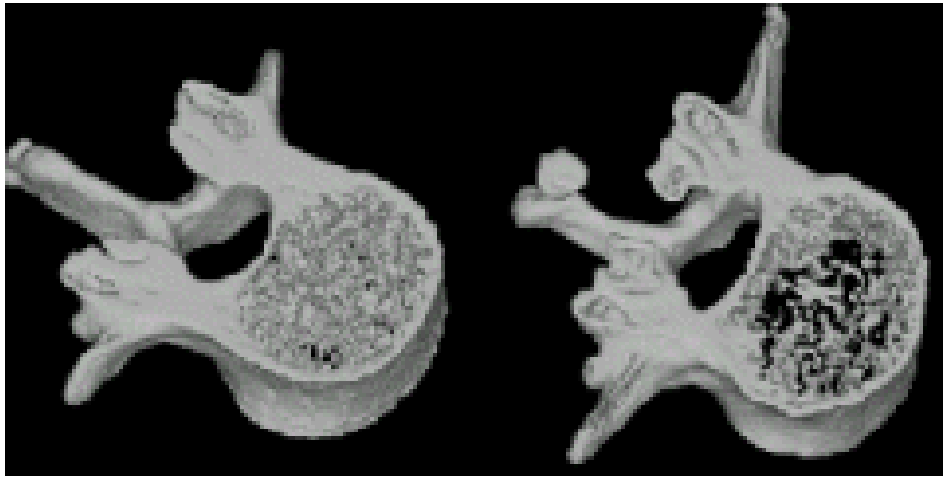
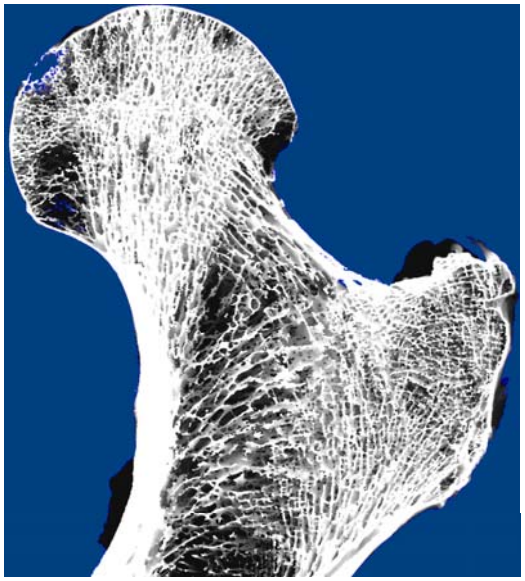
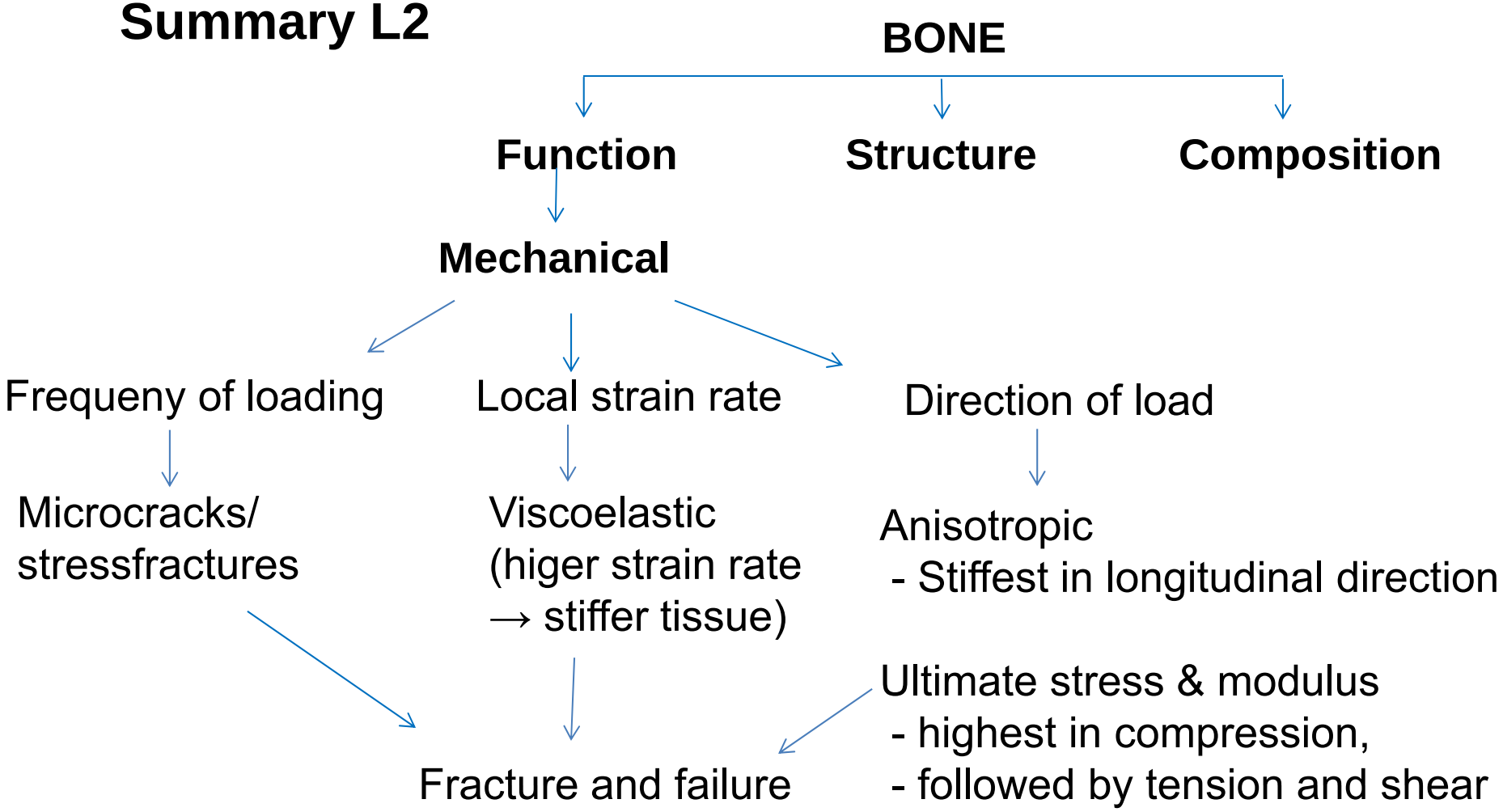
L3: Degenerative diseases and bone remodelling





