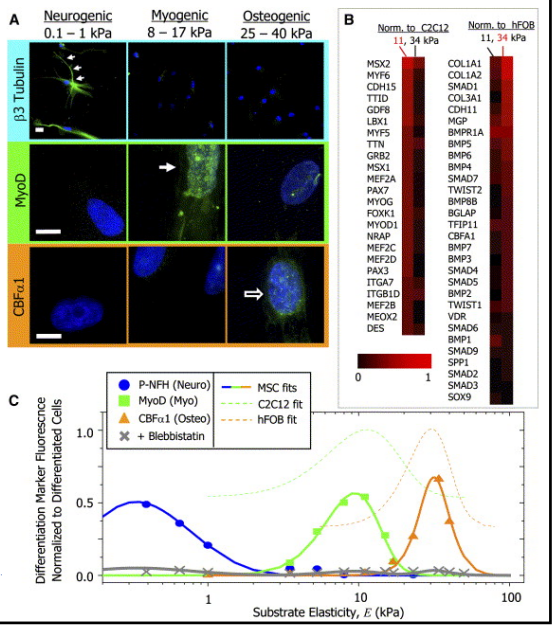
At cellular level, e.g., mechanical properties of healthy and infected/abnormal cells



Suresh et al., *Acta Biomaterialia* 2005

BONE MECHANOBIOLOGY

Cell-extracellular matrix interaction, e.g., cellular differentiation dependent on the matrix elasticity

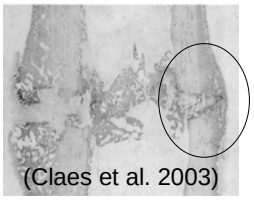


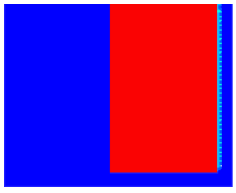
Engler et al., *Cell* 2006

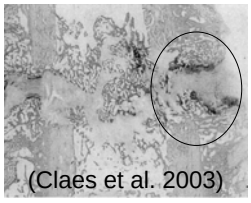
BONE MECHANOBIOLOGY

At tissue level, e.g., bone healing

0 días


(Claes et al. 2003)


2 mm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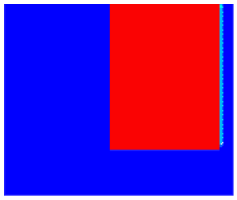
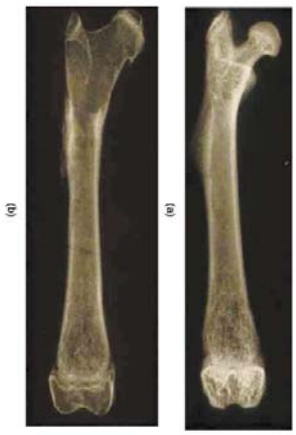

6 mm

(Gómez-Benito et al, 2005)

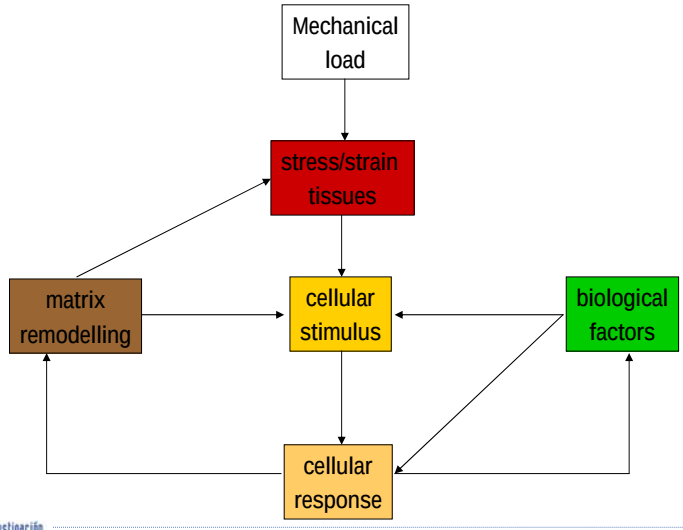
At organ level, e.g., mouse femora



(Chalmers & Ray, 1962)

Figure 1 Two mouse femora illustrate the effects of genetics and the effects of normal mechanical loading and genetics. (*a*) Normal morphology of a mouse femur developed within a normal functional loading environment. (*b*) Morphology of a mouse femur deprived of its normal mechanical loading. This femur was produced by transplanting the primordial template to the spleen and allowing it to develop there. The experiment thus provides insight into the nature of the primordial template for the mouse femur. From Chalmers & Ray (9).

HOW CAN BONE CELLS SENSE THE MECHANICAL LOAD?



HOW CAN BONE CELLS SENSE THE MECHANICAL LOAD?

- The mechanosensory mechanisms in bone include:
  - The mechanoreception system that identifies the process that transmits the informational content of an extracellular mechanical stimulus to a receptor cell.

BONE MECHANOBIOLOGY

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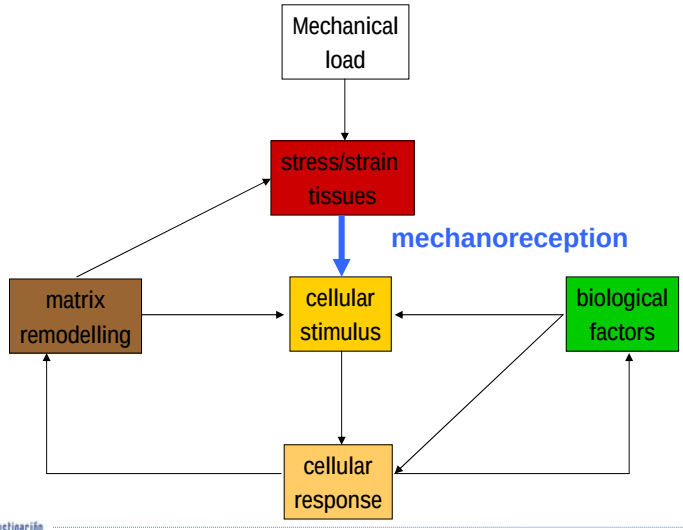

HOW CAN BONE CELLS SENSE THE MECHANICAL LOAD?

- The mechanosensory mechanisms in bone include:
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  - The mechanotransduction system that describes the process that transforms the mechanical stimulus content into an intracellular signal.

BONE MECHANOBIOLOGY

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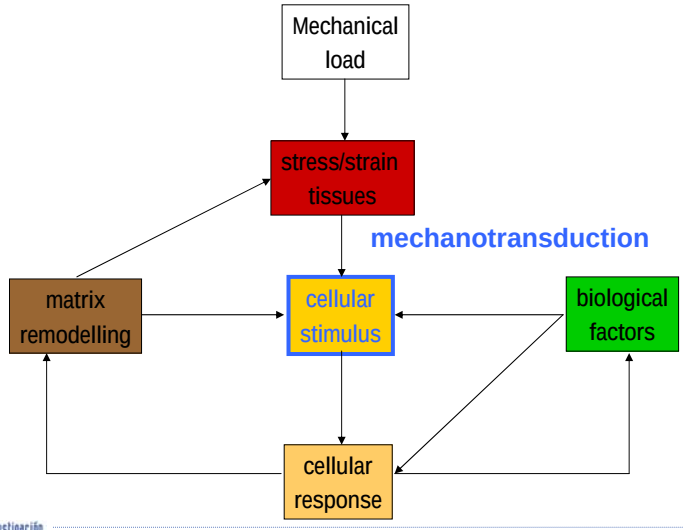

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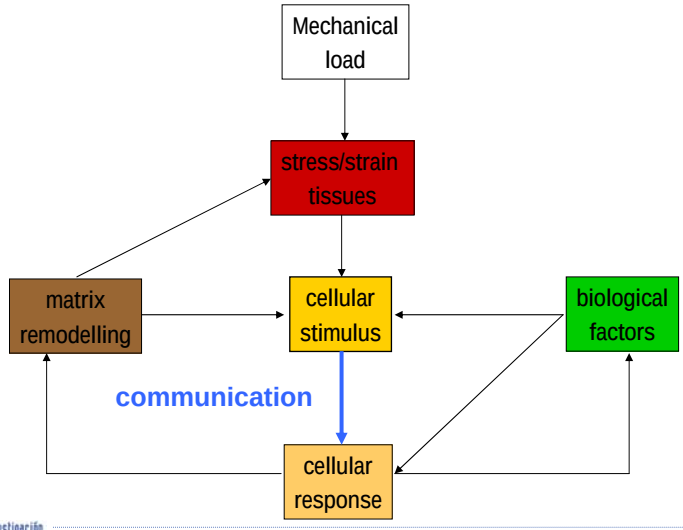
  - The mechanoreception system that identifies the process that transmits the informational content of an extracellular mechanical stimulus to a receptor cell.
  - The mechanotransduction system that describes the process that transforms the mechanical stimulus content into an intracellular signal.
  - The communication system that transmits that signal to the effector cells (osteoblasts and osteoclasts).

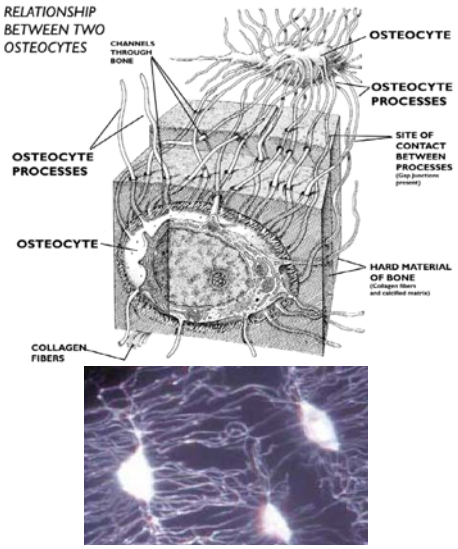
BONE MECHANOBIOLOGY

HOW CAN BONE CELLS SENSE THE MECHANICAL LOAD?

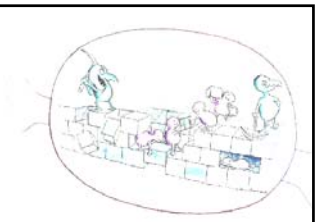


COMMUNICATION SYSTEM

- All bone cells except osteoclasts are extensively interconnected by the cell process of the osteocytes forming a syncytium or connected cellular network (CNN). This syncytium provides a route for rapid passage of ions and signal molecules. (Cowin, S.C. and Moss, M.L. in *Textbook of Tissue Engineering*. Lanza, R., Langer, R., Chick, W. (eds.). Academic Press, 723-738, 2000).



OVERVIEW



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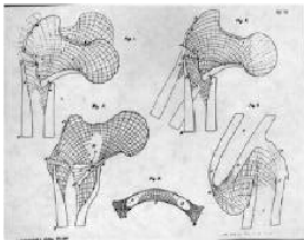
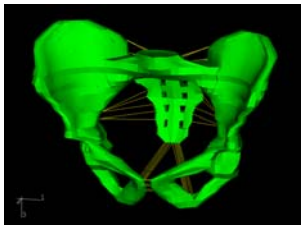
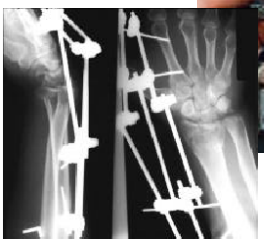
METHODS OF SCIENCE

- Theory
- Empiry
- Computer Simulation

J. Kelly, “The Third Culture”, Science 1998







METHODS OF SCIENCE: Computer Simulation

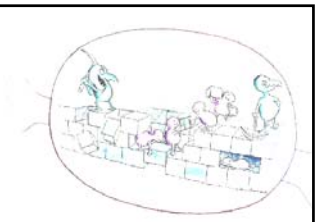
- Computational Modelling:

  “A computational model is a simplified and mathematical representation of a system for the purposes of analysing the behaviour of this system under different conditions”

METHODS OF SCIENCE: Computer Simulation

- Why computational modelling in mechanobiology?
  - Great difficulty of many experimental tests and practical impossibility of their customisation.
  - Possibility of comparing many different conditions and factors: mechanical, biological, pharmacological, etc.
  - Simulations closer to reality in some cases due to the possibility of considering and controlling factors that cannot be controlled or measure in experimental essays.
  - Economical impact: low cost.
  - Reduction of animal experiments

OVERVIEW



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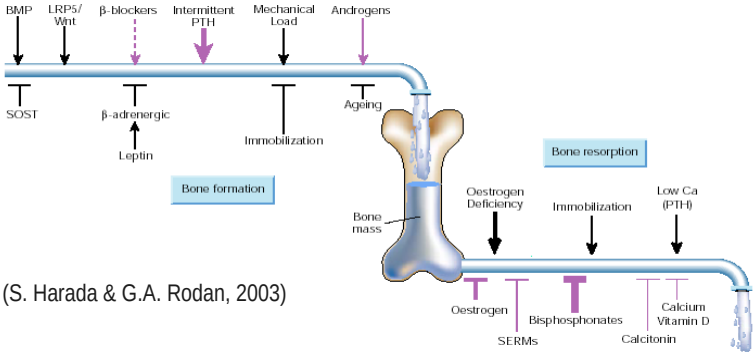
OBJECTIVES?

- Mechanical factors
- Biochemical factors

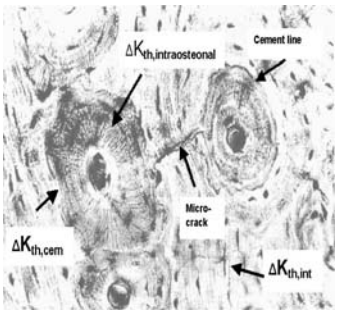


(S. Harada & G.A. Rodan, 2003)

BONE REMODELLING

OBJECTIVES?

- **Mechanical factors**
  - A mechanism to repair damage, reducing the risk for fracture (internal remodelling)
  - Optimize the stiffness and strength with minimum weight (external remodelling)
- Biochemical factors



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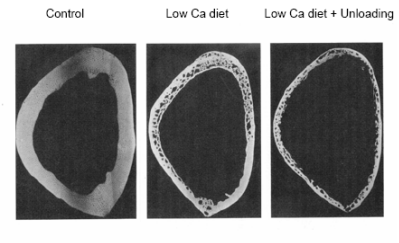
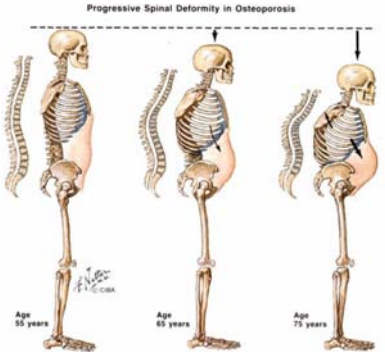
OBJECTIVES?

- Mechanical factors
- **Biochemical factors**
  - Regulate minerals and hormones
  - Nutrition
  - Osteoporosis

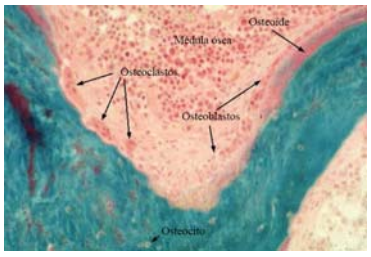


Lanyon et al. 1986

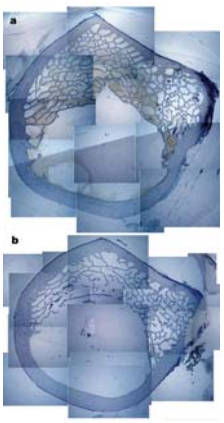


INTERNAL AND EXTERNAL REMODELLING

- Occur at bone surfaces where are located the bone lining cells
- Two types:
  - *Internal remodelling* or *remodelling*: in the trabeculae surfaces
  - *External remodelling* or *modelling*: in the periosteum and endosteum



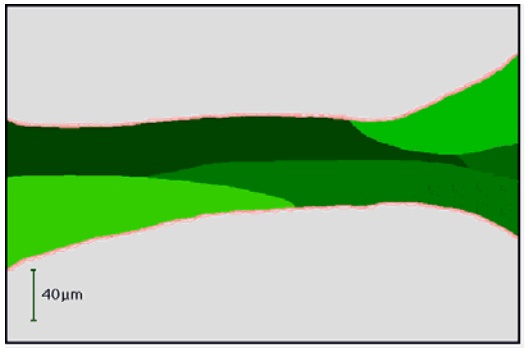
Internal remodelling or remodelling



external remodelling or modelling

INTERNAL BONE REMODELLING: BMUs

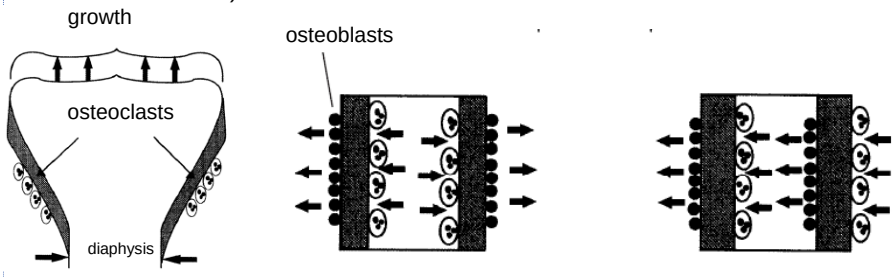
- It is accomplished by packets of cells, (Basic Multicellular Units, ***BMUs***) composed by osteoclasts and osteoblasts.
- It always follows the same sequence: Activation, Resorption, Reversal, Formation



http://uwcme.org/site/courses/legacy/bonephys/opgallery.php

EXTERNAL BONE REMODELING

- External bone remodelling (or modelling) may be resorptive or formative, there is an uncoupled process
- It could appear in the following:
  - Resorptive modelling beneath the growth plate to form the diaphysis form the metaphysis
  - Formative (periosteal surface) and resorptive (endosteal surface) modelling to enlarge the diaphysis
  - Modelling to "drift" the diaphysis to the left (thereby altering diaphyseal curvature)



FIRST THEORIES

- **Wolff's law**: "dependence between bone structure and the load that it supports".
- **Roux's theory:** "bone adapted itself in order to support stresses in an optimal way with minimum mass"

(Cowin, S.C. "The false premise in Wolff's law", in *Bone Mechanics. 2nd Ed.* (Cowin, S.C. ed.), **30**;1-15)

PHENOMENOLOGICAL VS MECHANOBIOLOGICAL MODELS

Phenomenological

- predict bone remodelling: direct relationships between mechanical stimulus and bone response
- follow experimental evidences

Mechanobiological

- Mechanobiology (Carter et al., 1998):

"the study of how mechanical or physical conditions can regulate biologic processes"

- follow mechanobiological facts

PHENOMENOLOGICAL MODEL

PHENOMENOLOGICAL VS MECHANOBIOLOGICAL MODELS

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- follow experimental evidences

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"the study of how mechanical or physical conditions can regulate biologic processes"

- follow mechanobiological facts

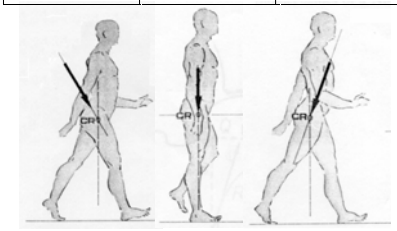
MECHANOBIOLOGICAL MODEL

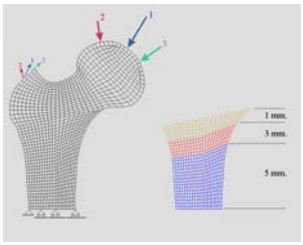
SOME PHENOMENOLOGICAL MODELS

- Models based on global optimality criteria: Rodrigues, 1998; Fernandes, Rodrigues and Jacobs, 1998; Terrier and Rakotomanana, 1997,..Pedersen, 1993).
- Models based on achieving a homeostatic state of strain or stress: Pauwels and Kummer 1965, 1972; Cowin and Hegedus, 1977; Carter et al., 1987; Huiskes et al. (1987), Beaupré et al, 1990a, 1990b; Cowin et al. (1992), Jacobs, 1994, 1997; Fyhrie y Schaffler, 1995; Terrier et al, 1997a; Mikic y Carter, 1995; Petermann et al, 1997; Stülpner et al, 1997; Turner et al., 1997; Luo et al., 1995, ***Doblaré and García, 2001***, and many others.
- Models based on damage repairing: Prendergast and Taylor, 1994; Ramtani, 2000,2001.