Summary L2


BONE
Function
Structure
Composition
Mechanical
Frequeny of loading
Local strain rate
Direction of load
Microcracks/
stressfractures
Viscoelastic
(higer strain rate
→ stiffer tissue)
Anisotropic
- Stiffest in longitudinal direction
Ultimate stress & modulus
- highest in compression,
- followed by tension and shear
Fracture and failure

Example 2: Torsion and shear

Calculate on your own

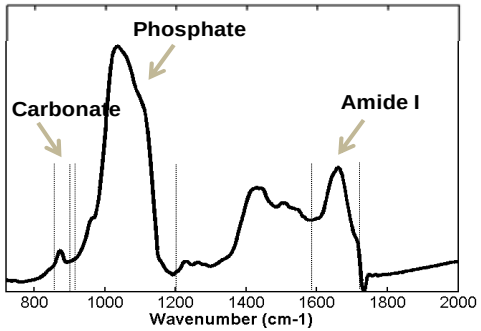
Suppose a human bone shaped like cylindrical shaft with periosteal and endosteal diameters of 2 and 1 cm, respectively. Shear yield stress of a human bone can be assumed to be 54 MPa and ultimate torque capacity 99Nm. Due to some metabolic bone disease, the shear strength is diminished by 20% and 1mm of bone is lost from the endosteal surface during time.

A. How much must the periosteal diameter increase to compensate for these changes?
B. If all these occurred simultaneously over 30-year period, what would the mean periosteal apposition rate be? Are those values realistic?

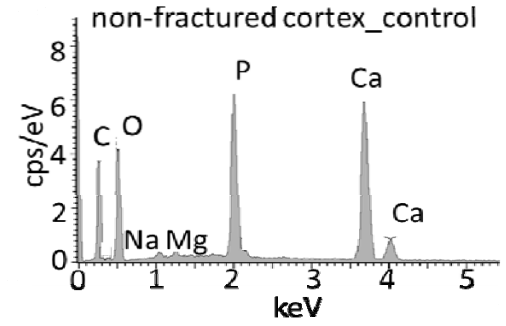
Example 3: Bone quality and composite theory

Calculate on your own

In a research project, small pieces of bones from patients with osteomalacia are compared to healthy normal patients. The bones are investigated using infrared spectroscopy and scanning electron microscopy to measure the molecular and atomic composition of the bone.