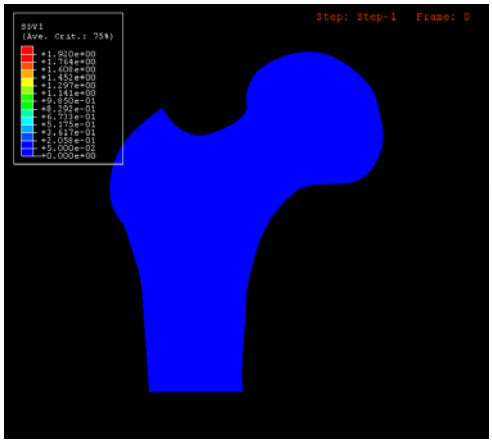
2D SIMULATION OF THE REMODELLING PROCESS OF THE PROXIMAL FEMUR

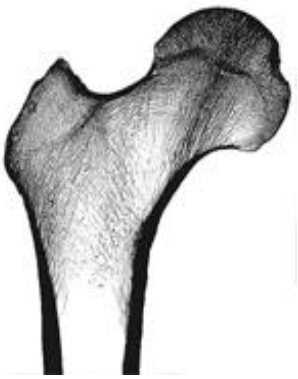
Load cases	Cycles per day	Load over the femoral head		Reaction at the abductor	
		Magnitude (N)	Orientation (º)	Magnitude (N)	Orientation (º)
1	6000	2317	24	703	28
2	2000	1158	-15	351	-8
3	2000	1548	56	468	35





- Prediction of apparent density distribution

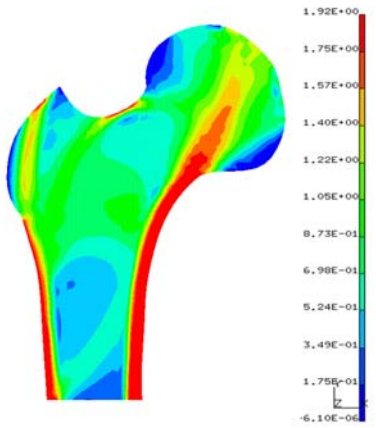




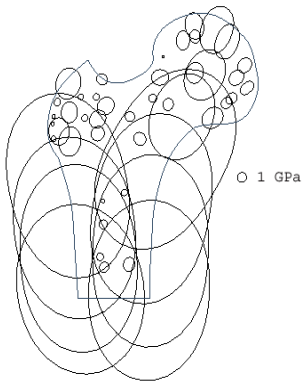
(Doblaré & García, 2001, 2002)

BONE REMODELLING EXAMPLES

- Prediction of anisotropy



300 days



(Doblaré & García, 2001, 2002)

BONE REMODELLING

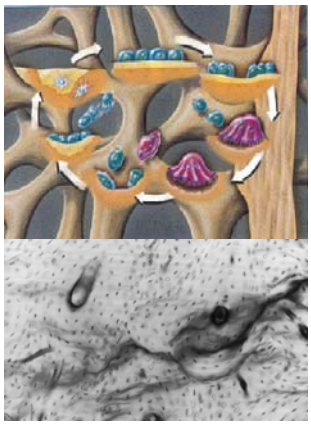
SOME MECHANOBIOLOGICAL MODELS

- Mechanobiological models: Huiskes et al, 2000; Hernandez et al., 2000; Hazelwood et al, 2001; ***García-Aznar et al., 2005***

MECHANOBIOLOGICAL MODEL: main purpose

- Development and validation of a computational model able to:
  - simulate bone remodelling process
  - predict bone stress fractures

  considering:
  - biological effects are controlled by BMU activity
  - actual damage evolution



(García-Aznar et al., 2005)

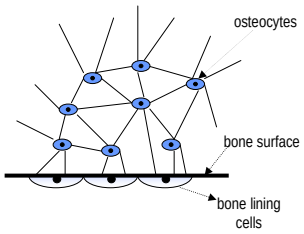
BONE REMODELLING

MECHANOBIOLOGICAL MODEL: main assumptions

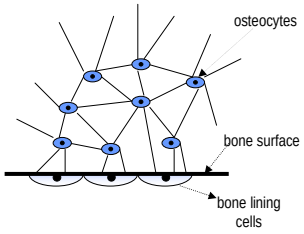
- The occurrence of BMUs is mainly activated by disuse (Martin, 2000):
  - a low mechanical stimulus
  - microcraks (microdamage) break the communication channels between cells reducing the level of mechanical signal and causing an effect similar to disuse.

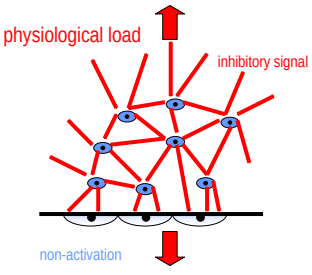
instituto de investigación en ingeniería de Aragón Universidad de Zaragoza
Santiago de Compostela, Julio 2010

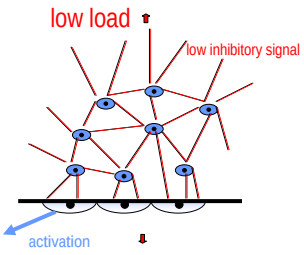
Unifying Theory of Bone Remodelling (Martin, 2000)

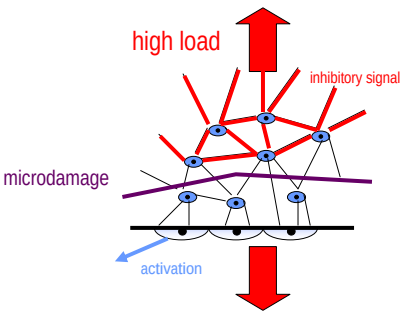


Unifying Theory of Bone Remodelling (Martin, 2000)









MECHANOBIOLOGICAL MODEL: main assumptions

- The occurrence of BMUs is mainly activated by disuse (Martin, 2000):
  - a low mechanical stimulus
  - microcraks (microdamage) break the communication channels between cells reducing the level of mechanical signal and causing an effect similar to disuse.
- The born rate of BMUs depends on this inhibitory signal, the specific surface and patient and organ-dependent biological factors.
- The inhibitory signal depends on the damage level and a strain measure that characterizes the daily loading history.
- Damage growth and elastic modulus degradation is different for tension and compression.
- Damage is uniformly distributed.
- The mechanical behaviour is linear elastic, heterogeneous and isotropic with the local stiffness depending on the porosity, mineralisation degree and damage level.

MECHANOBIOLOGICAL MODEL: definition

- basic variables
- mechanical stimulus
- BMU birth-rate
- BMU progression
- evolution of bone volume fraction
- focal bone balance
- mineralization
- damage
- material behaviour

MECHANOBIOLOGICAL MODEL: definition

- Basic variables

  - subdivision of reference volume:

$$V_T = V_B + V_V$$

$$V_B = V_M + V_O + V_D$$

  - bone volume fraction $\quad v_b = \frac{V_B}{V_T} = 1 - p, \;\; p = \frac{V_V}{V_T}$

  - ash fraction $\quad \alpha = \frac{M_M}{M_d} = \frac{\rho_M V_M}{\rho_M V_M + \rho_O V_O}$

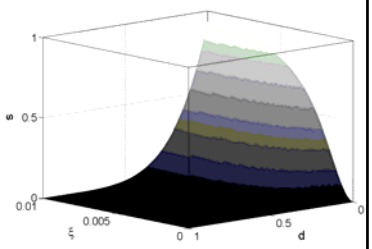
  - continuum damage variable $\quad d = \frac{V_D}{V_B} = 1 - \frac{E}{E_0}$

MECHANOBIOLOGICAL MODEL: definition

- Inhibitory signal
  - Transmitted by the osteocyte network
  - Level of the received signal

$$s = \frac{\xi}{\xi + c}(1 - d)^k$$

($(1-d)^k$: damage)



  - Daily loading history $\quad \xi = \left(\sum_i N_i \, \bar{\varepsilon}_i^{\,m} \right)^{1/m}$

    with $\bar{\varepsilon} = \sqrt{\frac{2U}{E}}$ and U the strain energy density

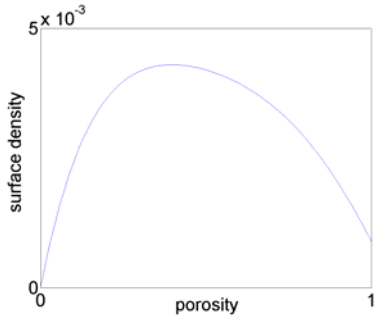
    N_i the daily number of cycles of each load case i

MECHANOBIOLOGICAL MODEL: definition

- BMU birth-rate $\dot{N}_{BMU} = f_{Or}\, S_V$
  - S_V is specific surface density and function of porosity (Martin, 1984)
  - Origination frequency

$$f_{Or} = f_{bio}\,(1 - s)$$

with f_{bio} a specific biological factor and s the inhibitory signal

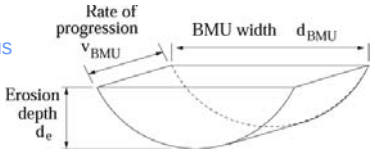


BONE REMODELLING

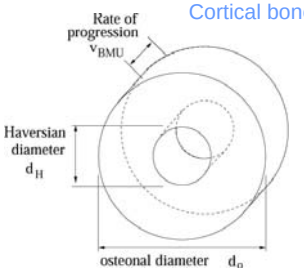
MECHANOBIOLOGICAL MODEL: definition

- BMUs' progression: Spatial evolution

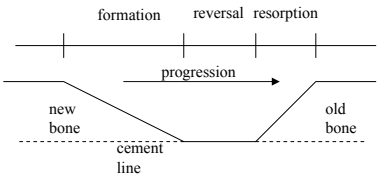
Cancellous bone



Cortical bone

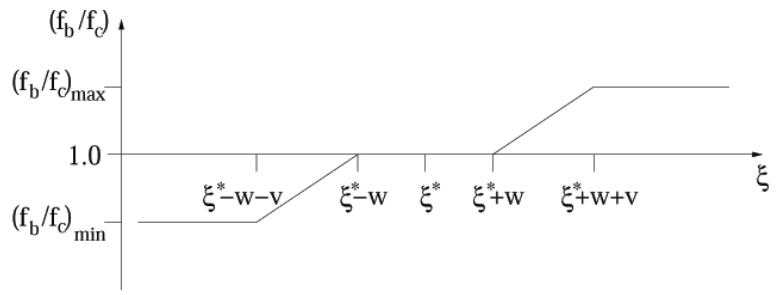


- BMUs' progression: Time evolution
  - *Resorption interval* T_r
  - *Reversion interval* T_l
  - *Formation interval* T_F



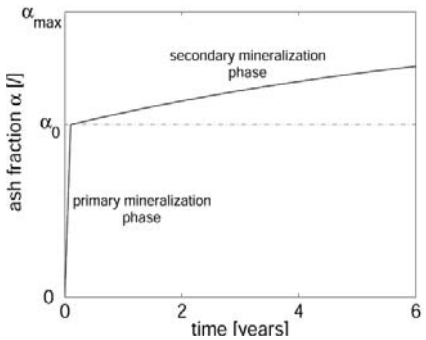
MECHANOBIOLOGICAL MODEL: definition

- Focal bone balance
  - rate of the osteoblasts and osteoclasts activity
  - reference stimulus adaptation $\xi^* = \xi - \left(\xi - \xi_0^*\right)e^{-\varphi t}$



MECHANOBIOLOGICAL MODEL: definition

- Mineralisation
  - time-dependent process
  - two phases
  - the secondary phase takes into account the influence of the remodelling



$$\overline{\alpha}(t) = \frac{v_{b,0}\,\alpha(t) + \int_0^t \dot{v}_F(\tau)\alpha(t-\tau) - \dot{v}_R(\tau)\overline{\alpha}(\tau)\,d\tau}{v_b(t)}$$

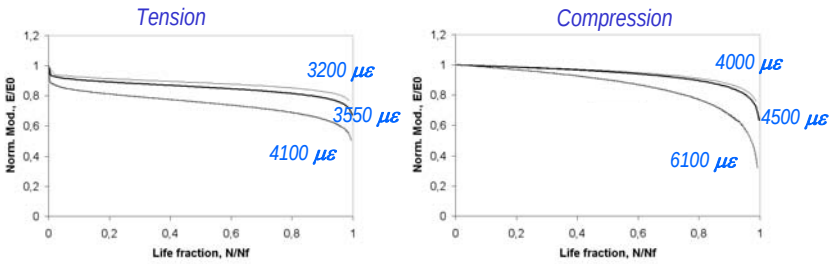
MECHANOBIOLOGICAL MODEL: definition

- Damage Growth
  - Continuum Damage Mechanics (CDM)
  - non-linear damage with different effect for tension and compression

$$\frac{\partial d_c}{\partial N} = G_c(d,\tilde{\varepsilon}) = \frac{C_1}{\gamma_1} e^{\gamma_1 d} \tilde{\varepsilon}^{\delta_1}$$
$$\frac{\partial d_t}{\partial N} = G_t(d,\tilde{\varepsilon}) = \frac{C_2}{C_3\gamma_2} (1-d)^{1-\gamma_2} e^{-C_3(1-d)^{\gamma_2}} \tilde{\varepsilon}^{\delta_2}$$

MECHANOBIOLOGICAL MODEL: definition

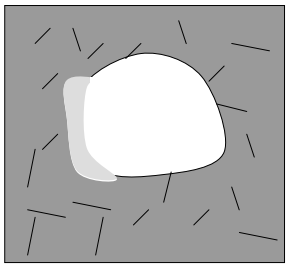
- Damage Growth
  - constants were determined from experimental tests for human femoral bone loaded in different levels for tension and compression (Pattin et al., 1996)



MECHANOBIOLOGICAL MODEL: definition

- Damage Repair
  - damage is uniformly distributed
  - damage is repaired as remodelling progresses

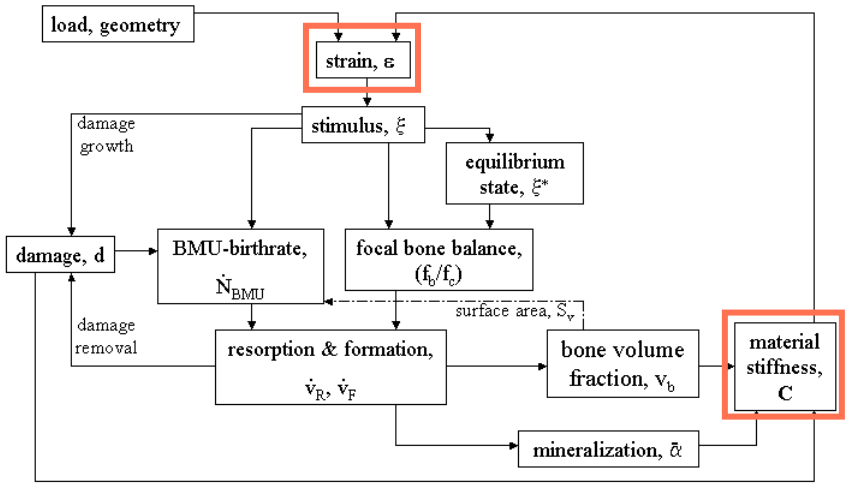
$$d = \frac{V_d}{V_B} => \begin{cases} \dot{d} = 0 & \text{(resorption)} \\ \dot{d} = -\dot{v}_F \dfrac{d^2}{D} & \text{(formation)} \end{cases}$$



MECHANOBIOLOGICAL MODEL: definition

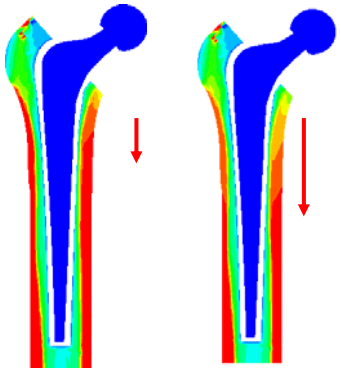
- The ***mechanical behaviour*** is linear elastic, heterogeneous and isotropic with the local stiffness depending on the porosity, mineralisation degree and damage level.
  - elastic modulus $E = 84,370\ v_b^{2.58}\ \alpha^{2.74}\ (1-d)\ MPa$
  - Poisson's ratio $\nu = 0.3$
  - constitutive law $\sigma = \frac{E\nu}{(1+\nu)(1-2\nu)} tr\,\varepsilon\ 1 + \frac{E}{1+\nu}\varepsilon$

GLOBAL CONSTITUTIVE SCHEME

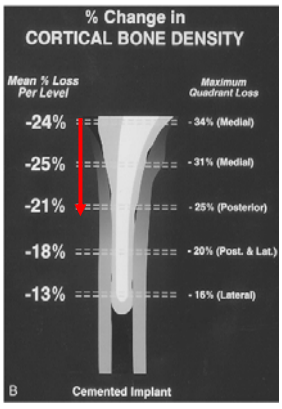


BONE REMODELLING EXAMPLES

- Prediction of bone remodelling after implantation of the hip prosthesis: reasonable agreement with clinical results



f_{bio}=0.03 f_{bio}=0.05



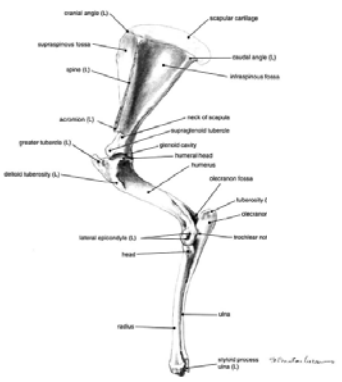
(Maloney et al., 2002)

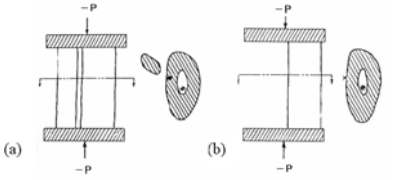
(García-Aznar et al, 2005)

BONE REMODELLING EXAMPLES

SIMULATION OF LANYON EXPERIMENTS (1982) ON ADULT SHEEP (Martínez et al., 2006)

- Ulna osteotomy to change the mechanical environment

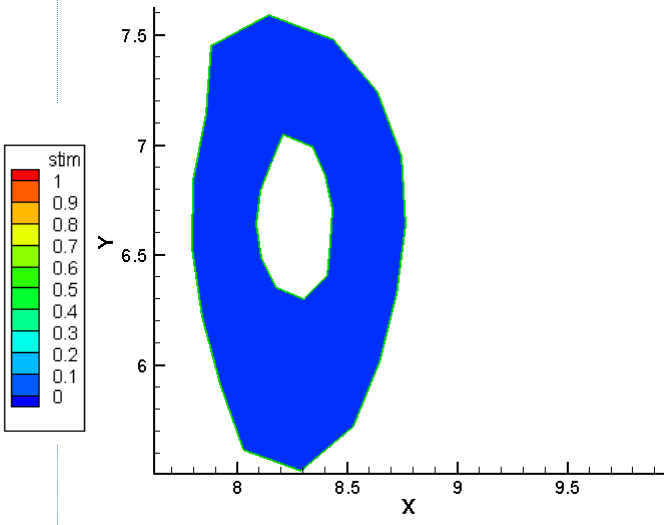




Cowin et al (1985)

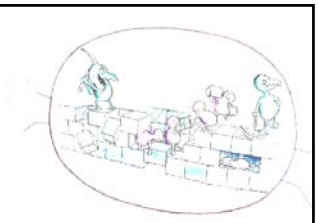
Lanyon et al (1982)

BONE REMODELLING EXAMPLES



After 9 months
(Lanyon et al,1982)

OVERVIEW

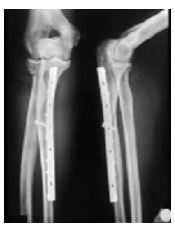


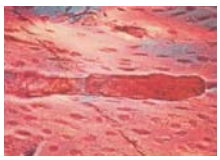
- ***Bone properties***
- ***Role of mechanical factors: bone mechanobiology***
- ***Methods of Science: computer simulation***
- ***Modelling Bone Mechanobiology:***
  - ***Bone Remodelling***
  - ***Bone Healing***
  - Bone Distraction
  - Bone Tissue Engineering
- Final conclusions

BONE HEALING

Primary healing

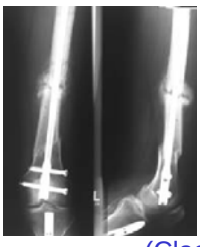
- callus free
- absolute stability
- no interfragmentary movement
  - ✓ perfect anatomic reduction
  - ✓ interfragmentary compression

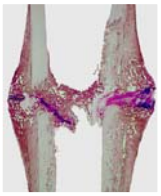




Secondary healing

- healing via callus or granulation tissue
- similar to bone growth
- involving tissue differentiation in the fracture gaps
- relative stability: less rigid or flexible stabilisation





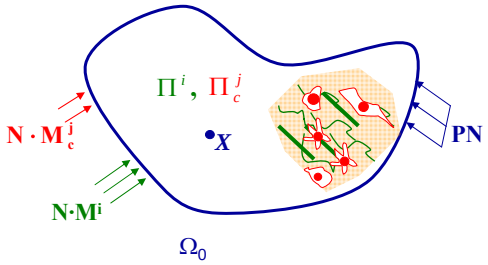
(Claes et al, 2003)

SOME MODELS

- Computational estimation of differentiation rules -> level of strain/stress in a time point of the healing process: Davy and Connolly, 1982; DiGioia et al., 1986; Claes et al. , 1996, 1998, 1999; Carter et al., 1998.
- Evolutive differentiation models: Kuiper et al., 2000; Ament and Hofer, 2000; Lacroix and Prendergast, 2002; Bailón-Plaza and Van der Meulen, 2001, 2003; Simons et al., 2004; Isaksson et al, 2006.
- Callus growth and tissue differentiation: ***Gómez-Benito et al., 2005, 2006; García-Aznar et al., 2007.***

- Balance equations of continuum multiphasic and multicellular tissue mixtures including possible growth have been developed in the continuum setting (generalization of previous formulations by Lubarda & Hoger,2002; Garikipati et al.,2004, etc.).
- The treatment is macroscopic considering:
  - Tissue growth, differentiation, remodelling and damage
  - Multiple tissues and different types of cells.
  - Sources (sinks) and diffusion of both mass and cells.
  - Energy transfer between the different tissues and cells.

MECHANOBIOLOGICAL MODEL



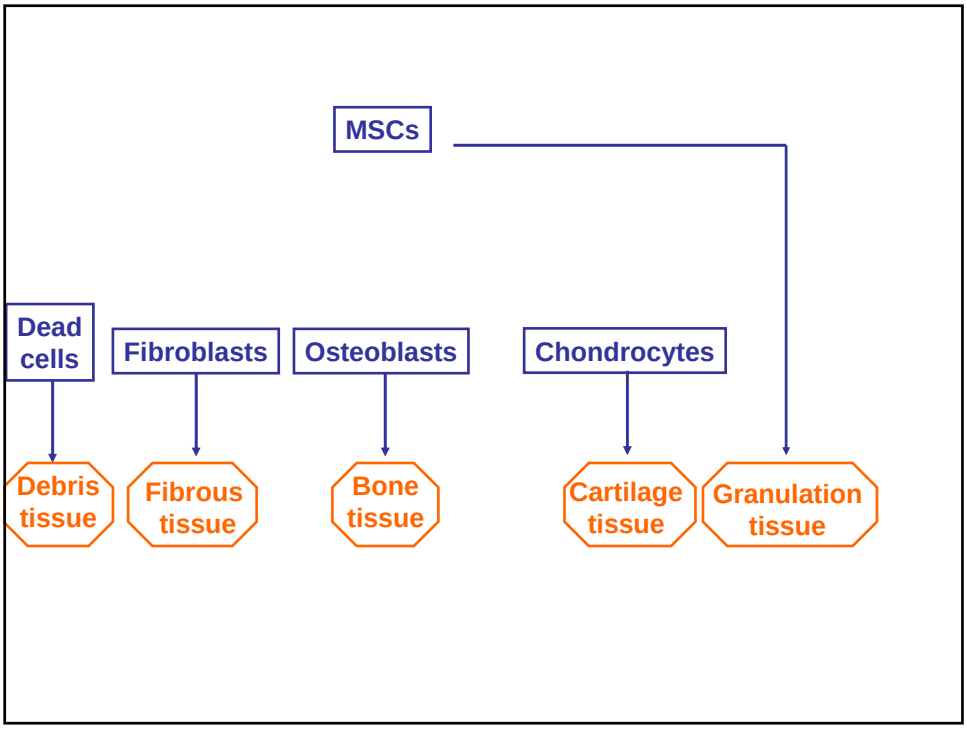
N tissues (*i*)

M cellular types (*j*)

$$\rho_0^i = \overline{\rho}_0^i V_m^i (1 - d_0^i)$$

ρ_0^i apparent density; $\overline{\rho}_0^i$ real density; V_m^i volume fraction; d_0^i percentage of damage; c_0^j

Generally each cell *j* is associated to one tissue *i*

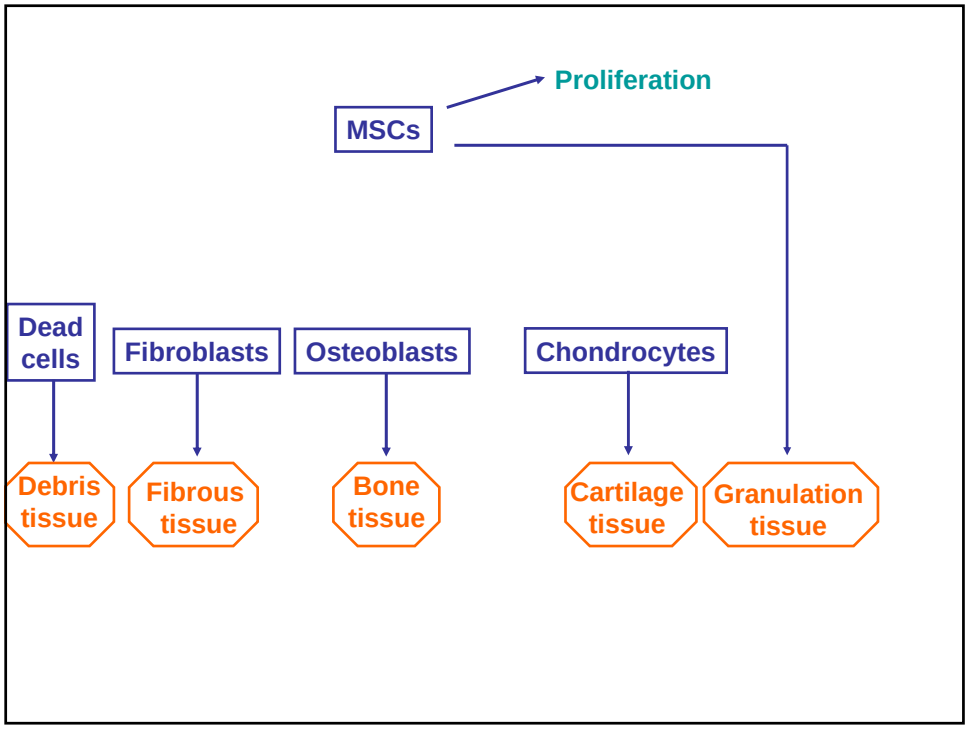


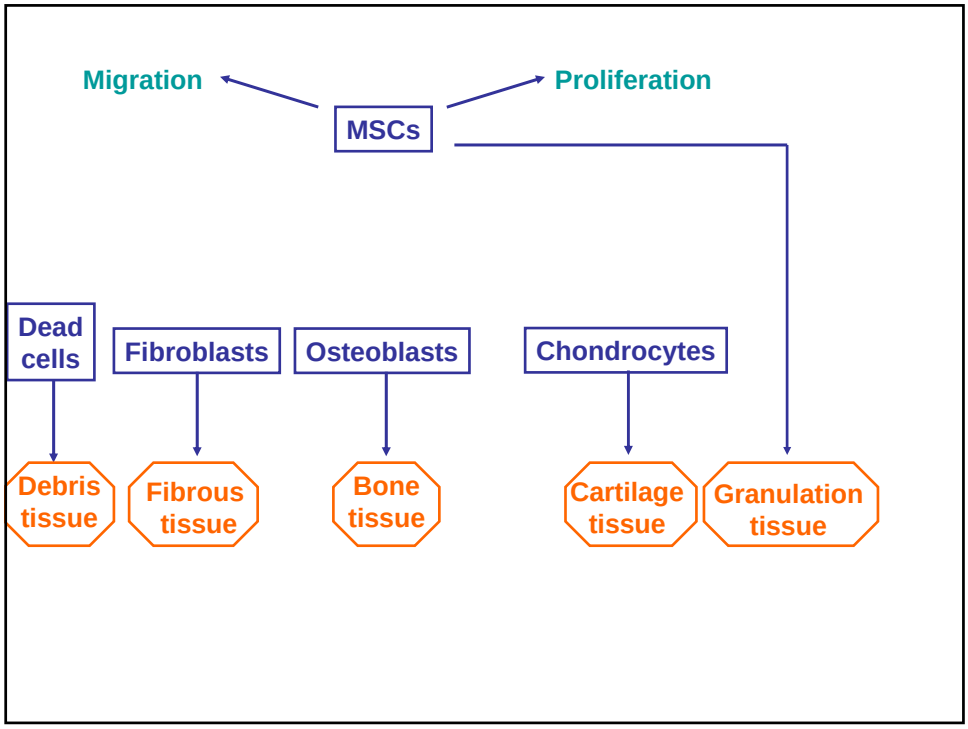
MECHANOBIOLOGICAL MODEL

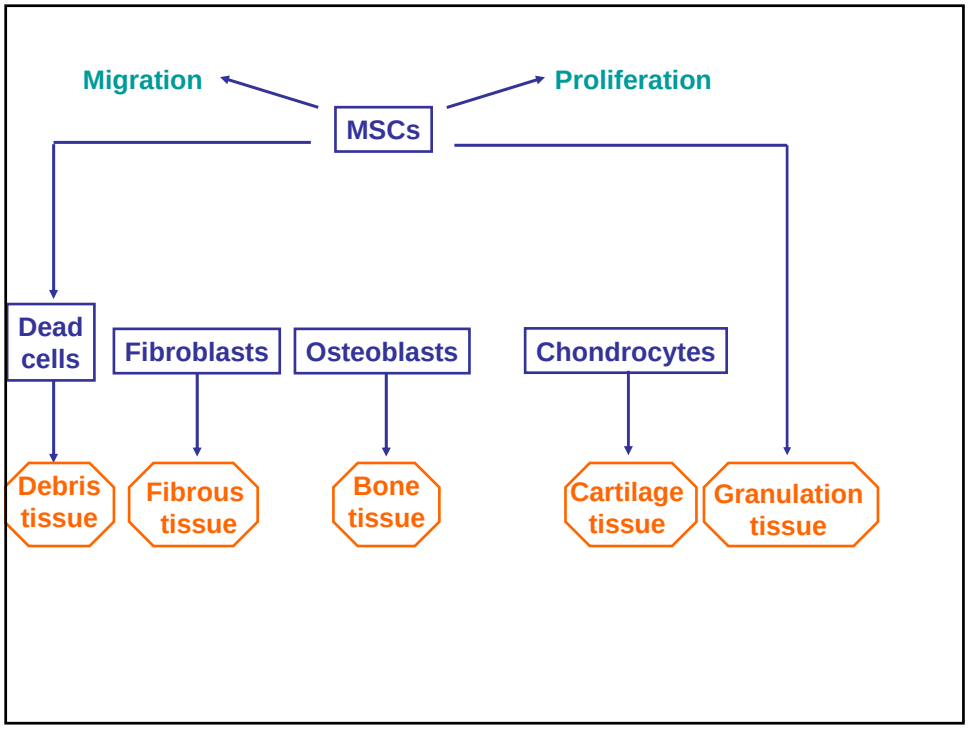
Equation of cell conservation

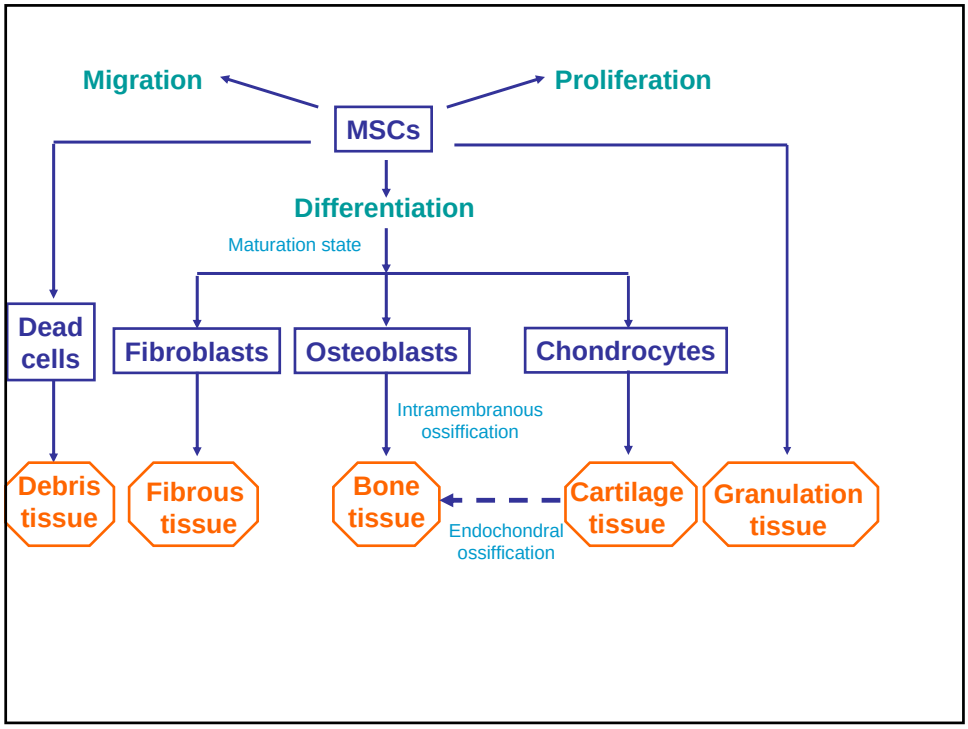
$$\frac{Dc(x,t)}{Dt} = f_{proliferation}(c,\Psi) + f_{migration}(c, V_{disrupted}) - f_{differentiation}(\Psi, m)$$

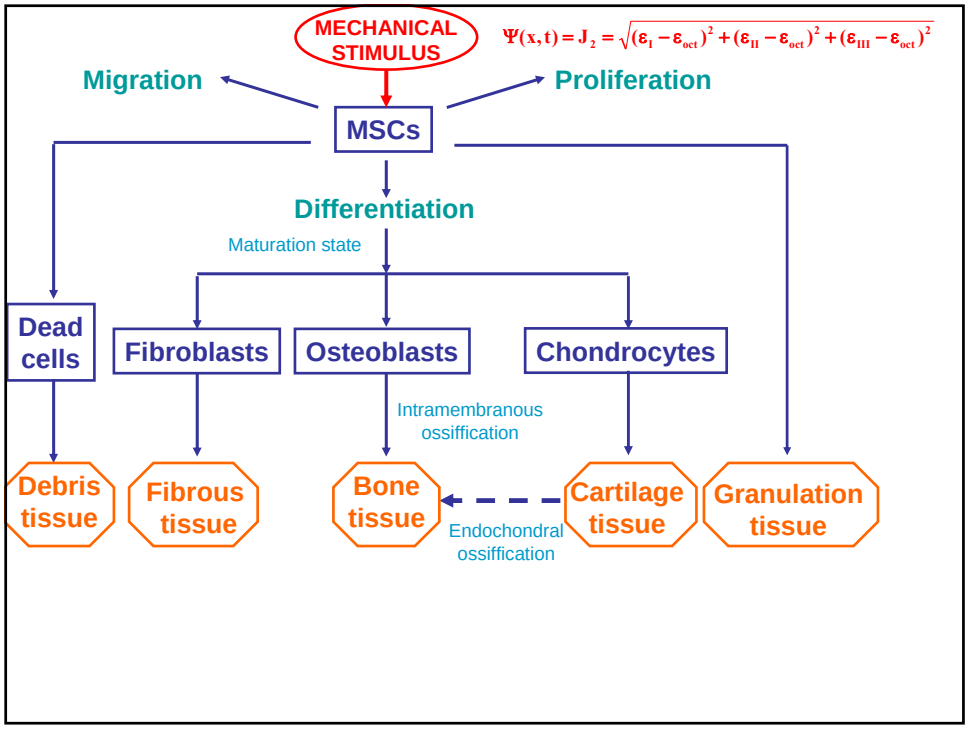
Proliferation (mitosis) — Migration — Differentiation




Migration
Proliferation
MSCs
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue

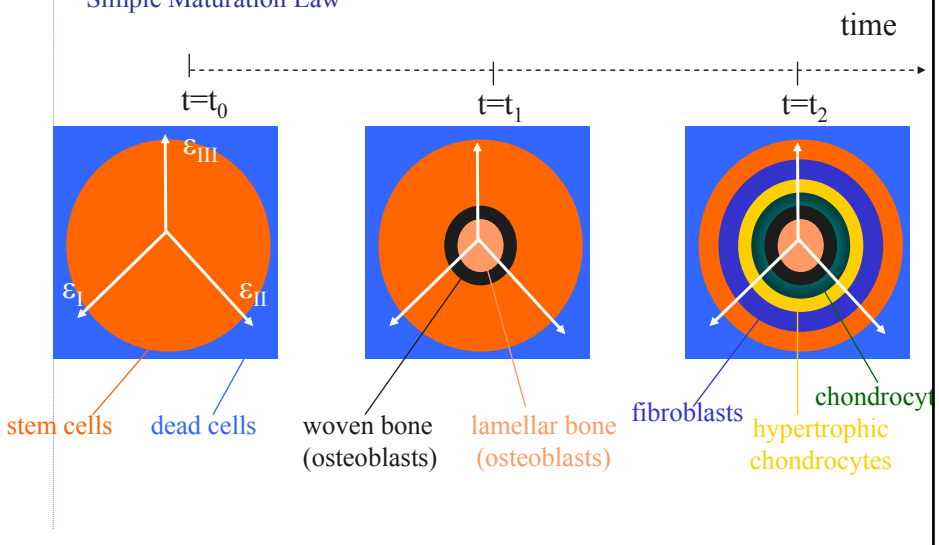

Migration
Proliferation
MSCs
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue

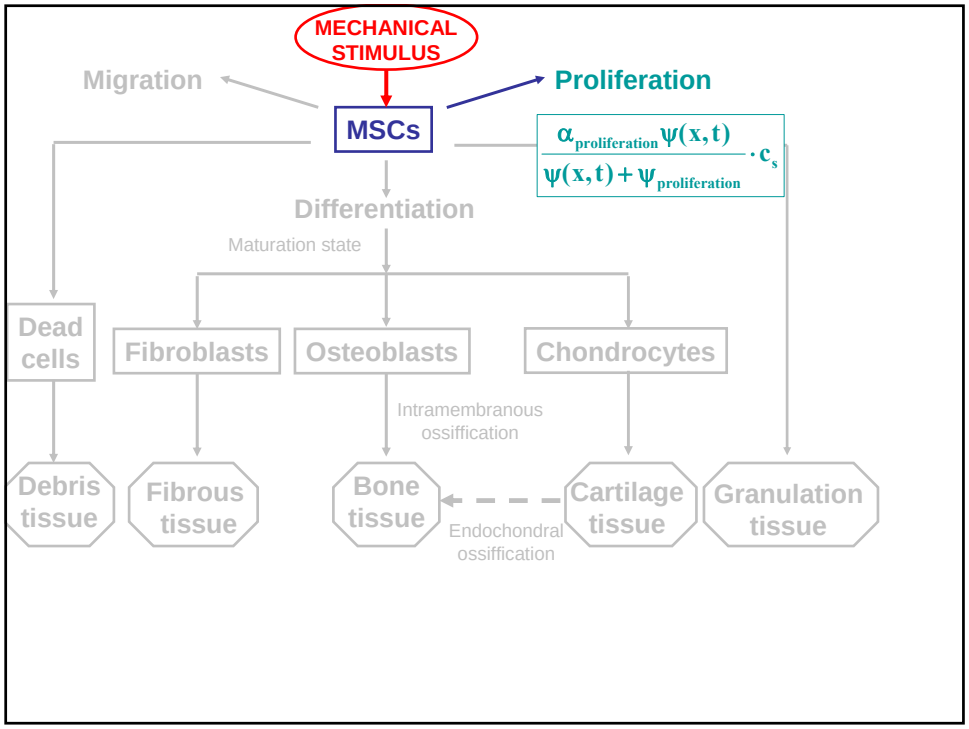

Migration
Proliferation
MSCs
Differentiation
Maturation state
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Intramembranous ossiffication
Debris tissue
Fibrous tissue
Bone tissue
Endochondral ossiffication
Cartilage tissue
Granulation tissue

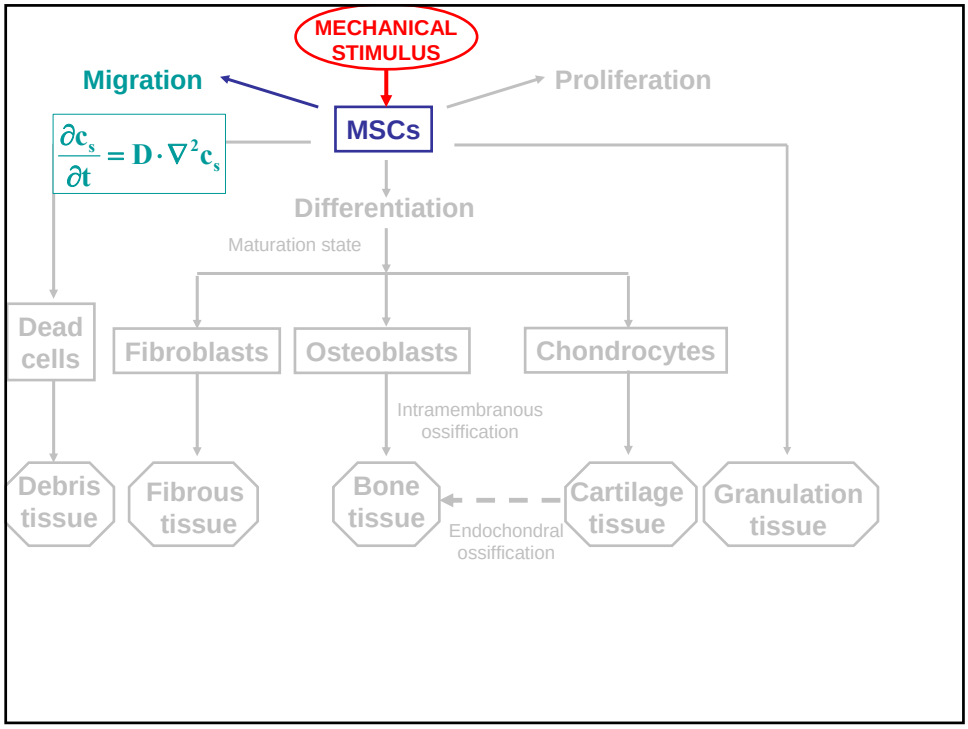

MECHANICAL STIMULUS
$\Psi(x,t) = J_2 = \sqrt{(\varepsilon_I - \varepsilon_{oct})^2 + (\varepsilon_{II} - \varepsilon_{oct})^2 + (\varepsilon_{III} - \varepsilon_{oct})^2}$
Migration
Proliferation
MSCs
Differentiation
Maturation state
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Intramembranous ossiffication
Debris tissue
Fibrous tissue
Bone tissue
Endochondral ossiffication
Cartilage tissue
Granulation tissue