It is found that healthy bone contains 25 weight % Calcium, whereas osteomalacia bone only contains 21 weight %. The researchers are interested in knowing how much this decrease in calcium content affects the elastic modulus of the bone, but do not have enough tissue to perform mechanical test. Estimate **E** by calculating it using composite theories by Voigt and Reuss.



Assume that bone only contains hydroxyapatite (HA) and collagen. Hence volume fractions: $\Phi_M + \Phi_C = 1$.
Modulus of HA mineral E_M is 100 GPa, and of collagen, E_C, is 2.5 GPa

Hints: To estimate the mineral volume fraction, first convert the calcium weight % to mineral volume % Φ_M using stoichiometric relation of HA wt. % = 2.51 x Ca Wt. %.
Collagen density $\rho_c = 1.47$ g/cm^3
Mineral density $\rho_{HA} = 3.18$ g/cm^3
The volume fraction can be estimated from the rule of mixture

$$\Phi_M = \frac{HA_{WT}}{HA_{WT} + (1 - HA_{WT})(\rho_{HA} / \rho_C)}$$

Outline

- **Degenerative diseases**
  - Degenerative changes with aging
  - Examples of diseases
  - Diagnosis of degenerative diseases

- **Bone mechanobiology**
  - Bone adaptation
  - History
  - Today's "truth"
  - Remodelling simulations

Literature week 1
Lecture 1-3, Hard tissue mechanics

Book chapters

- Bone, Chapter 2.3: by Nigg and Herzog
- Definitions, Chapter 2.1: by Nigg and Herzog

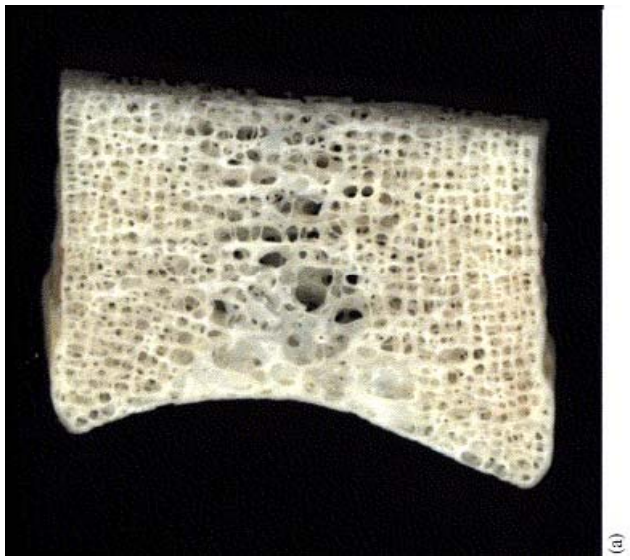
Research articles

- Turner and Burr, 1993. Basic biomechanical measurements of bone. A tutorial
- van der Meulen et al., 2001. Understanding bone strength. Size isn't everything
- **van der Meulen, 2002. Why mechanobiology?**