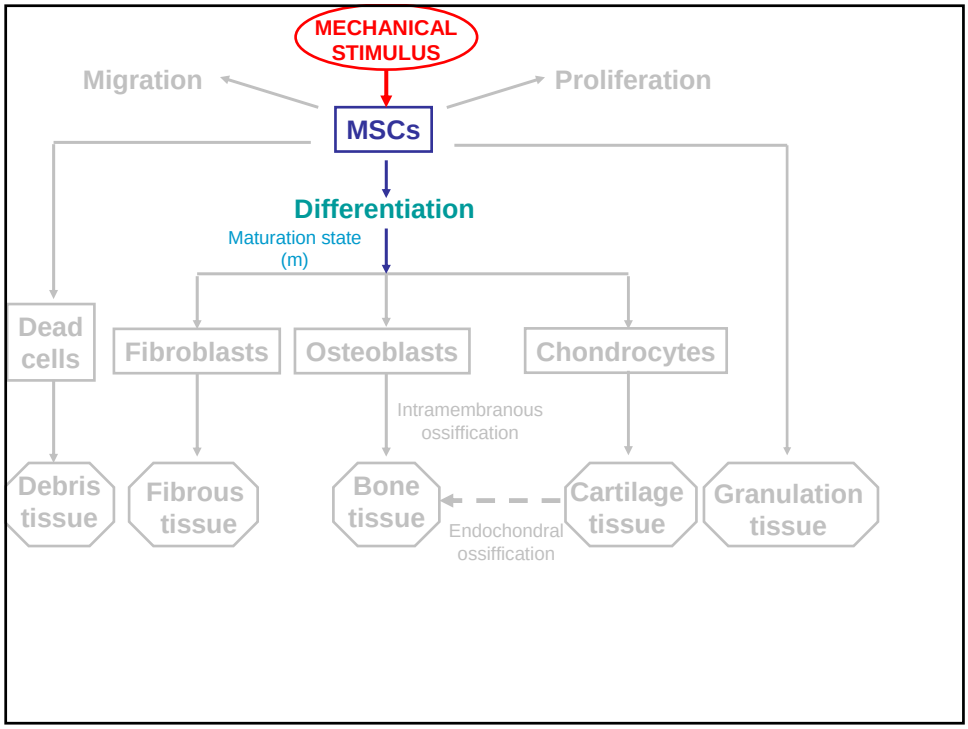
MECHANOBIOLOGICAL MODEL

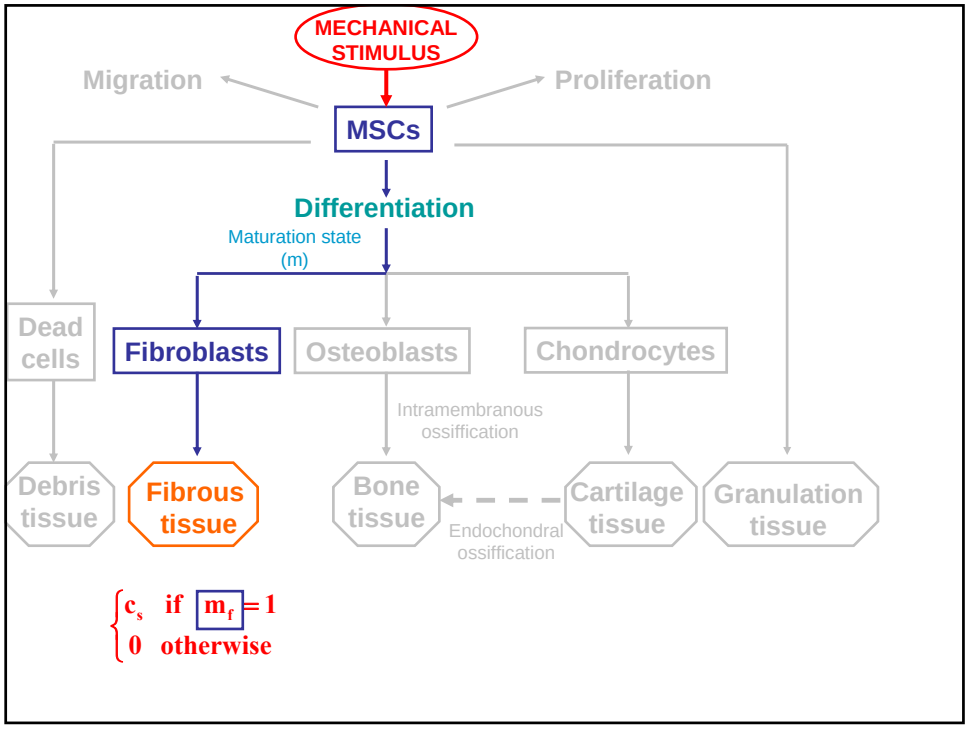
Simple Maturation Law

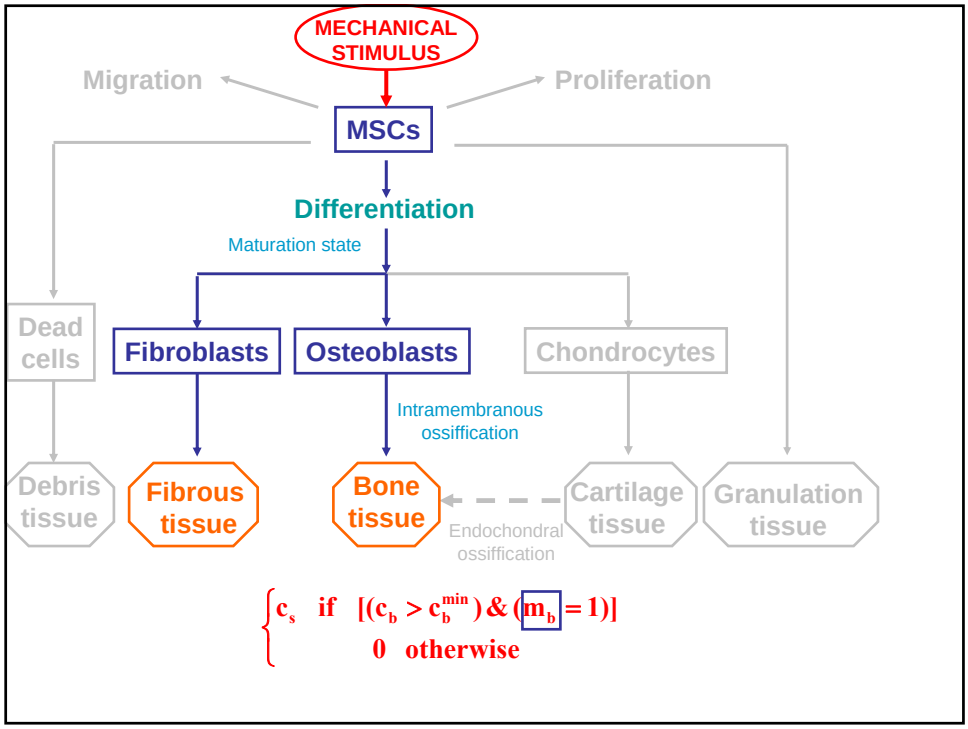


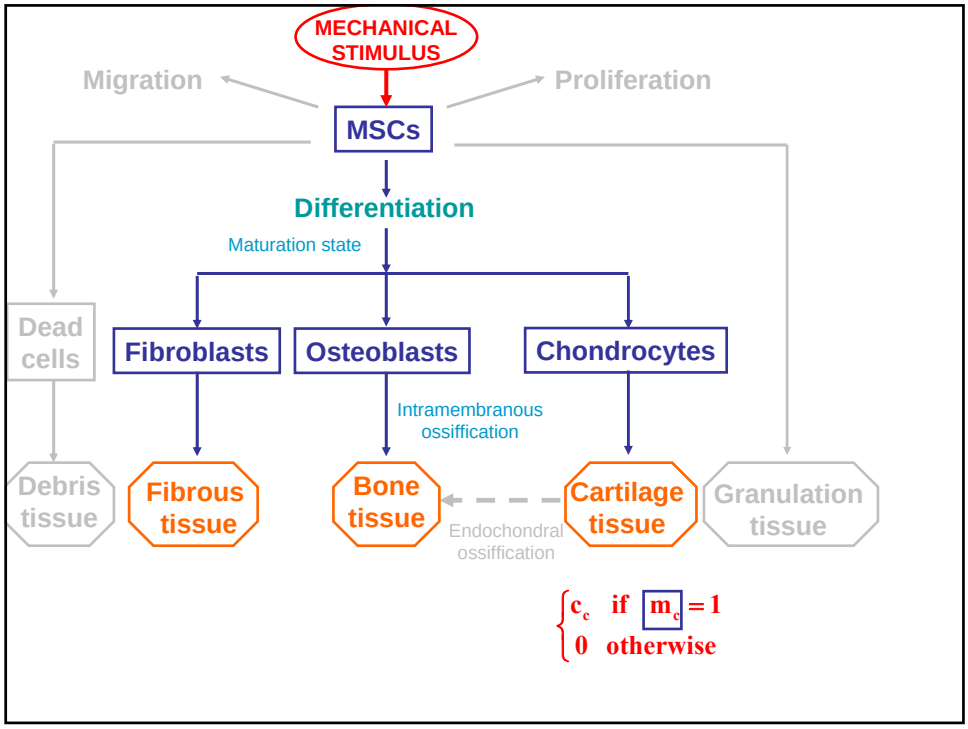


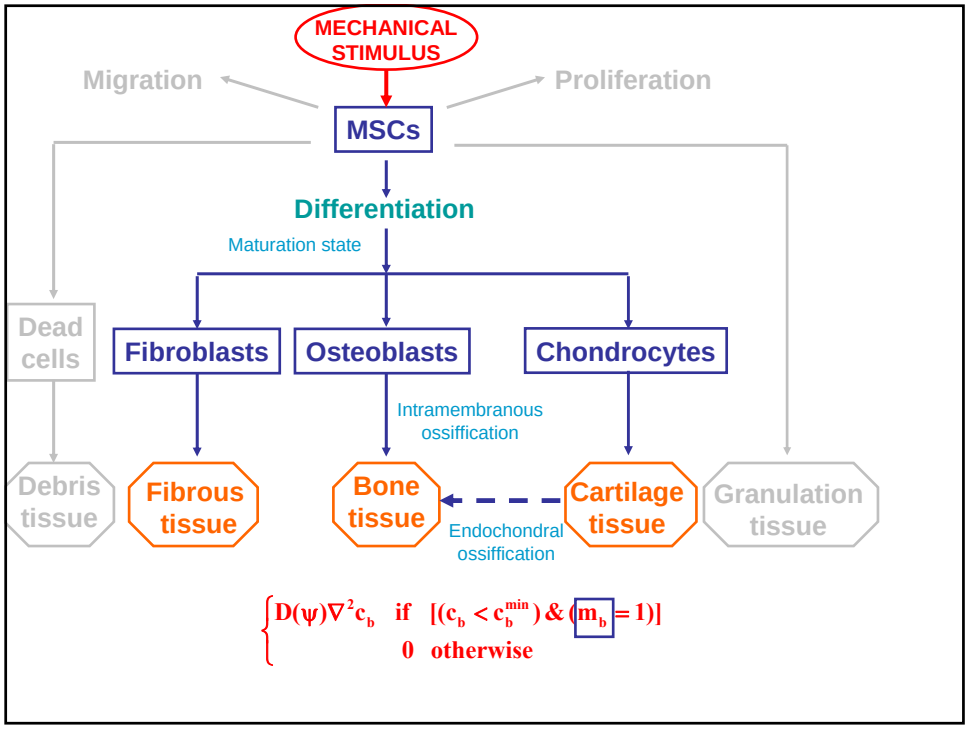

MECHANICAL STIMULUS
Migration
Proliferation
$\frac{\partial c_s}{\partial t} = D \cdot \nabla^2 c_s$
MSCs
Differentiation
Maturation state
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Intramembranous ossiffication
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue
Endochondral ossiffication

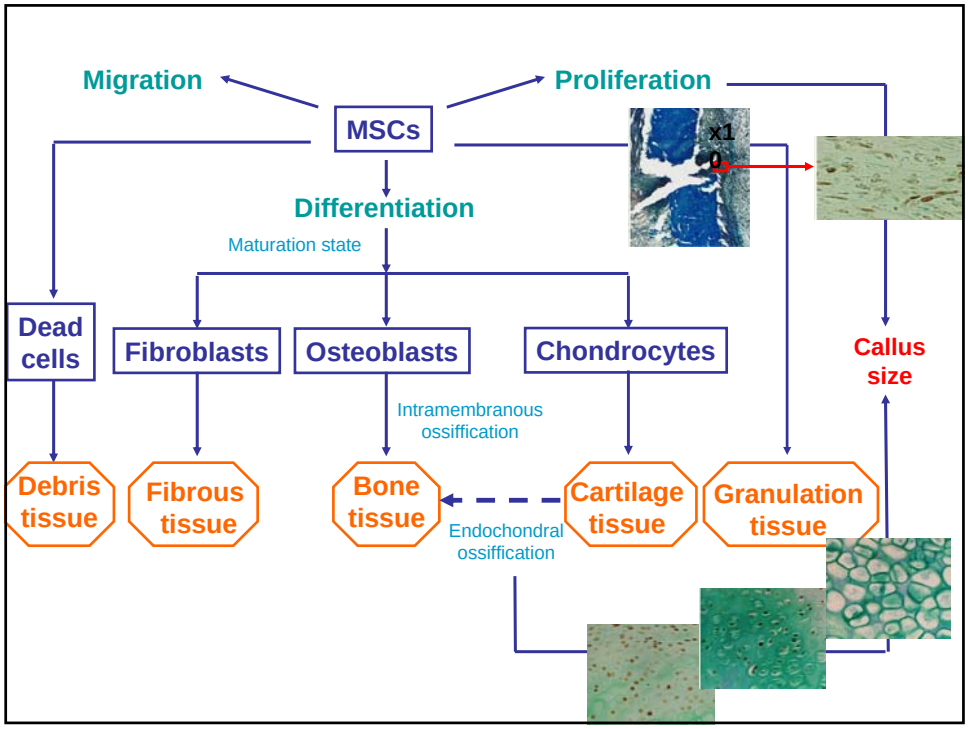

MECHANICAL STIMULUS
Migration
Proliferation
MSCs
Differentiation
Maturation state (m)
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Intramembranous ossiffication
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue
Endochondral ossiffication

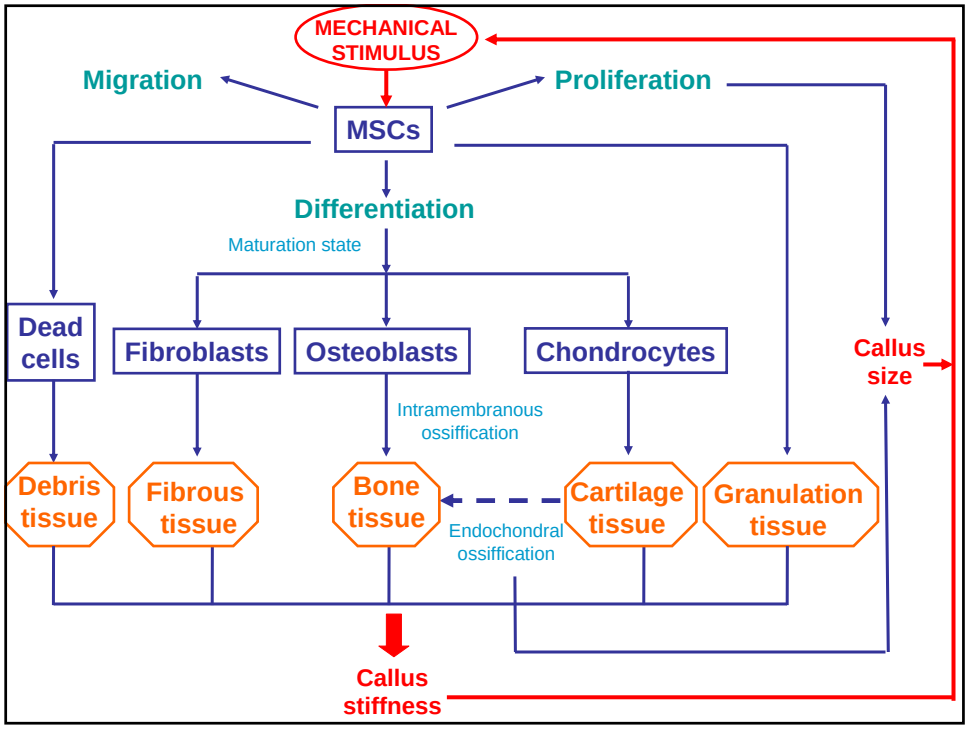

MECHANICAL STIMULUS
Migration
Proliferation
MSCs
Differentiation
Maturation state (m)
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Intramembranous ossiffication
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue
Endochondral ossiffication
c_s if $m_f = 1$
0 otherwise


MECHANICAL STIMULUS
Migration
Proliferation
MSCs
Differentiation
Maturation state
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Intramembranous ossiffication
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue
Endochondral ossiffication
c_s if $[(c_b > c_b^{min}) \& (m_b = 1)]$
0 otherwise


MECHANICAL STIMULUS
Migration
Proliferation
MSCs
Differentiation
Maturation state
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Intramembranous ossiffication
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue
Endochondral ossiffication
$\begin{cases} c_c & \text{if } m_c = 1 \\ 0 & \text{otherwise} \end{cases}$

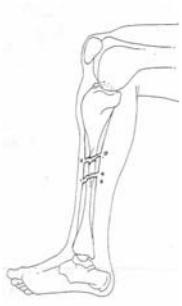

MECHANICAL STIMULUS
Migration
Proliferation
MSCs
Differentiation
Maturation state
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Intramembranous ossiffication
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue
Endochondral ossiffication
$\begin{cases} D(\psi)\nabla^2 c_b & \text{if } [(c_b < c_b^{min}) \,\&\, (m_b = 1)] \\ 0 & \text{otherwise} \end{cases}$


Migration
Proliferation
MSCs
x1
0
Differentiation
Maturation state
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Callus size
Intramembranous ossification
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue
Endochondral ossification

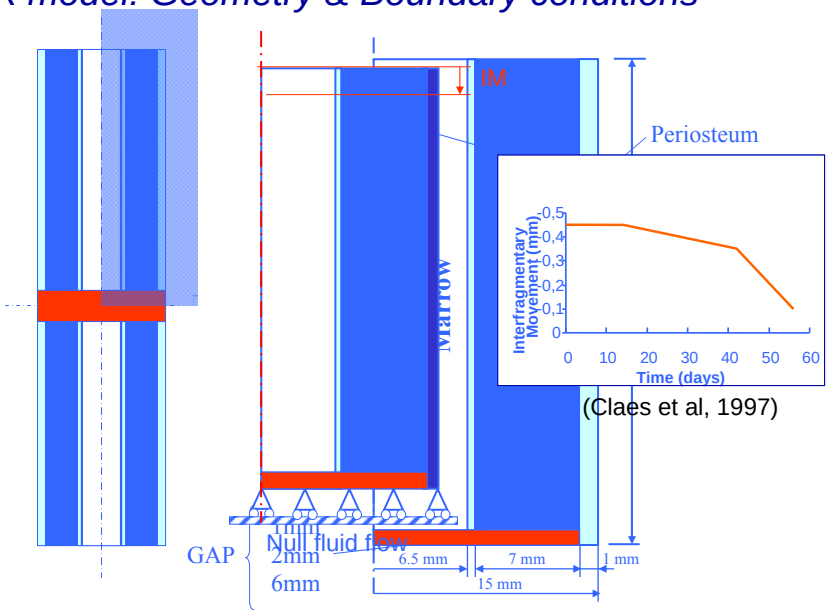

MECHANICAL STIMULUS
Migration
Proliferation
MSCs
Differentiation
Maturation state
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Callus size
Intramembranous ossification
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue
Endochondral ossification
Callus stiffness

- Axysimmetric human model under compression

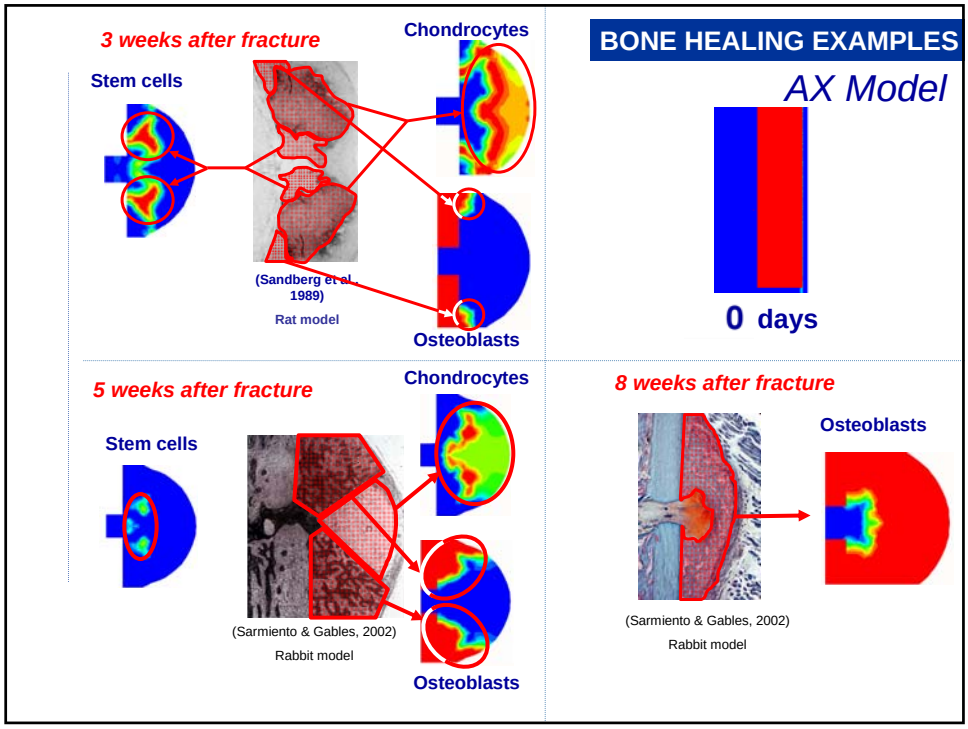
- Sheep's model:
  - Interfragmentary movement
  - Bilateral fixator



AX model: Geometry & Boundary conditions



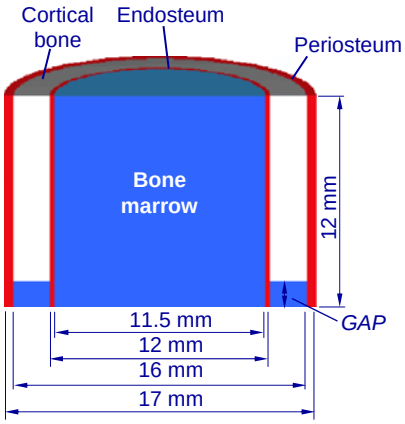
(Claes et al, 1997)



BONE HEALING EXAMPLES

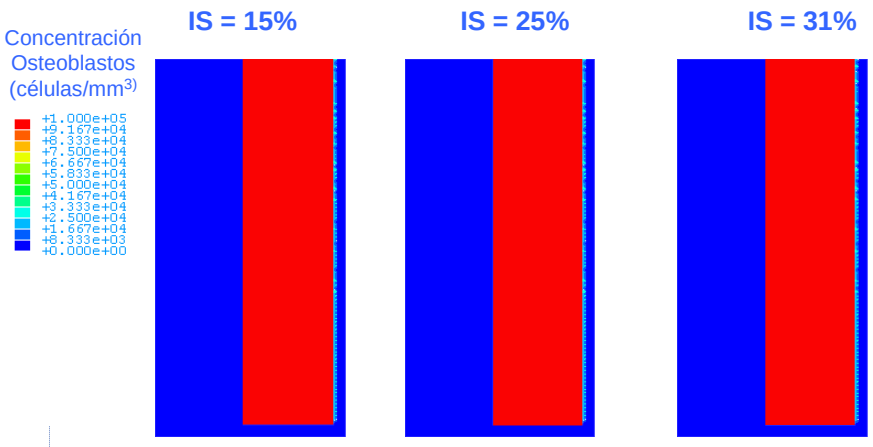
- Axysimmetric human model under compression
- ***Sheep's model:***
  - ***Interfragmentary movement***
  - Bilateral fixator

Sheep's geometry



(Augat et al., 2003)

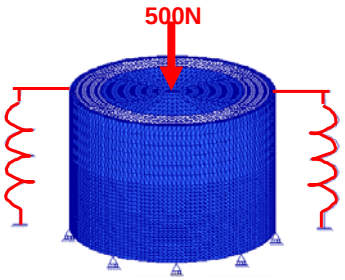
Influence of interfragmentary strain



BONE HEALING EXAMPLES

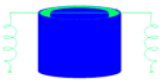
- Axysimmetric human model under compression

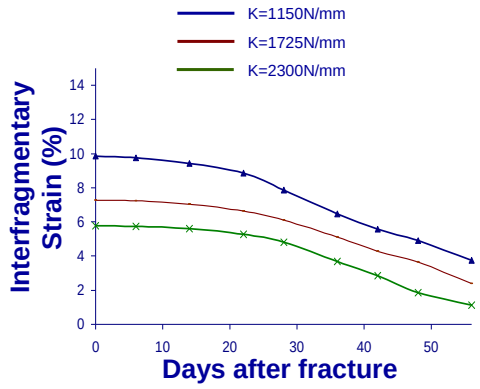
- ***Sheep's model:***
  - ***Interfragmentary movement***
  - ***Bilateral fixator***

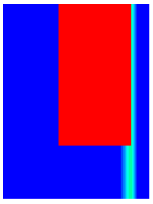


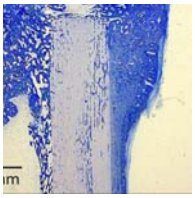
BONE HEALING EXAMPLES

External Fixator







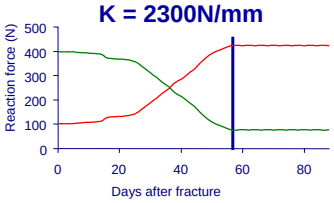


(Augat et al., 2003)

BONE HEALING EXAMPLES

External Fixator

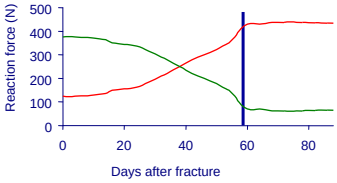
K = 2300N/mm



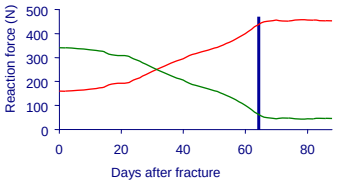
Bone

Fixator

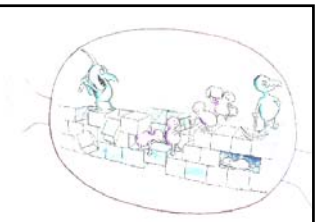
K = 1725 N/mm



K = 1150 N/mm



OVERVIEW



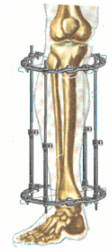
- ***Bone properties***
- ***Role of mechanical factors: bone mechanobiology***
- ***Methods of Science: computer simulation***
- ***Modelling Bone Mechanobiology:***
  - ***Bone Remodelling***
  - ***Bone Healing***
  - ***Bone Distraction***
  - Bone Tissue Engineering
- Final conclusions

BONE DISTRACTION

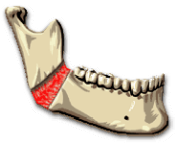
What is distraction osteogenesis?

A useful technique aimed to induce bone formation in widespread clinical applications. Main fields of application:

Orthopaedics

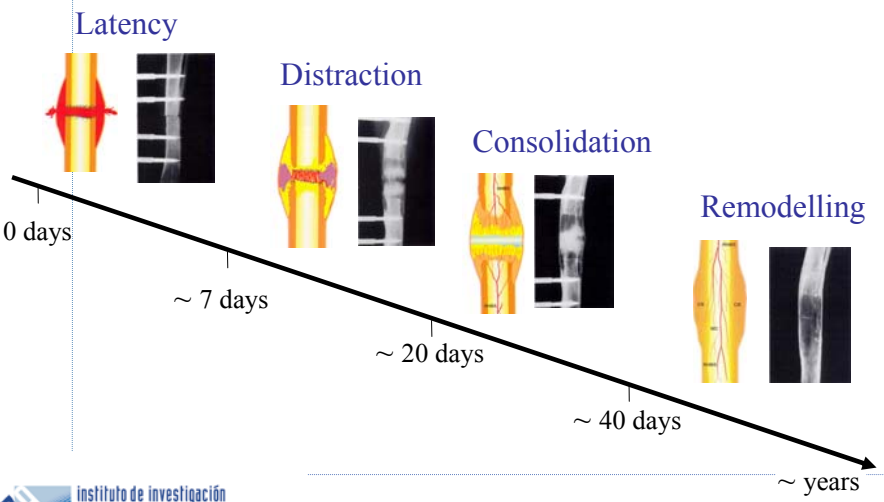


Craneofacial surgery



BONE DISTRACTION

Which are the main stages in distraction osteogenesis?



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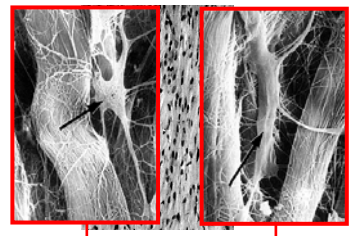
Santiago de Compostela, Julio 2010

BONE DISTRACTION

Mechanical factors

Biological factors



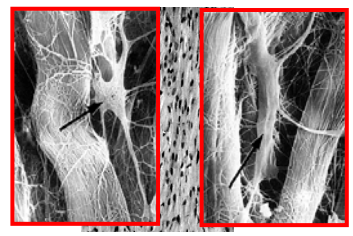
Non stimulated

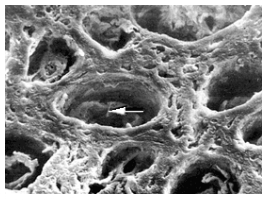
Under tension

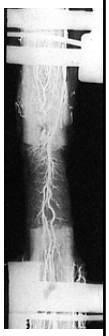
BONE DISTRACTION

Mechanical factors

Biological factors







http://www.globalmednet.com/do-cdrom/Biol/Histomor/rh07.htm

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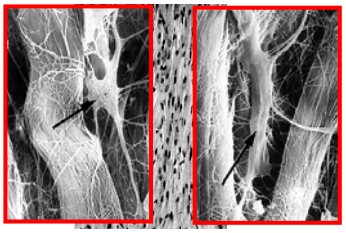
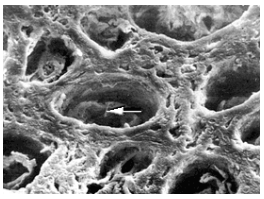
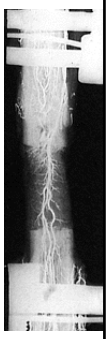
Mechanical factors

Biological factors





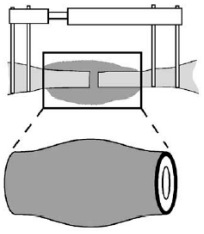


Bone tissue formation is 6 times faster than in a child growth plate

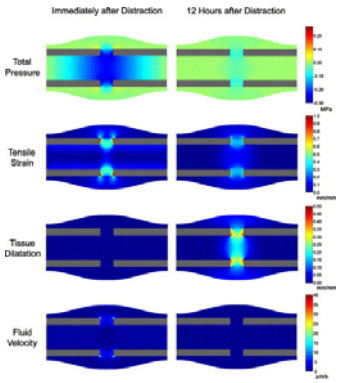
(Anderson *et al*., J. Bone Joint Surg. 45A.10, 1963)

Previous models

- Non-evolutive models (Loboa *et al*., 2004, Boccaccio *et al*., 2005, Cattaneo *et al*., 2005, Morgan *et al*., 2005)

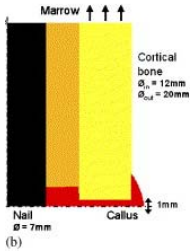


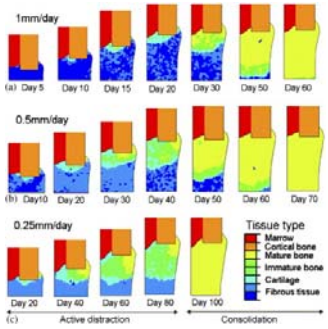
(Morgan *et al*., 2005)



Previous models

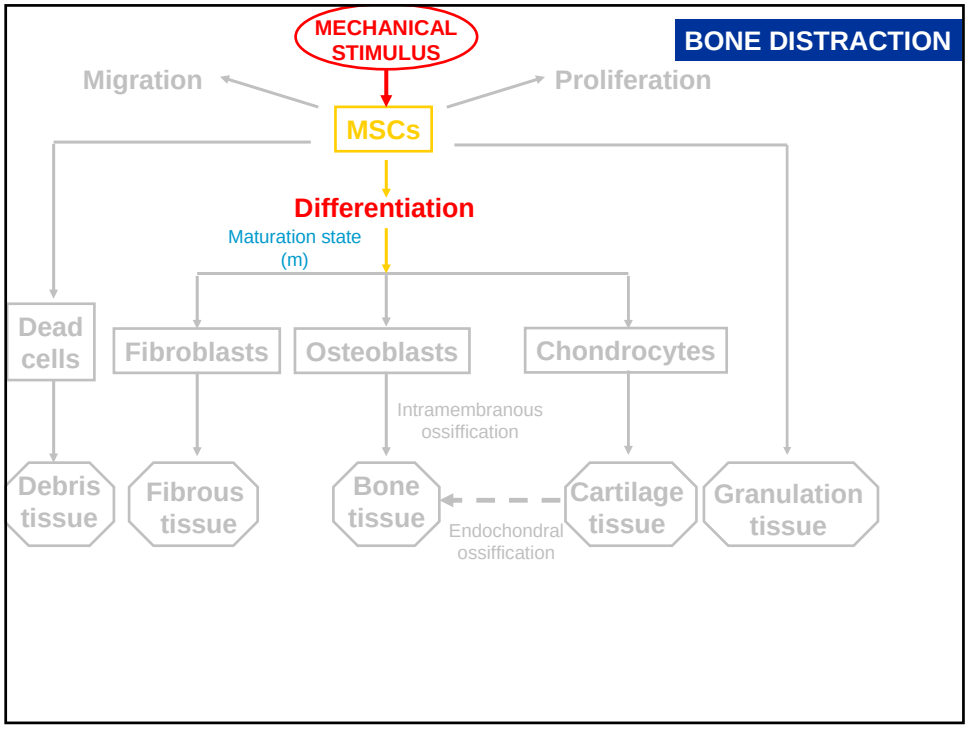
- Non-evolutive models (Loboa *et al*., 2004, Boccaccio *et al*., 2005, Cattaneo *et al*., 2005, Morgan *et al*., 2005)
- Evolutive models (Isaksson *et al*., 2007, Boccaccio *et al*., 2008)

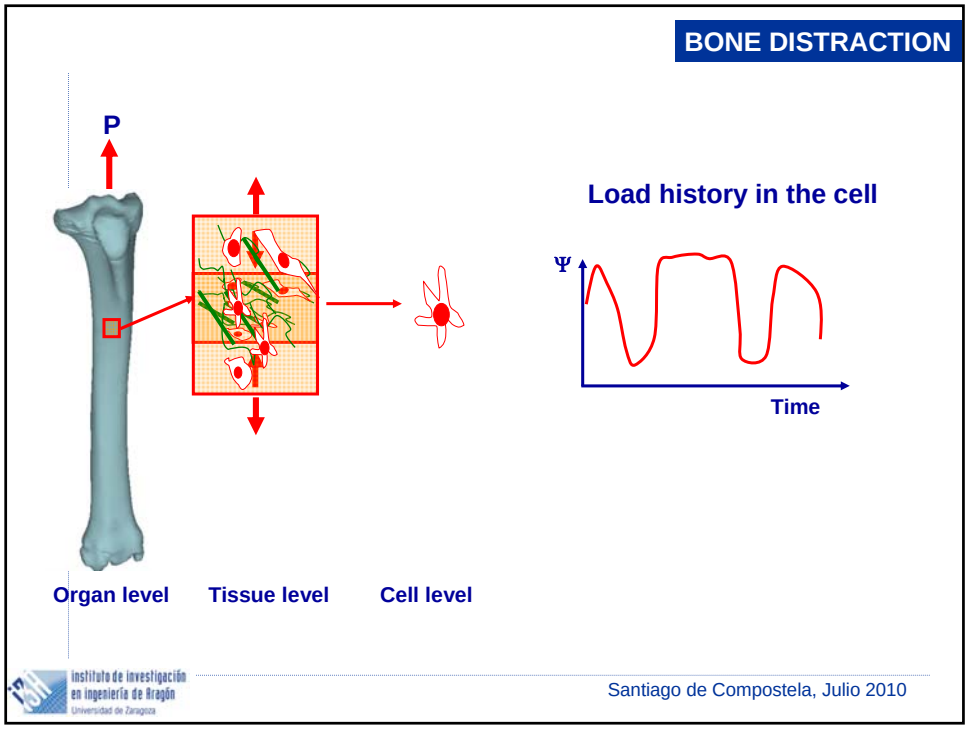




(Isaksson *et al.*, 2006)

- The application of the mechanobiological model of bone healing to distraction osteogenesis presents **limitations**:
  - It is **not able to predict the effect of different distraction rates** => include the **influence of the load history** on cell differentiation
  - **Neglect** the effect of **pre-traction stresses**


BONE DISTRACTION
MECHANICAL STIMULUS
Migration
Proliferation
MSCs
Differentiation
Maturation state (m)
Dead cells
Fibroblasts
Osteoblasts
Chondrocytes
Intramembranous ossiffication
Debris tissue
Fibrous tissue
Bone tissue
Cartilage tissue
Granulation tissue
Endochondral ossiffication


BONE DISTRACTION
P
Load history in the cell
Ψ
Time
Organ level
Tissue level
Cell level
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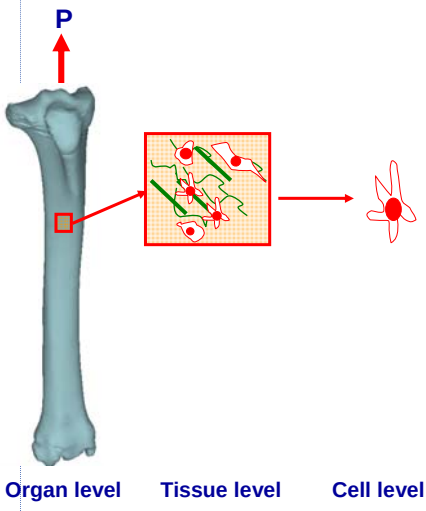
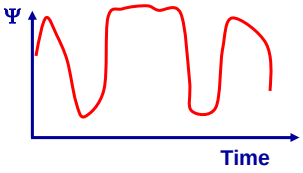
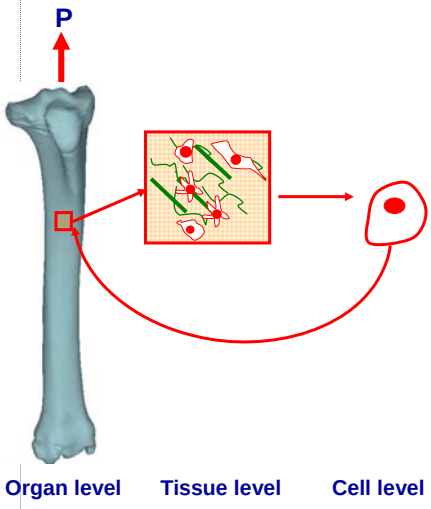
BONE DISTRACTION



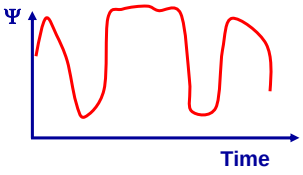
Load history in the cell



BONE DISTRACTION



Load history in the cell



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Maturation state of the cell (m_i) – Miner's Rule:

$$m_i = \sum \frac{n}{N_f(\Psi)}$$

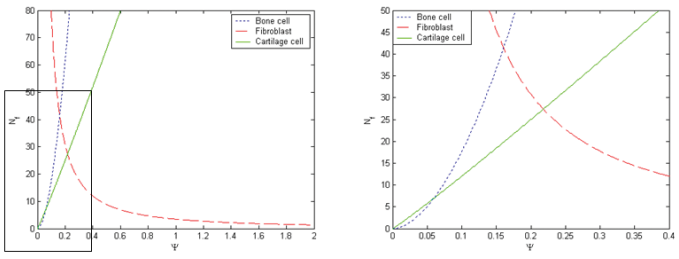
$$N_f = A\Psi^b$$

number of days a cell needs to completely mature at a stimulus level

BONE DISTRACTION

Maturation state of the cell (m_i) – Miner's Rule:

	Bone cells	Fibroblast	cartilage cells
A_i	$1.13 \cdot 10^3$	3.47	137.08
b_i	1.81	-1.36	1.05