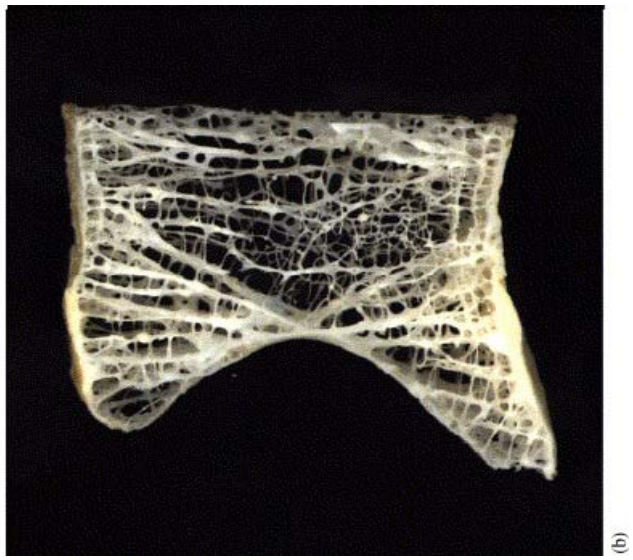
Effects of aging on bone

- Vertebral cross-section from autospy specimens of

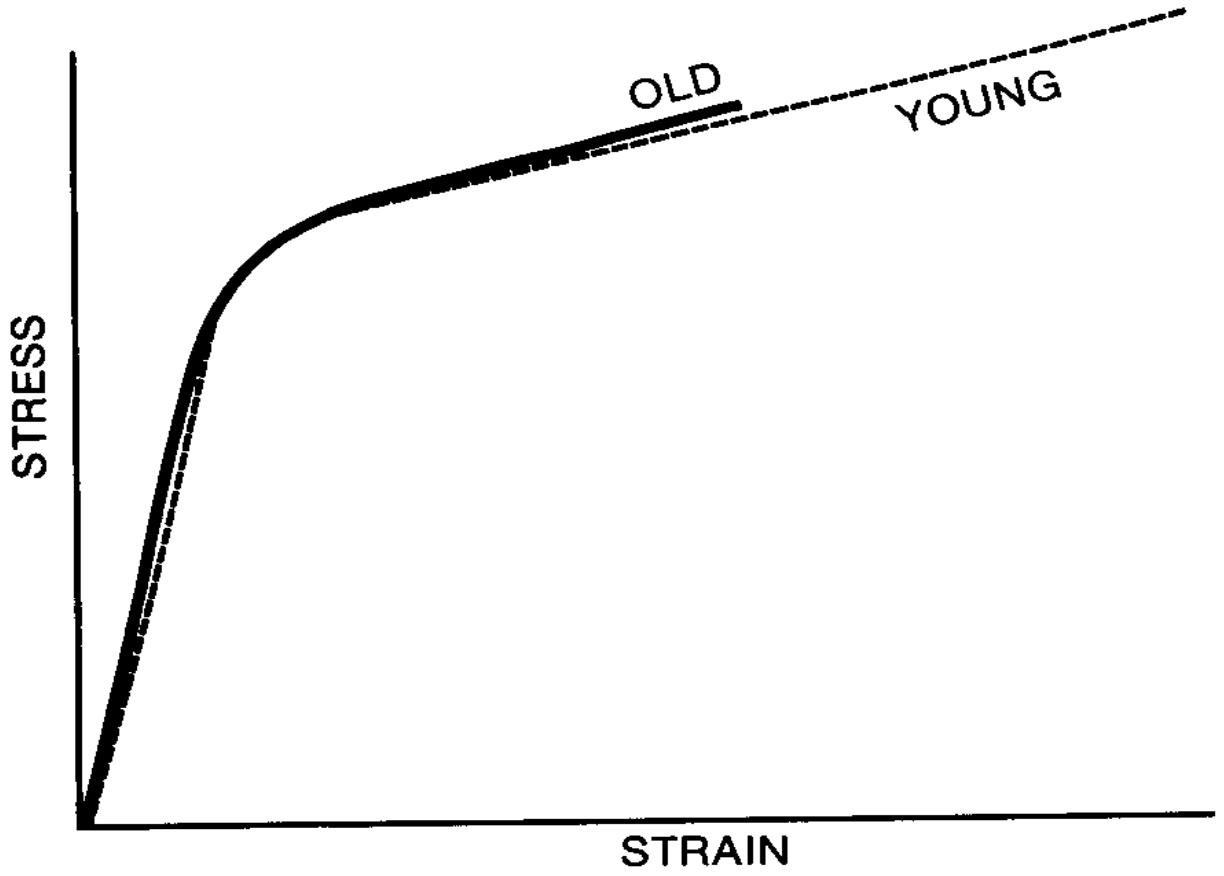
young bone



old bone



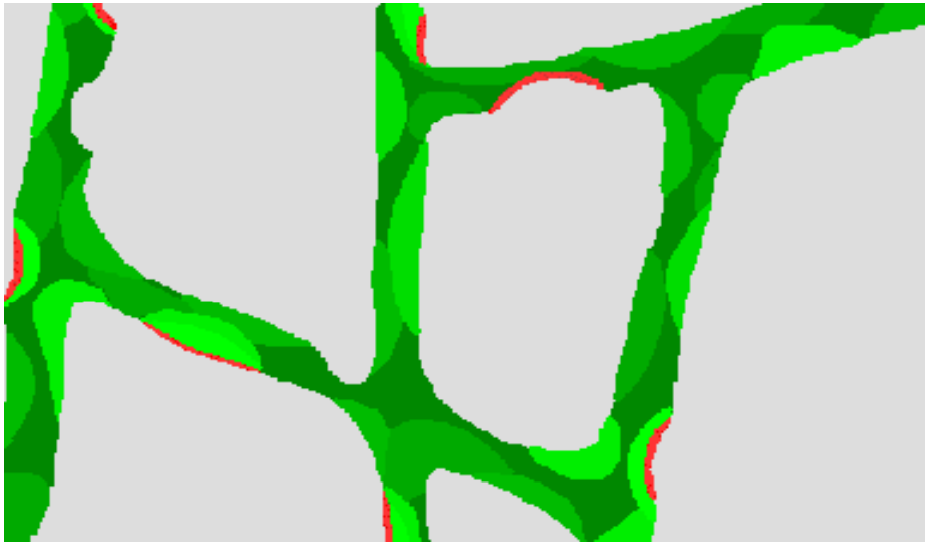
Effects of aging on bone properties

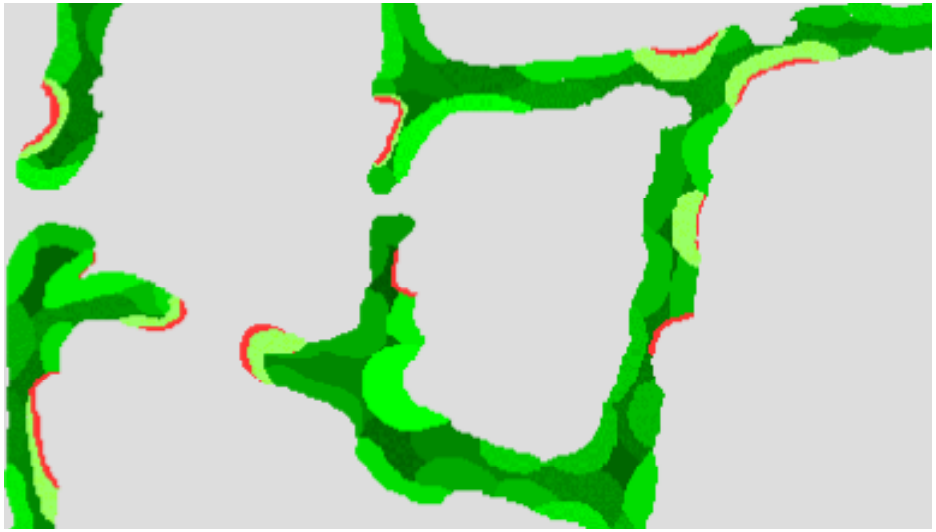


Stress-strain curves for samples of adult human tibia of two widely differing ages tested in tension

Osteoporosis