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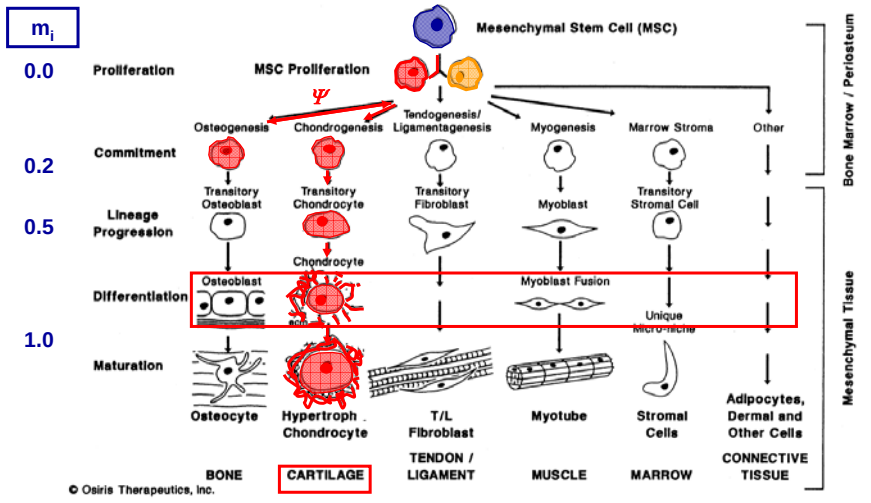
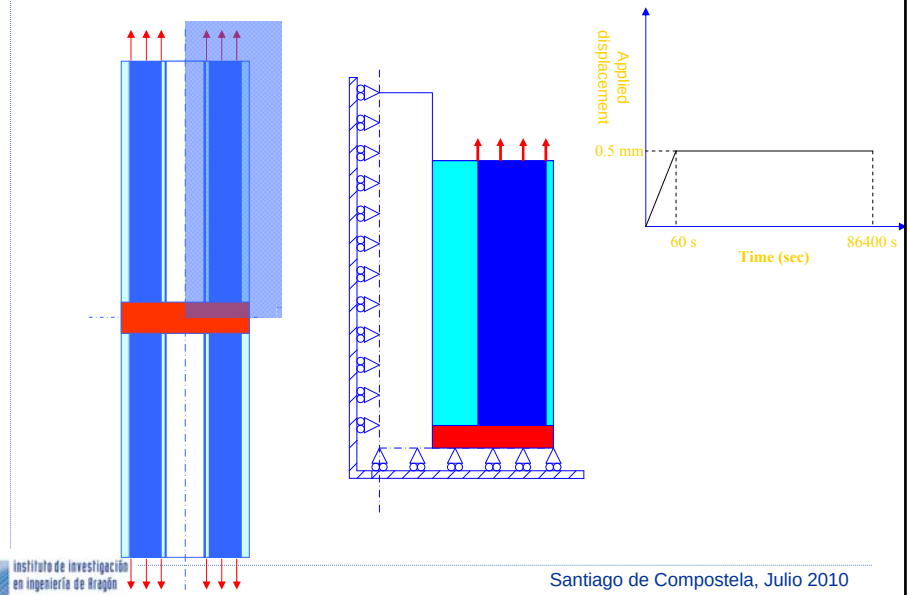
BONE DISTRACTION



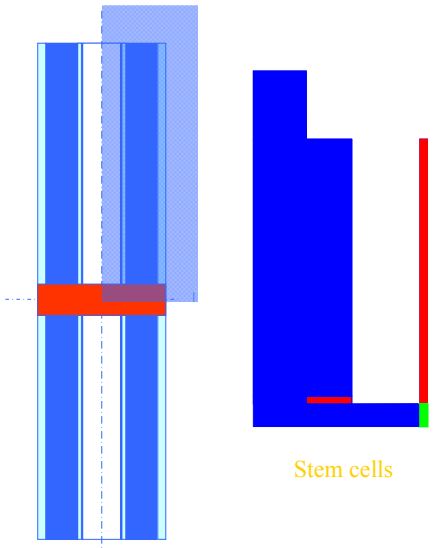
Application

Geometry and loading conditions



Application

Geometry and initial conditions



MSCs source (Gerstenfeld *et al*., 2003):

- Periosteum
- Surrounding soft tissues
- Marrow

Application

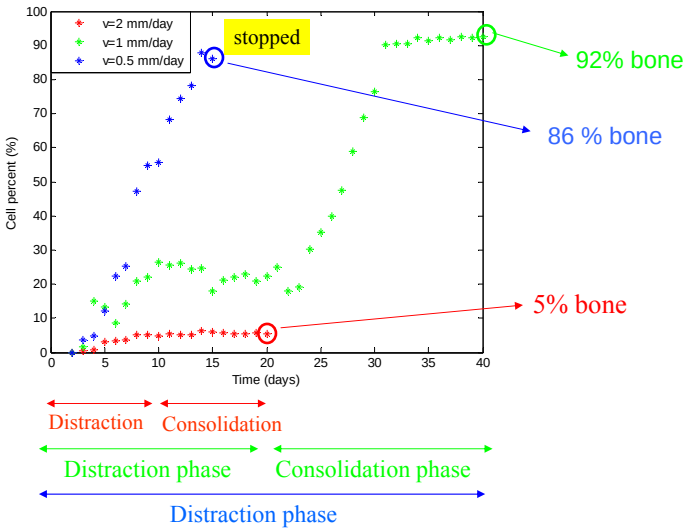
Results

CASE A	CASE B	CASE C
v = 1 mm/day	v = 2 mm/day	v = 0.5 mm/day
DO protocol: 20 days distract. 20 days consolid.	**DO protocol:** 10 days distract. 10 days consolid.	**DO protocol:** 40 days distract. 40 days consolid.

Distraction length= 20 mm

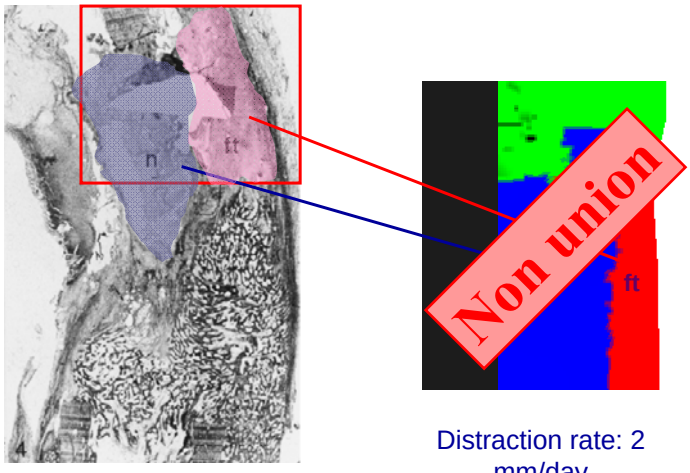
Application

Results



Application

Results



(Li *et al.*, 2000)

Distraction rate: 2 mm/day

Conclusions

- The model of fracture healing (Gómez-Benito et al., 2005) has been extended with the inclusion of the load history in order to predict the main features of distraction osteogenesis under different mechanical environments.

- The inclusion of the load history has allowed the simulation of tissue distributions during limb lengthening at different distraction rates:
    - At low rates, it predicts premature bony union
    - At moderate rates, it predicts succesfully bony unions
    - At high rates, it predict fibrous unions or non unions

Conclusions

- The main limitations of this model are:

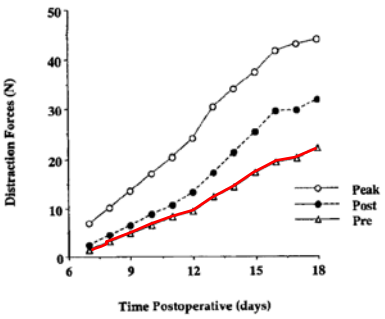
    - the mathematical formulation is developed under the small deformations assumption.

    - we considered a free stress state as initial condition for each day analyzed numerically.

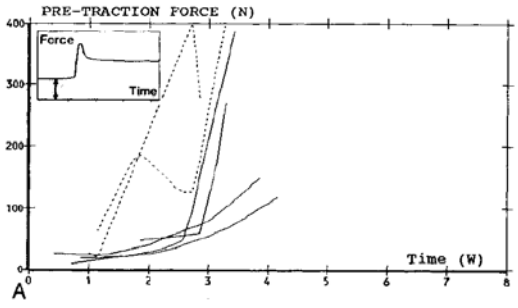
    - the axisymmetric finite element model represents an idealized cylindrical bone under axial loading.

- The application of the mechanobiological model of bone healing to distraction osteogenesis presents **limitations**:
  - It is **not able to predict the effect of different distraction rates** => include the **influence of the load history** on cell differentiation
  - **INCLUDE** the effect of **pre-traction stresses**

Experimental Results



(Waanders et al Clin Orthop Relat Res. 1998)



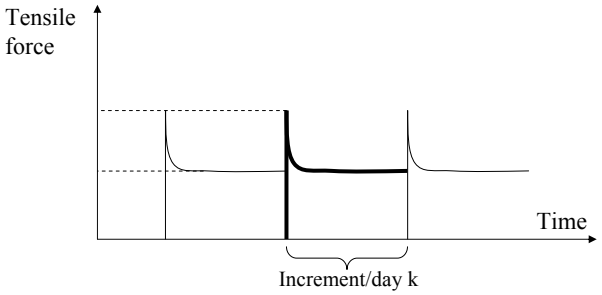
(Brunner et al Clin Orthop Relat Res. 1994)

Pre-traction stresses are significant in distraction osteogenesis and need to be considered

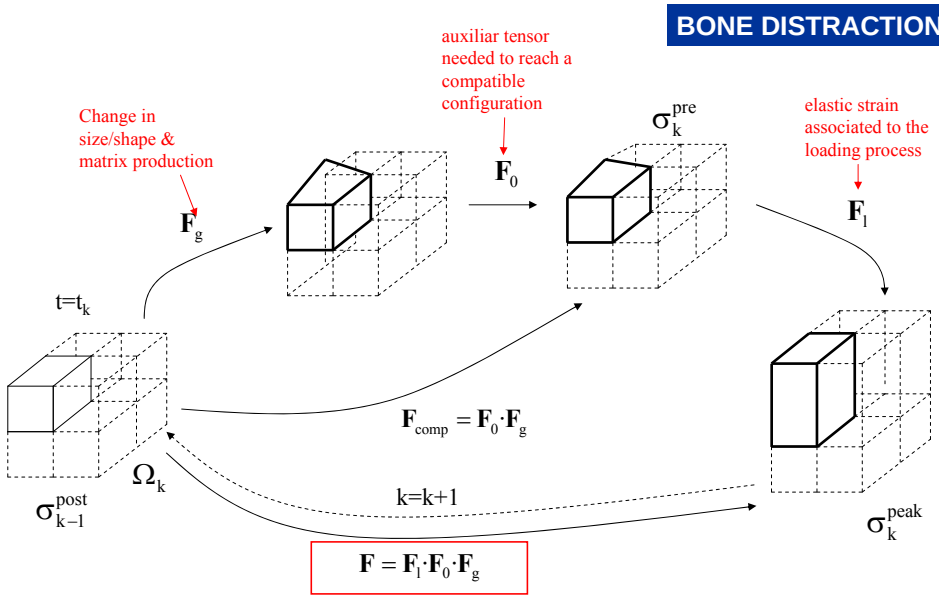
BONE DISTRACTION

Numerically

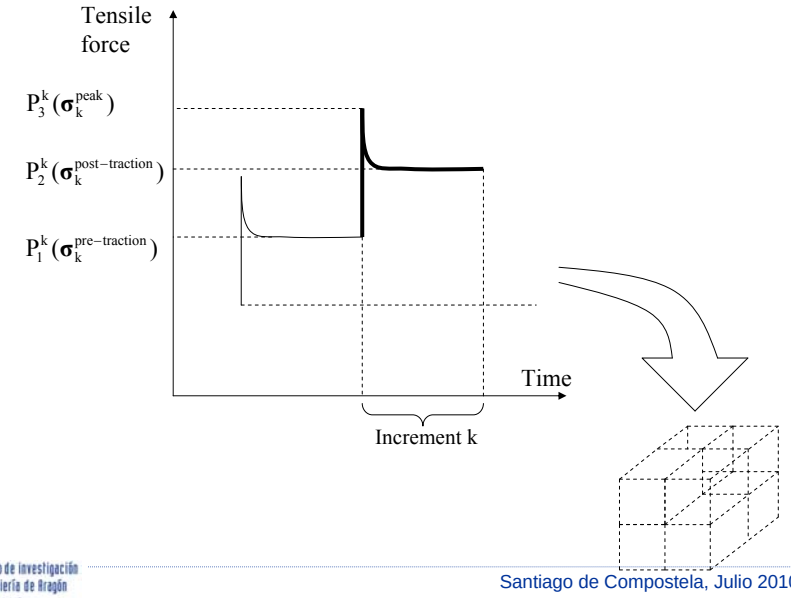
Existing mechanobiological models assume that pre-traction stresses are null assuming therefore no stress accumulation after each load step (Isaksson *et al.*, 2007; Boccaccio *et al.*, 2007; Reina-Romo *et al.*, 2009).



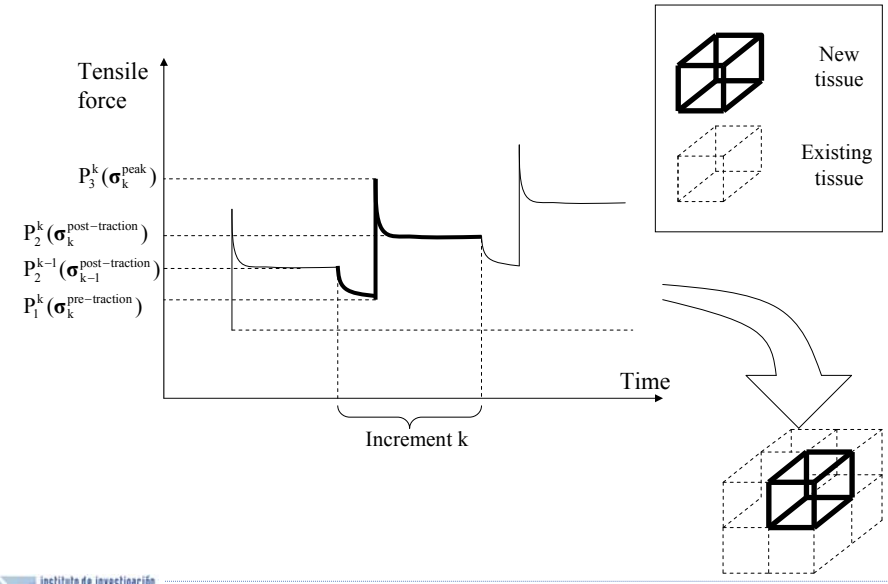
BONE DISTRACTION



BONE DISTRACTION



BONE DISTRACTION



BONE DISTRACTION

Constitutive equation

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}_{fl} + \boldsymbol{\sigma}_{eff}$$

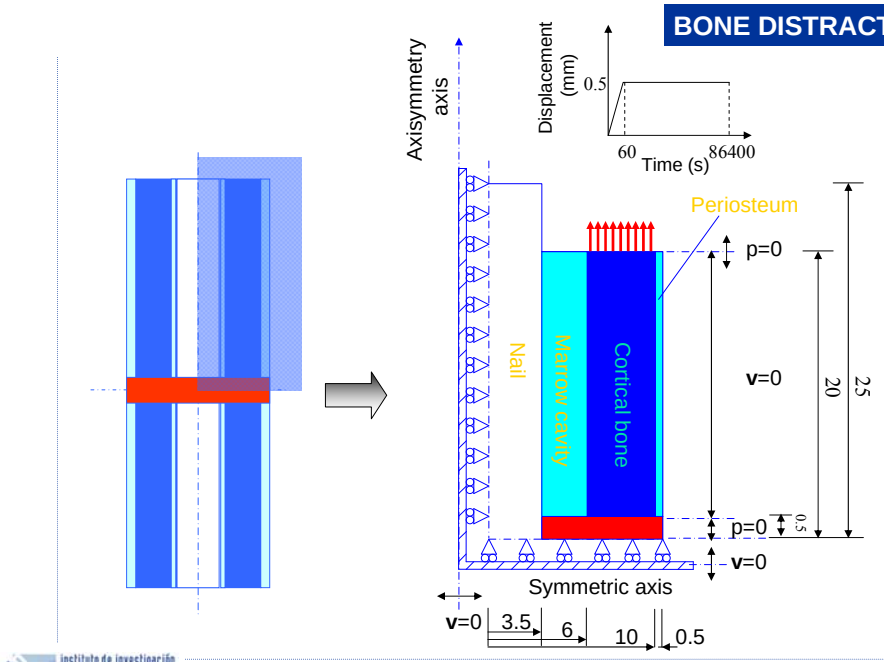
$$\boldsymbol{\sigma}_{fl} = -p\mathbf{1}$$

$$\boldsymbol{\sigma}_{eff} = \sum_{i=1}^{N} \upsilon_{m_0}^{i} \boldsymbol{\sigma}_{k}^{i} + \sum_{i=1}^{N} \frac{1}{\rho^{i}} \frac{1}{\det \mathbf{F}_k} \int_0^{t_k} \pi^{i}(\tau) \boldsymbol{\sigma}^{i}(\mathbf{F}_k, \tau) \det \mathbf{F}_k \, d\tau$$

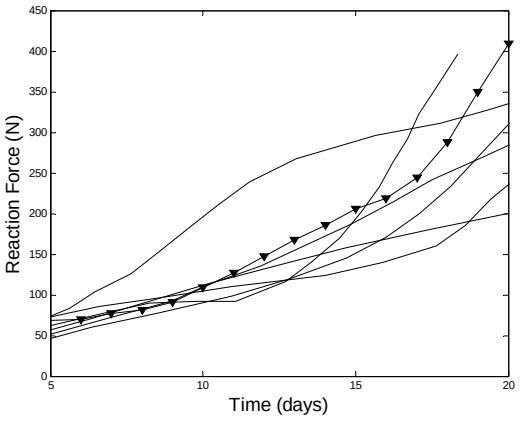
new matrix produced of tissue *i* per unit volume and time at time τ

stress response for tissue *i* evaluated at time t_k with respect to the time $\tau \in [0, t_k]$ in which the tissue was created

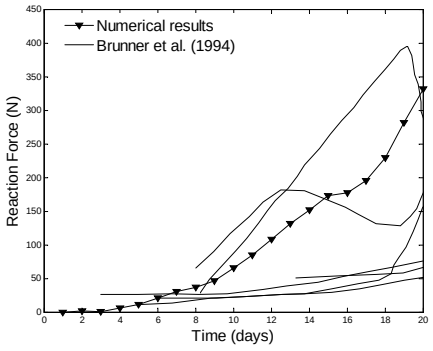
BONE DISTRACTION



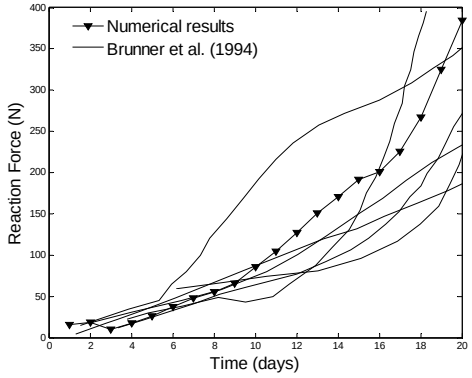
Peak force



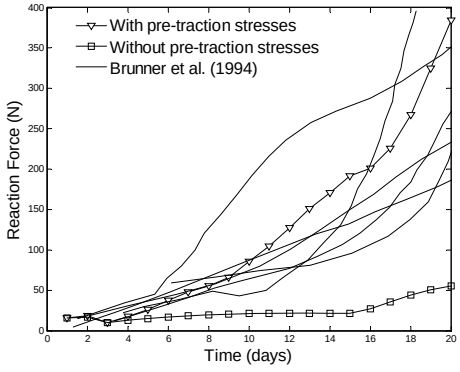
Pre-distraction force



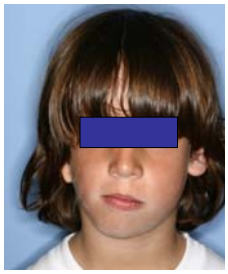
Post-distraction force



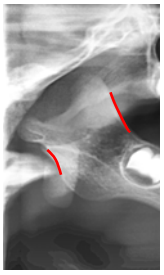
Comparison: with and without pre-traction stresses

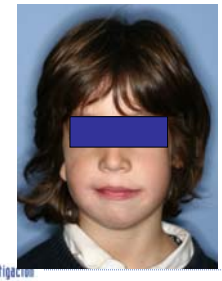


BONE DISTRACTION: A CLINICAL CASE



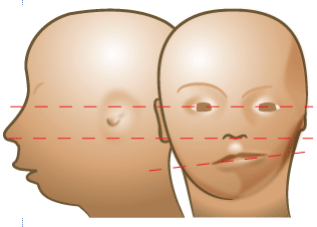
START

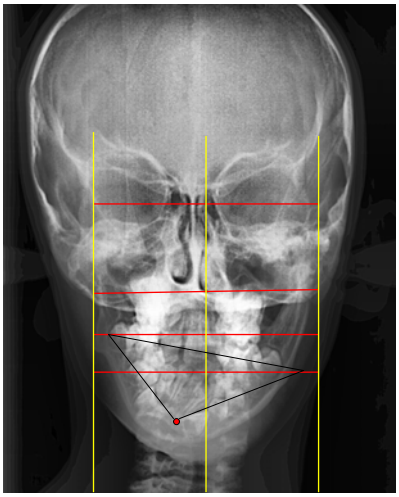




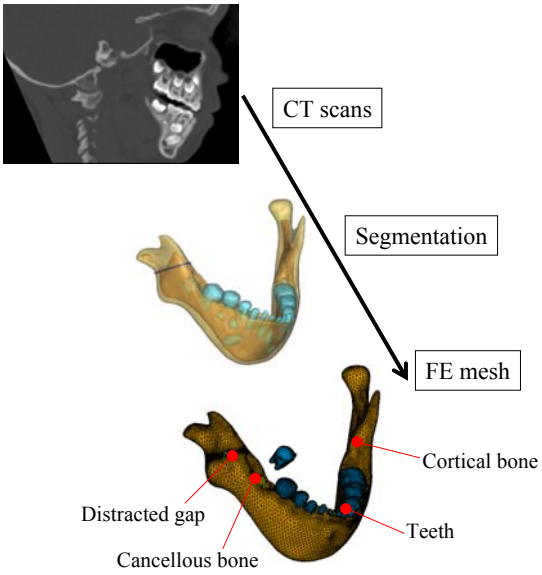
END

BONE DISTRACTION: A CLINICAL CASE





BONE DISTRACTION: A CLINICAL CASE

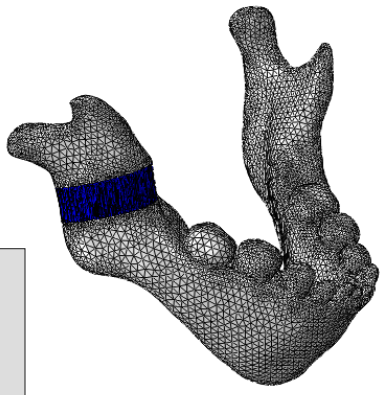


BONE DISTRACTION: A CLINICAL CASE

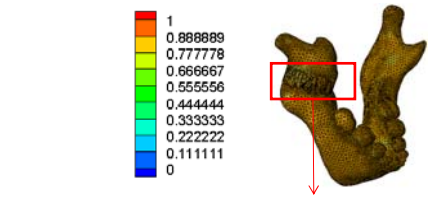
Initial state
Geometry, mesh, load, initial conditions