- With age, the bone remodeling balance becomes negative: more bone is resorbed than what is formed. Result in a net loss!
- When loss is big enough → osteoporosis





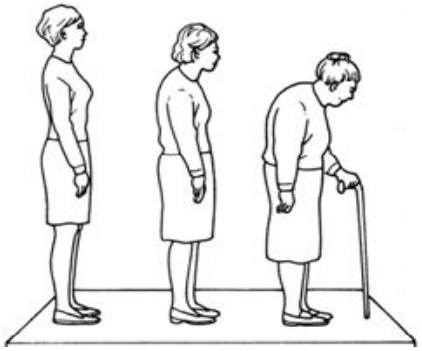
Osteoporosis

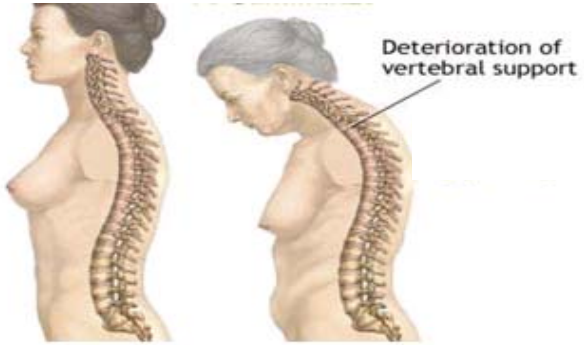
- Osteoporosis = 'Porous bones'

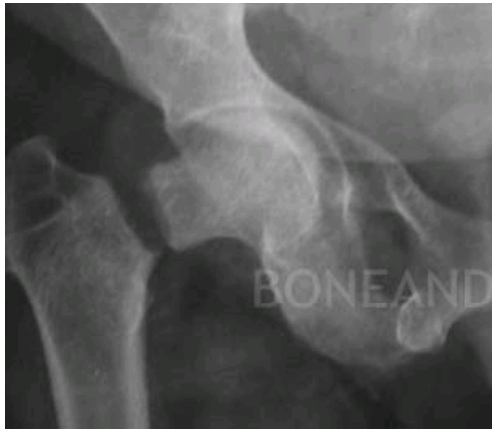
- Major health problem in elderly
- Pain, morbidity and mortality
- In Europe
  - 800 000 hip fractures/year
  - Vertebral deformity 12 % in 50+
  - Total cost of fractures ~25 billion euros/year

- Altered hormonal balance (e.g. decreased levels of estrogen) leads to altered bone remodeling

  - **balance between formation (osteoblasts) and resorption (osteoclasts) change**







Types of osteoporosis

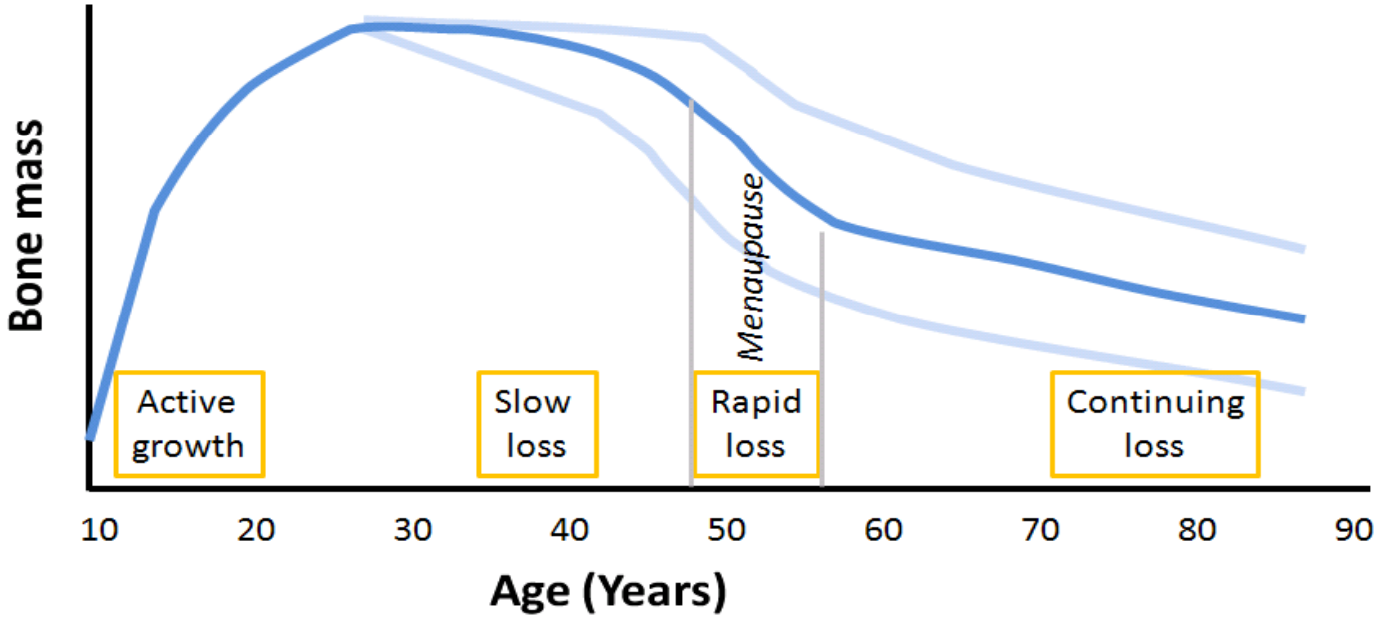
- **Primary**:
  - Postmenaopausal, senile

- **Seconday**:
  - Resulting from other endocrine disorders
  - e.g. hyper- and hypoparathyroidism
  - diabetes type 1
  - use of steroids etc

Osteoporosis and bone mass

- Loss in bone mass due to aging or due to osteoporosis? Difference?

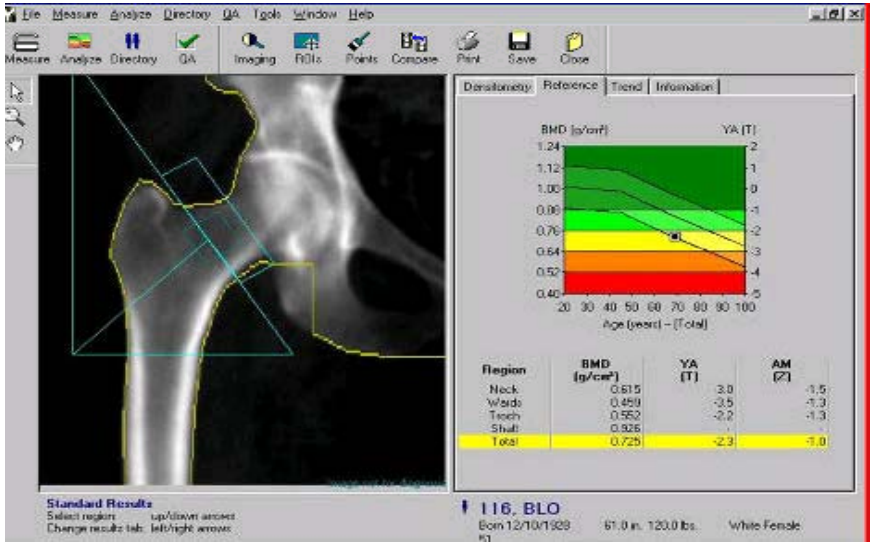
- Women affected more than men
- Risk factors
  - Sex, age, race, family history, etc
  - Previous fractures, low BMI, smoking, not enough exercise etc.