FEA

1. **Poroelastic analysis** → Ψ_{max}, Ψ_{mean} → differentiation, proliferation.
2. **Thermoelastic analysis** → gap growth.
3. **Diffusion analysis** *(MSC)* → MSC migration.
4. **Diffusion analysis** (osteoblasts) → vascularization



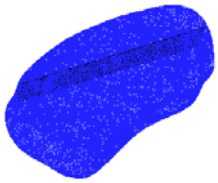
BONE DISTRACTION: A CLINICAL CASE

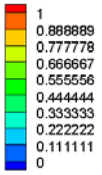


Granulation Cartilage Bone

0 days

BONE DISTRACTION: A CLINICAL CASE

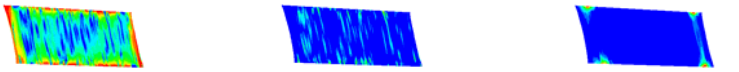




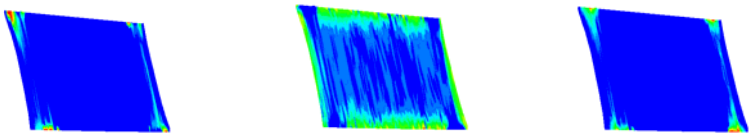
Granulation Cartilage Bone

Day 1

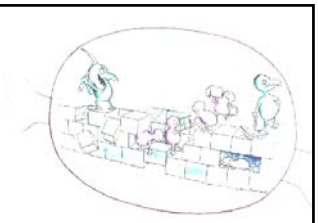
Day 10



Day 20

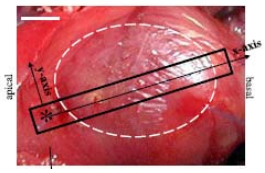


OVERVIEW

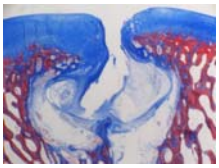


- ***Bone properties***
- ***Role of mechanical factors: bone mechanobiology***
- ***Methods of Science: computer simulation***
- ***Modelling Bone Mechanobiology:***
  - ***Bone Remodelling***
  - ***Bone Healing***
  - ***Bone Distraction***
  - ***Bone Tissue Engineering***
- Final conclusions

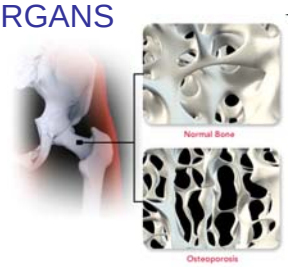
BONE TISSUE ENGINEERING



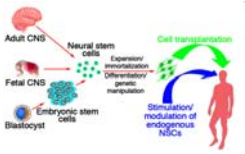
REGENERATIVE MEDICINE:



TO RESTORE THE FUNCIONALITY OF DAMAGED TISSUES AND ORGANS

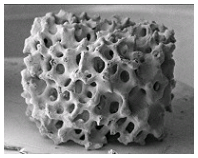


BONE TISSUE ENGINEERING



Cell Therapy

Tissue Engineering

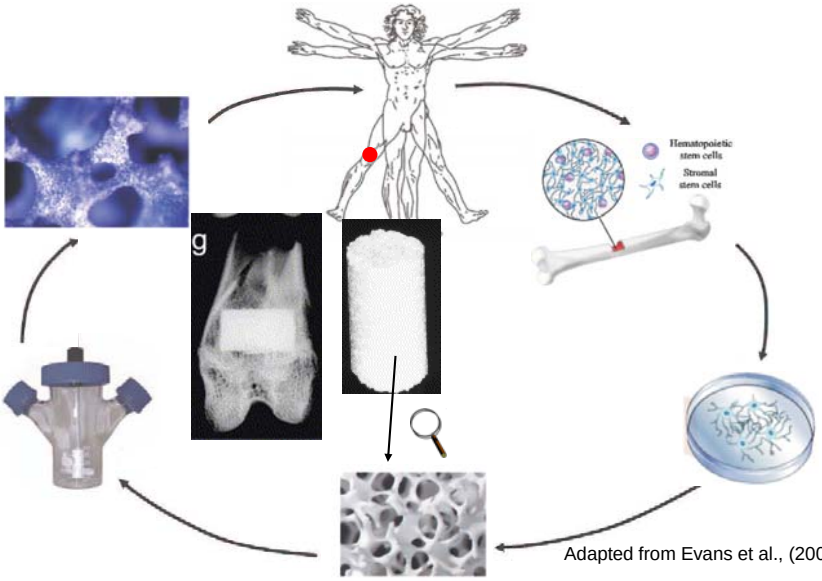


REGENERATIVE MEDICINE

Transplant

Biomedical Engineering

BONE TISSUE ENGINEERING



Adapted from Evans et al., (2007

In-silico BTE: literature review

- Modelling from a macroscopic perspective:
  - Simulate osteochondral defects using scaffolds: Kelly and Prendergast (2006).
- Modelling from a microscopic perspective:
  - Macroscopic properties characterization of scaffolds and optimization: Hollister and co-workers (1998-).
  - Simulate bone tissue regeneration and scaffold degradation within a scaffold unit cell. Adachi et al., (2006).
  - Influence of scaffold properties on tissue regeneration: Byrne et al., (2007).

BONE TISSUE ENGINEERING

- Objectives:
  - To **evaluate** the potential of **numerical methods** against **experimental measurements**
  - To establish a **multiscale** numerical **model** of BTE taking into account the most relevant biophysical phenomena.
  - Try to elucidate the role of **scaffold parameters** on **bone** tissue **regeneration** from a numerical point of view.
  - To evaluate the effect of scaffold microstructural **anisotropy** on bone regeneration.
  - Add some light in the task of being BTE a clinical viable reality.

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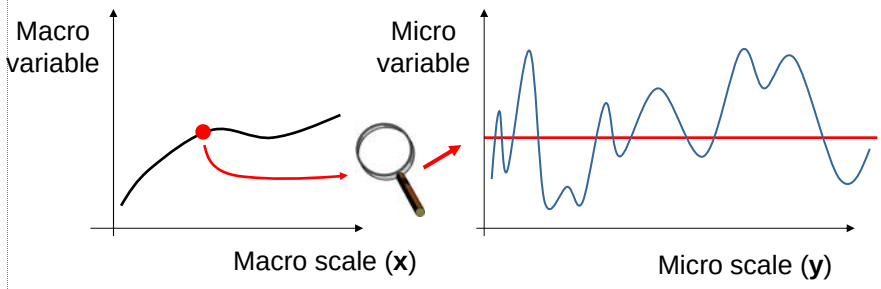
Asymptotic homogenization theory (AHT)

Babuska (1978), Sánchez-Palencia (1980), Suquet (1983), Bakhvalov (1984), Nemat-Nasser (1993), Terada and Kikuchi (1998)...

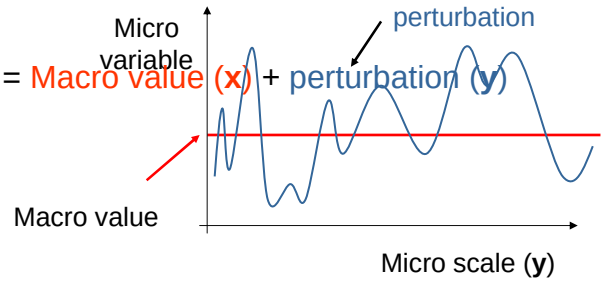


BONE TISSUE ENGINEERING

Asymptotic homogenization theory (AHT)

Babuska (1978), Sánchez-Palencia (1980), Suquet (1983), Bakhvalov (1984), Nemat-Nasser (1993), Terada and Kikuchi (1998)...

Micro value (**x**,**y**) = Macro value (**x**) + perturbation (**y**)



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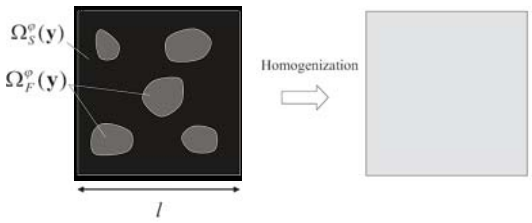
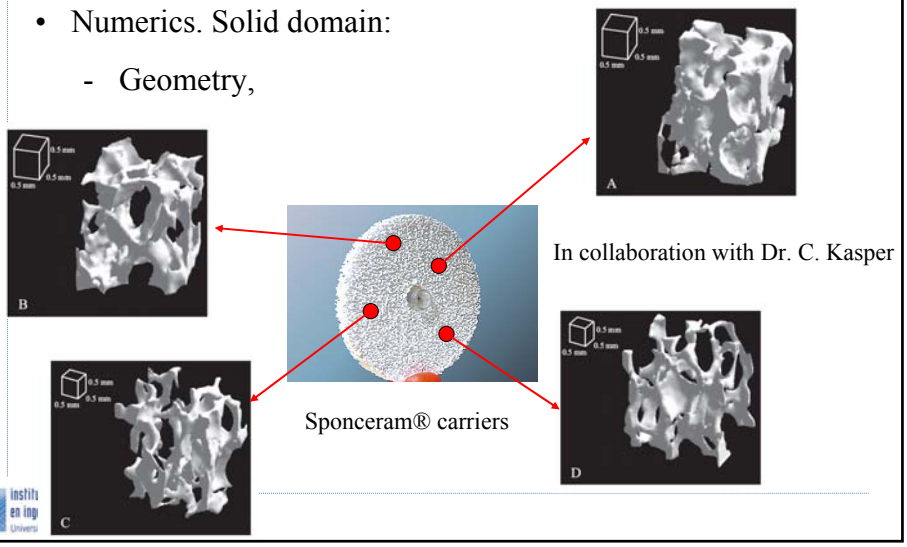
Asymptotic homogenization theory (AHT)

- Biphasic microstructure:
  - Solid domain: mechanics $\Omega_S^\varepsilon(\mathbf{y}) \Rightarrow \mathbf{C(x)}$
  - Fluid domain: fluids $\Omega_F^\varepsilon(\mathbf{y}) \Rightarrow \mathbf{K(x)}$



Application of AHT: properties characterization of scaffolds

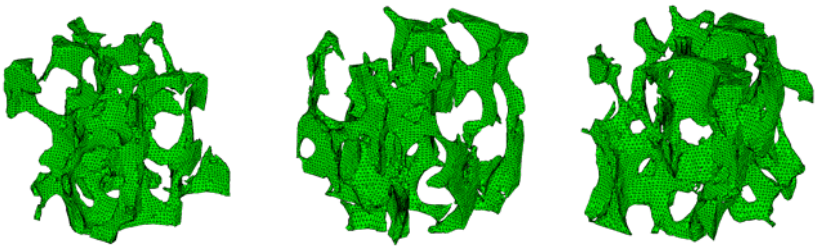
- Numerics. Solid domain:
  - Geometry,



In collaboration with Dr. C. Kasper

Application of AHT: properties characterization of scaffolds

- Numerics. Solid domain:
  - Finite element meshes (RVEs),



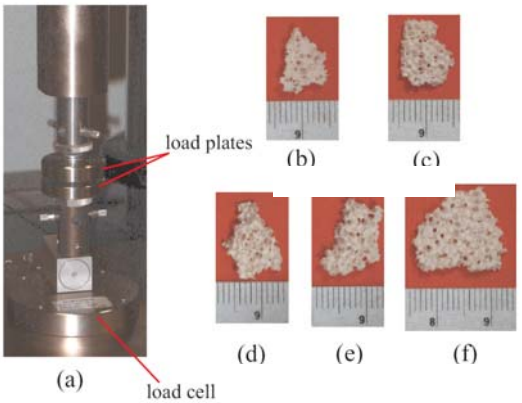
In collaboration with Dr. C. Kasper

Application of AHT: properties characterization of scaffolds

- Experiments. Solid domain:
  - Setup,

In collaboration with Dr. C. Kasper

Sponceram® carriers



Application of AHT: properties characterization of scaffolds

- Numerics vs Experiments. Solid domain:

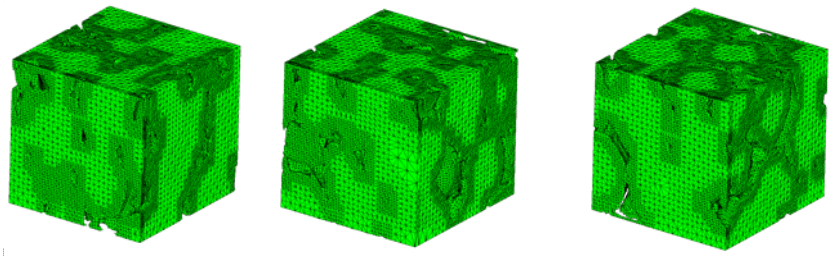
	Porosity %	Experimental $E\ (MPa)$	Numerical $E\ (MPa)$
S20-90	90.16±0.95	8.73±4.64	8.21±3.06
S30-90	88.75±0.36	11.03±2.24	9.07±1.43
S30-90HA	79.81±2.18	29.40±1.21	30.63±2.61

Sanz-Herrera et al., (JBMRB,2008)

In collaboration with Dr. C. Kasper

Application of AHT: properties characterization of scaffolds

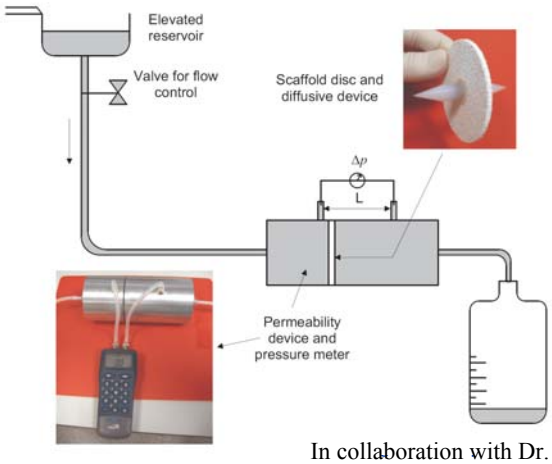
- Numerics. Fluid domain:
  - Finite element meshes (RVEs),



In collaboration with Dr. C. Kasper

Application of AHT: properties characterization of scaffolds

- Experiments. Fluid domain:
  - Setup,



In collaboration with Dr. C. Kasper

Application of AHT: properties characterization of scaffolds

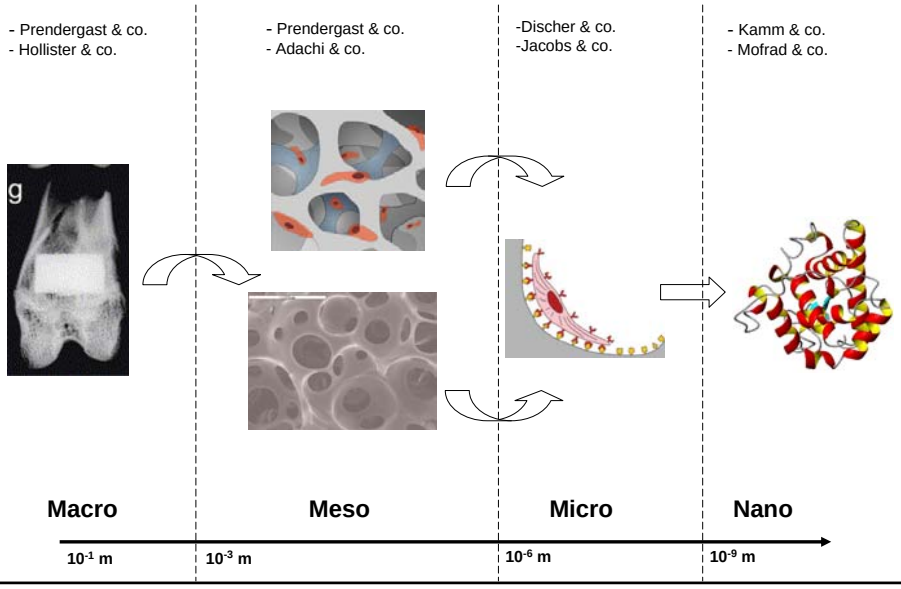
- Numerics vs Experiments. Solid domain:

	Porosity (%)	Experimental $k\ (m^2)$	Numerical $k\ (m^2)$
S20-90	90.16±0.95	$3.76 \cdot 10^{-8} \pm 4.38 \cdot 10^{-9}$	$3.49 \cdot 10^{-8} \pm 2.56 \cdot 10^{-9}$
S30-90	88.75±0.36	$3.17 \cdot 10^{-8} \pm 3.62 \cdot 10^{-9}$	$2.31 \cdot 10^{-8} \pm 6.25 \cdot 10^{-10}$
S30-90HA	79.81±2.18	$1.79 \cdot 10^{-8} \pm 4.09 \cdot 10^{-9}$	$1.88 \cdot 10^{-8} \pm 1.25 \cdot 10^{-9}$

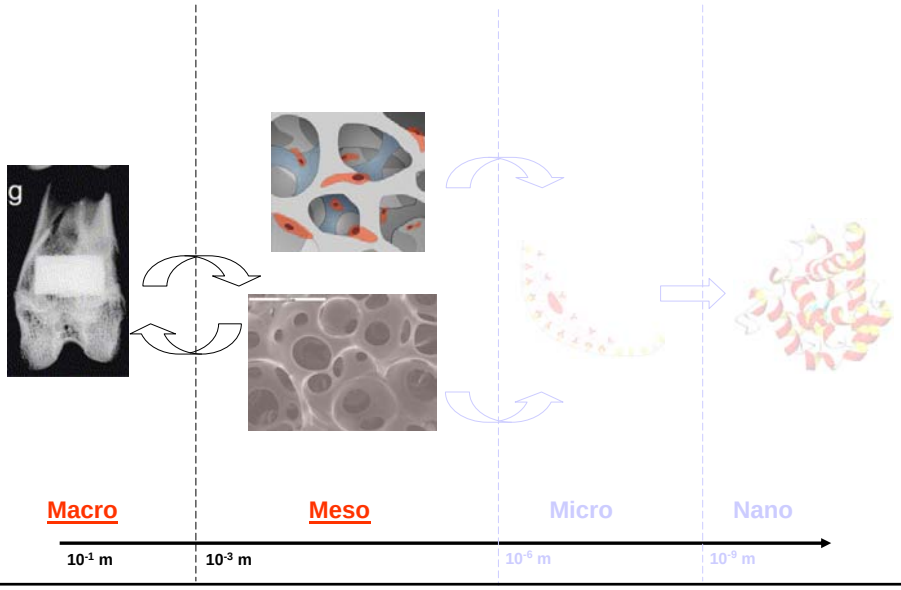
Sanz-Herrera et al., (JBMRB,2008)

In collaboration with Dr. C. Kasper

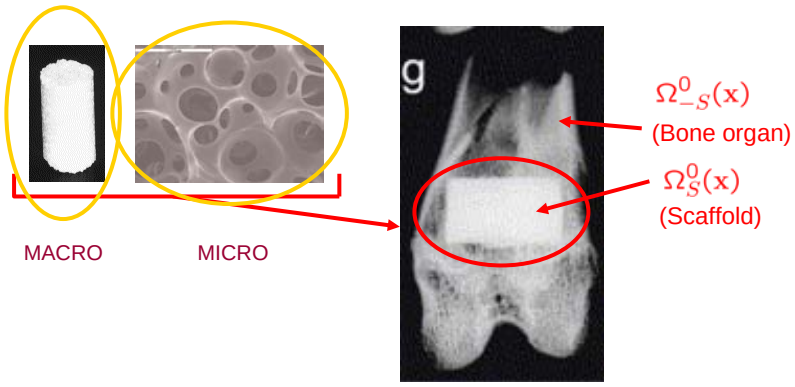
Mechanobiological modeling for BTE



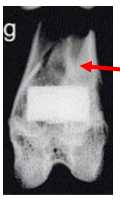
Mechanobiological modeling for BTE



Mechanobiological modeling for BTE



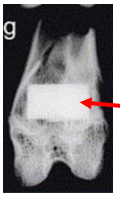
Mechanobiological modeling for BTE



Bone organ:
- Remodelling and adaptation

MACRO

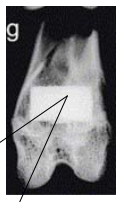
Mechanobiological modeling for BTE



Scaffold:
- Cell migration
- Mechanics

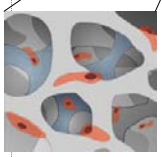
MACRO

Mechanobiological modeling for BTE



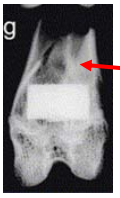
MACRO

MICRO



Scaffold microstructure:
- Homogenization (fluid and solid phases)
- Localization problem (solid phase)
- Microscopic model of bone growth
- Scaffold resorption

Analysis of the macroscale (bone organ)



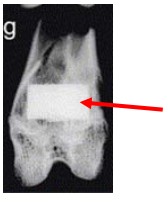
Bone organ:
- Remodelling and adaptation

MACRO

Analysis of the macroscale (bone organ)

- Macroscopic mathematical models of bone remodelling:
  - **Homeostatic value of a mechanical stimulus**: Pauwels (1960); Carter et al., (1987); Huiskes et al., (1987, 2000); **Beaupré et al., (1990);** Cowin et al., (1992).
  - **Global optimality criteria**: Terrier et al., (1997); Fernandes et al., (1999); Adachi et al., (2001).
  - **Damage repair models**: Prendergast and Taylor (1994); Zidi and Ramtani (2000); Doblaré and García (2001); Hazelwood et al. (2001); García-Aznar et al. (2005)
- As a first approach, we use the isotropic model proposed by Beaupré et al. (1990).