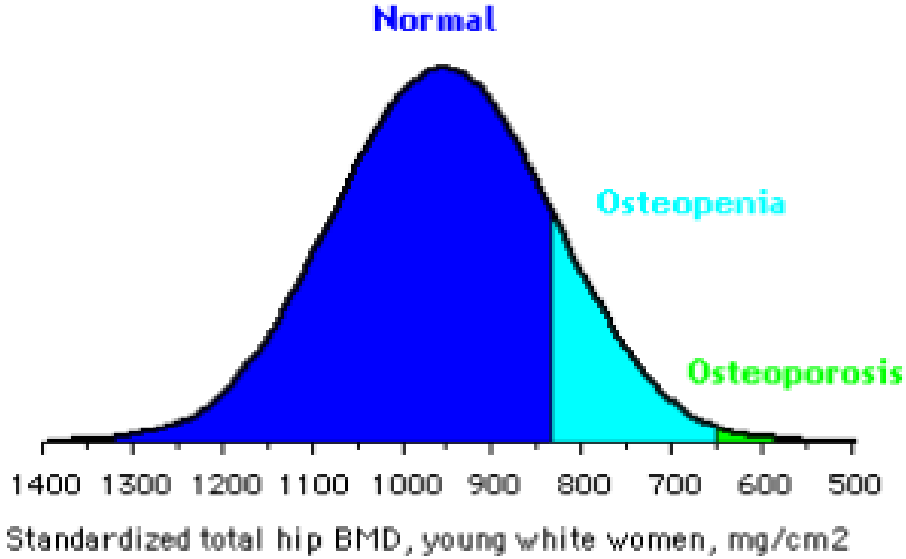


WHO diagnostics of osteoporosis

- Bone densitometry to measure bone mineral density
  - DXA – dual frequency X-ray absorptiometry

- Compared to a healthy reference population
  - Osteoporosis: T-score less than -2.5 SD
  - Osteopenic: T-score less than -1.0 SD (low bone density, but not yetosteoporosis)

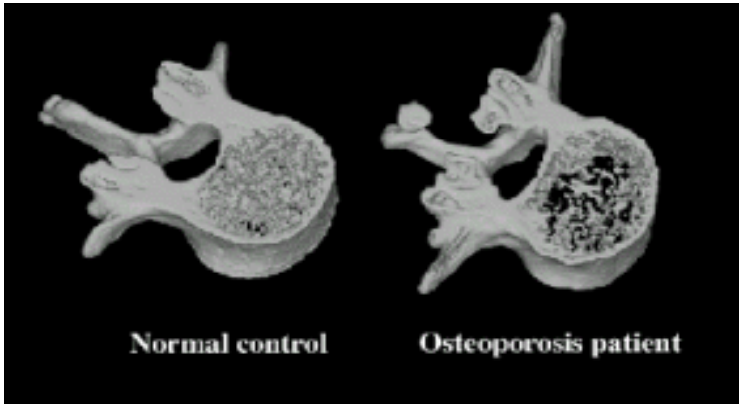


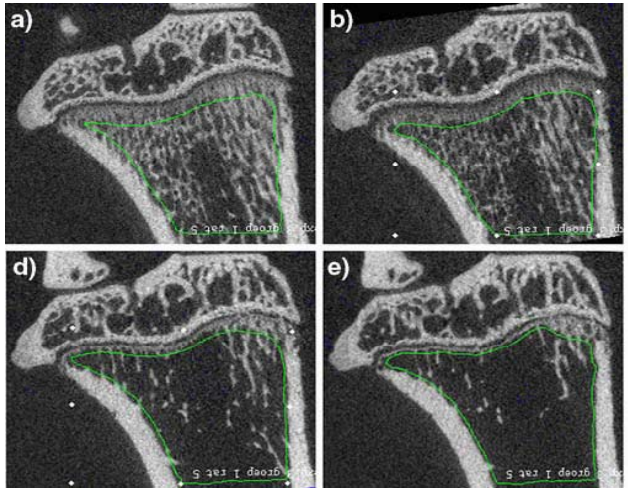


Treatment of osteoporosis

- Bisphosphonate
  - Drugs that prevent bone loss by inhibiting osteoclast resorption, and increasing the osteoclast apoptosis rate (cell suicide).
  - Concerns that long term use may lead to too many microcracks and therefore bone fractures