Analysis of the macroscale (scaffold)



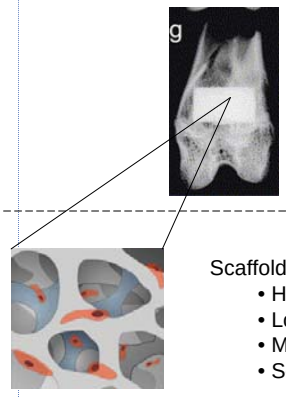
Scaffold:
- Cell migration
- Mechanics

MACRO

Analysis of the macroscale (scaffold)

- Model of scaffold bone ingrowth (Ohgushi and Caplan, 1999):
  - Insertion of the scaffold: immunological response and hematoma. Osteoprogenitor and MSC's migration.
  - Cell attachment onto the scaffold microsurface and biolayer formation.
  - Cell differentation to osteoblasts.
  - Osteoblasts synthesize immature (woven or primary) bone.
  - Primary bone becomes mature and fully mineralized bone.

Analysis of the microscale (scaffold)



MACRO

MICRO

Scaffold microstructure:

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- Localization problem (solid phase)
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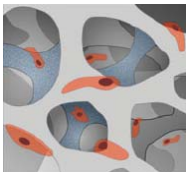
Analysis of the microscale (scaffold)

- Bone growth,

$$\dot{M} = \dot{M}(\bar{c}, \Psi) \qquad \text{in} \qquad \partial\Omega_S^{\varepsilon}(\mathbf{y})$$



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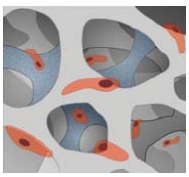
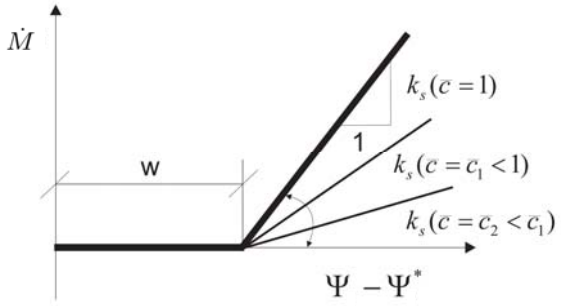
$$\dot{M} = \dot{M}(\bar{c}, \Psi) \qquad \text{in} \qquad \partial\Omega_S^{\varphi}(\mathrm{y})$$



$$\dot{M} = \begin{cases} k_s(\bar{c}) \cdot (\Psi - \Psi^* - w) & \text{if} \quad \Psi - \Psi^* > w \\ 0 & \text{otherwise} \end{cases}$$

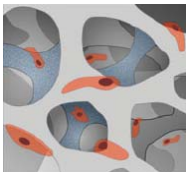


Hypothesis: no bone resorption during healing (Biskobing, 2000).

Analysis of the microscale (scaffold)

- Bone growth,

$$\dot{M} = \dot{M}(\bar{c}, \Psi) \qquad \text{in} \qquad \partial\Omega_S^{\varphi}(\mathrm{y})$$



$$\dot{M} = \begin{cases} k_s(\bar{c}) \cdot (\Psi - \Psi^* - w) & \text{if} \quad \Psi - \Psi^* > w \\ 0 & \text{otherwise} \end{cases}$$

Evaluated microscopically through,

$$\epsilon^{\varphi}(\mathbf{u}^{\varphi}) = \epsilon_{kh}^{0}(\mathbf{I}_{kh} + \epsilon^{\varphi}(\boldsymbol{\chi}_{kh}))$$

$$\Psi = \sum_{i=1}^{N} \left[n_i^{1/m} \left(\frac{\widehat{\rho}}{\rho} \right)^2 \bar{\sigma}_i \right] \qquad \bar{\sigma}_i = \sqrt{2EW}$$

Analysis of the microscale (scaffold)

- Scaffold degradation, hydrolysis, (Adachi et al., 2006),

Analysis of the microscale (scaffold)

- Scaffold degradation, hydrolysis, (Adachi et al., 2006),
  - Water content,

$$\dot{d} = \alpha \Delta d \qquad \text{in} \qquad \Omega_S^{\varphi}(\mathbf{y})$$
$$+\text{boundary and initial conditions}$$

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$$\dot{d} = \alpha \Delta d \qquad \text{in} \qquad \Omega_S^{\varphi}(\mathrm{y})$$
$$+\text{boundary and initial conditions}$$

  - Molecular weight rate,

$$\dot{W}(d) = -\beta d$$

Analysis of the microscale (scaffold)

- Scaffold degradation, hydrolysis, (Adachi et al., 2006),
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$$\dot{d} = \alpha \Delta d \qquad \text{in} \qquad \Omega_S^{\varphi}(\mathrm{y})$$
$$+\text{boundary and initial conditions}$$

  - Molecular weight rate,

$$\dot{W}(d) = -\beta d$$

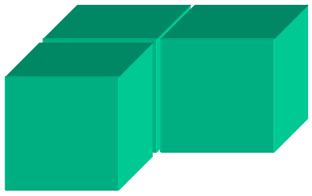
  - Mechanical properties,

$$\mathbb{C}^{\varphi}(W(t)) = \mathbb{C}^{\varphi}(t=0)\frac{W(t)}{W_0} \qquad \text{in} \qquad \Omega_S^{\varphi}(\mathrm{y})$$

instituto de investigación en ingeniería de Aragón Universidad de Zaragoza
Santiago de Compostela, Julio 2010

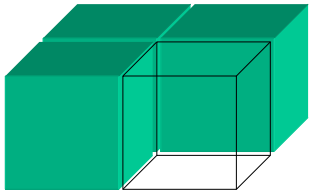
Computational implementation: voxel-FEM

- Bone growth



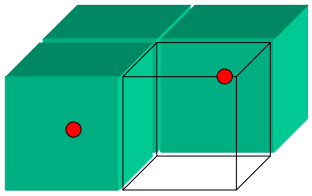
Computational implementation: voxel-FEM

- Bone growth
  - Identify voxel candidates.



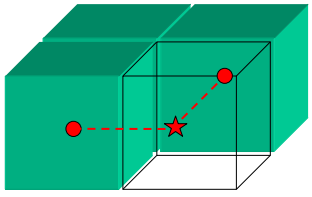
Computational implementation: voxel-FEM

- Bone growth
  - Identify voxel candidates.
  - Compute *M* at adjacent voxel candidate centroids.



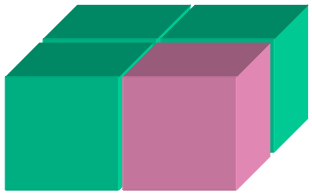
Computational implementation: voxel-FEM

- Bone growth
  - Identify voxel candidates.
  - Compute *M* at adjacent voxel candidate centroids.
  - Lagrangian interpolation of *M* to voxel candidate centroid.



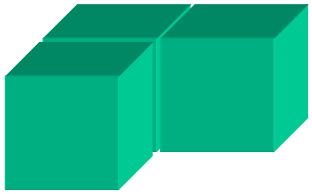
Computational implementation: voxel-FEM

- Bone growth
  - Identify voxel candidates.
  - Compute *M* at adjacent voxel candidate centroids.
  - Lagrangian interpolation of *M* to voxel candidate centroid.
  - If $M > M_c$ then shift voxel candidate into bone voxel.



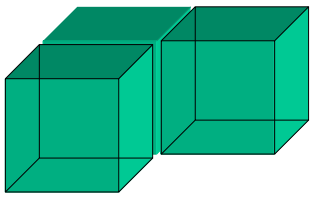
Computational implementation: voxel-FEM

- Scaffold degradation



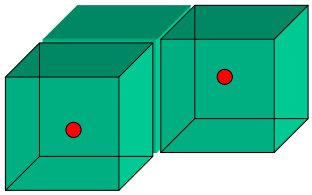
Computational implementation: voxel-FEM

- Scaffold degradation
  - Identify boundary voxels.



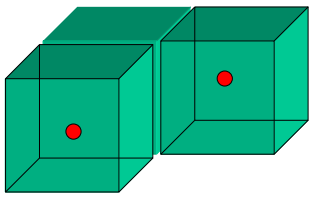
Computational implementation: voxel-FEM

- Scaffold degradation
  - Identify boundary voxels.
  - Compute *W* at boundary voxel centroids.



Computational implementation: voxel-FEM

- Scaffold degradation
  - Identify boundary voxels.
  - Compute W at boundary voxel centroids.
  - If $W < W_c$,

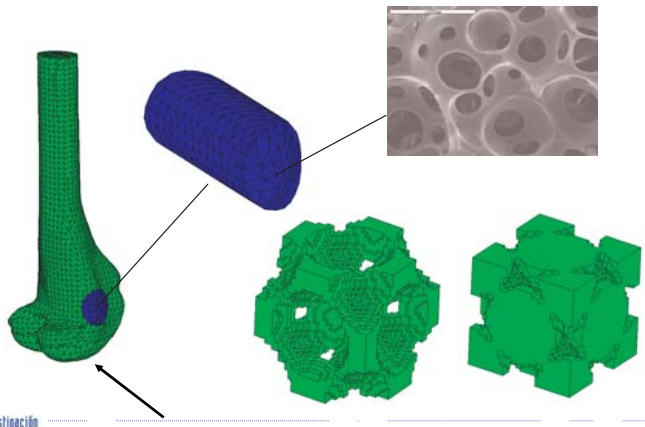


Computational implementation

- Scaffold degradation
  - Identify boundary voxels.
  - Compute W at boundary voxel centroids.
  - If $W < W_c$,
  - Then remove boundary voxel.

Example application: Distal femoral condyle

Problem definition (Sanz-Herrera et al, CMAME 2008)

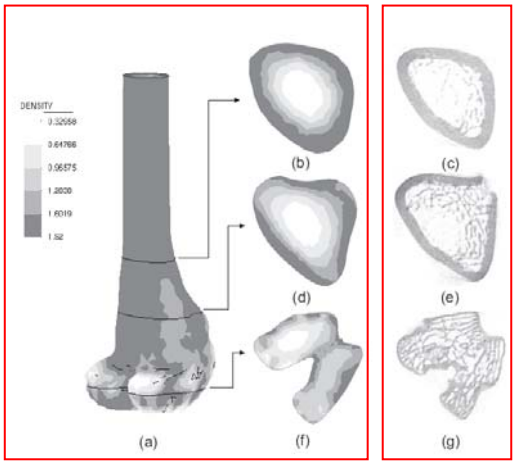


Load history: rabbit hopping (Gushue et al., 2005)

Example application: Distal femoral condyle

- Initial density distribution (g/cc),

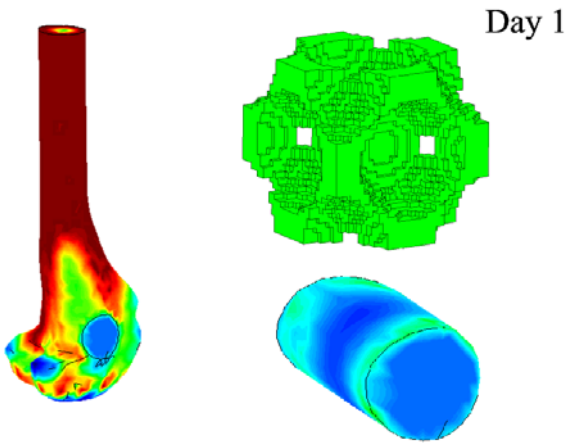
Simulated



Actual

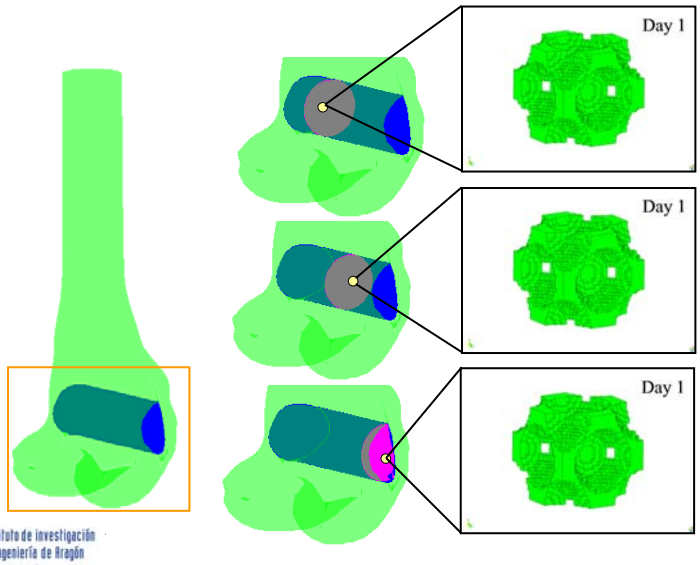
Doschak et al., (2005)

Example application: Distal femoral condyle



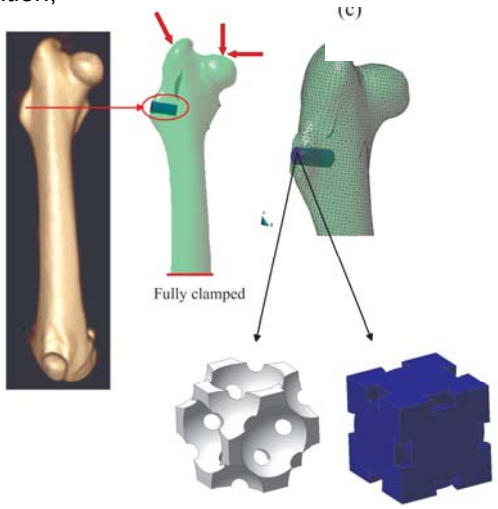
Example application: Distal femoral condyle

- Multiscale results,



Proximal femur: parametric analysis

- Problem definition,



Proximal femur: parametric analysis

- Parametric analysis, effects of:
  - Porosity.
  - Pore size.
  - Biomaterial stiffness.
  - Resorption kinetics.
  - Scaffold pre-seeding.

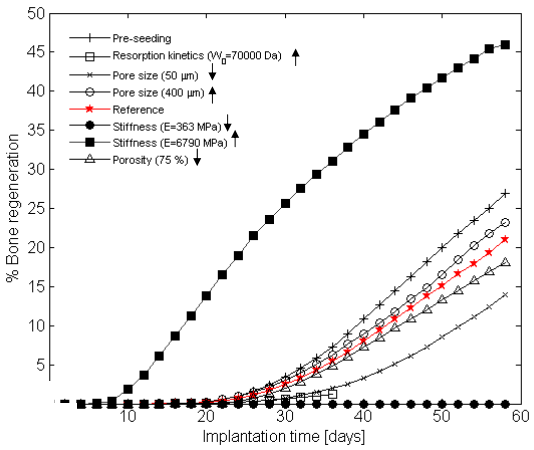
Reference scaffold parameters

Parameter	Description	Value
Φ	Scaffold porosity	0.9
E	Bulk biomaterial Young's modulus (MPa)	1570
ν	Bulk biomaterial Poisson's ratio	0.39
α	Hydrolysis model parameter ($mm^2\ day^{-1}$)	4×10^{-4}
β	Hydrolysis model parameter (day^{-1})	4000
W_0	Bulk biomaterial molecular weight (Da)	114,000
W_c	Molecular weight value under which the biomaterial degrades (Da)	10,000
R	Pore size (μm)	200

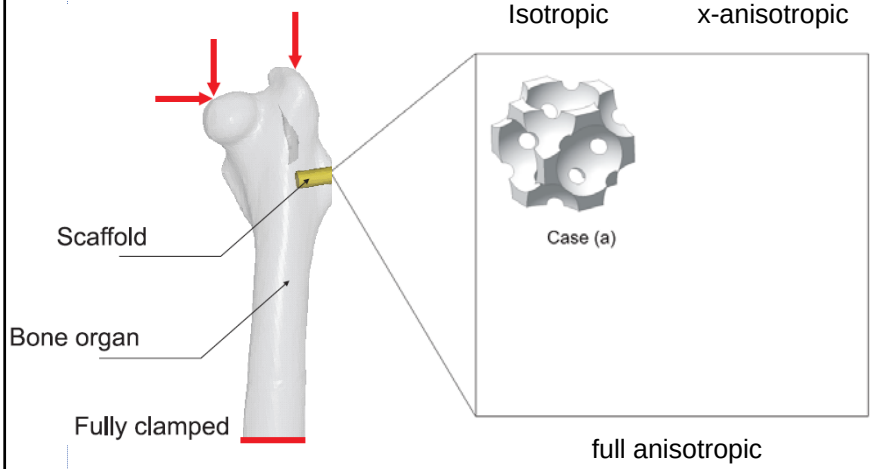
Proximal femur: parametric analysis

- Macroscopic quantities: bone regeneration,

Acta Biomaterialia (2008)



Analysis of scaffold microstructural anisotropy



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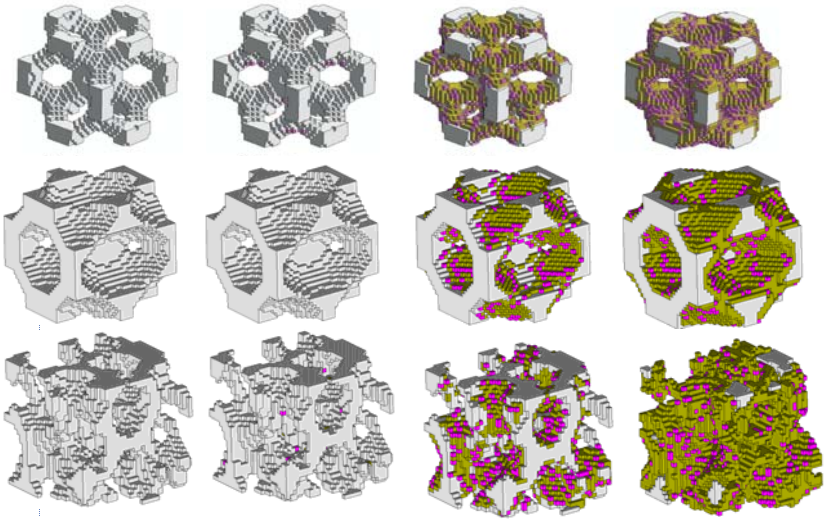
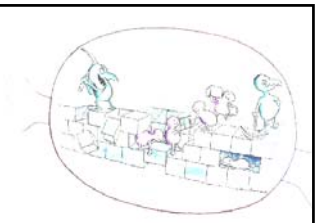


Day 1 Day 10 Day 20 Day 29

5.1. Some Conclusions

- The evolutionary microstructural geometry results into a non-usual non-linear problem in mechanics.
- Bone remodelling due to the implantation of a scaffold is negligible except in a localized zone surrounding the scaffold.
- Bone growth at scaffold microsurfaces occurs isotropically for symmetric patterns.
- Scaffold microstructure determines the subsequent architecture of the formed bone.
- When anisotropy is present in the scaffold microarchitecture, bone regeneration tends to follow the direction of maximum stiffness.

OVERVIEW



- ***Bone properties***
- ***Role of mechanical factors: bone mechanobiology***
- ***Methods of Science: computer simulation***
- ***Modelling Bone Regeneration:***
  - ***Bone Healing***
  - ***Bone Distraction***
  - ***Bone Tissue Engineering***
- ***Final conclusions***

FINAL CONCLUSIONS

- These models require further experimental validation.
- Check the influence of different mechanical stimulus and other mechanoregulation rules
- Incorporate additional coupled biophysical stimuli: ***multiphysics*** analysis
- Going down through scales trying to explore mechanotransduction at cellular level in connection with organ level: ***multiscale*** analysis
- But multiscale and multiphysics approach require a ***high computational cost***

Development of new numerical techniques that allow to reduce this cost

Acknowledgments

- **Regional Government of Aragón, Spanish Ministry of Science and Technology** & **CIBER** initiative through different research projects.
- Collaborators:

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J.A. Sanz-Herrera
V. Acosta
E. Reina
E. Javierre
I. Ochoa
L.A. González

GEMM
Group of Structural Mechanics and Material Modelling

MODELADO MATEMÁTICO DE LA MECANOBIOLOGÍA ÓSEA

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