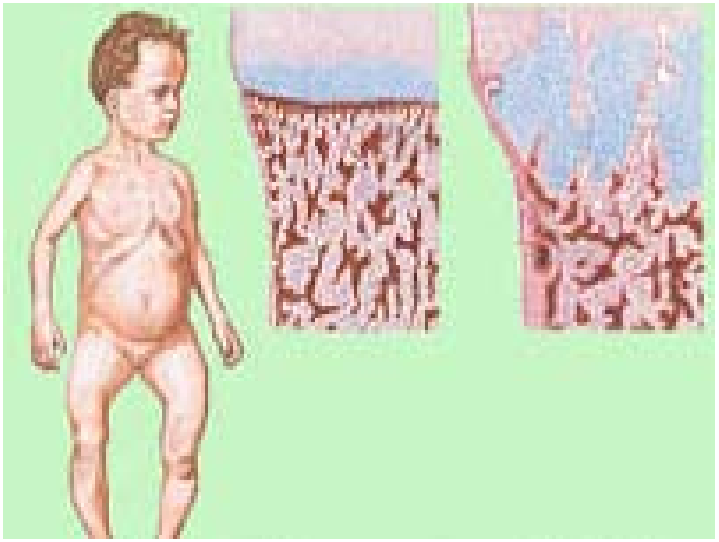
- Healthy lifestyle, exercise, and **avoid falling**!

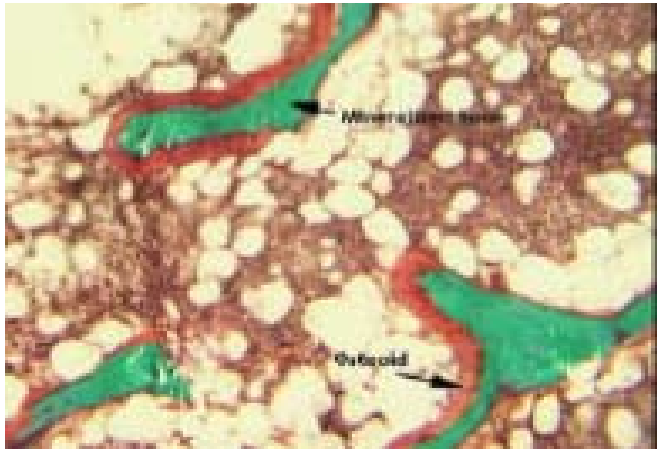




Osteomalacia and Rickets

- Called **rickets** in children and **osteomalacia** in adults (milder form).
- A person with osteomalacia have **“soft bones”**
- A dysfunction when the osteoid is mineralizing. Hence newly formed bone does not mineralize, but remains as osteoid/organic matrix
- Usually cased by
  - Deficiency or abnormal metabolism of vitamin D
  - Calcium or phosphate deficiency
- Physical deformities and pathologic fractures

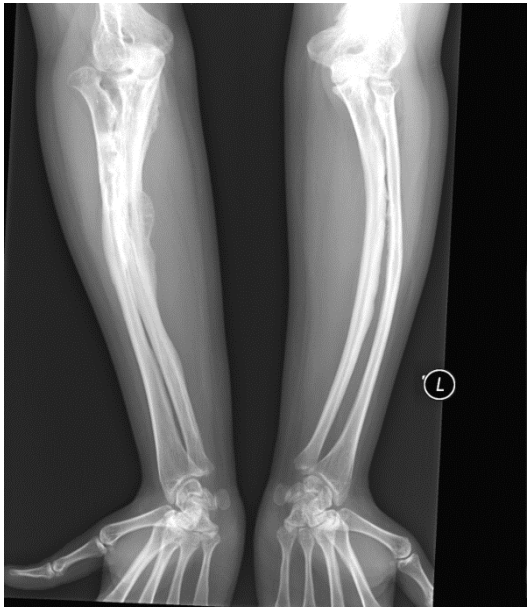




Osteogensis imperfecta

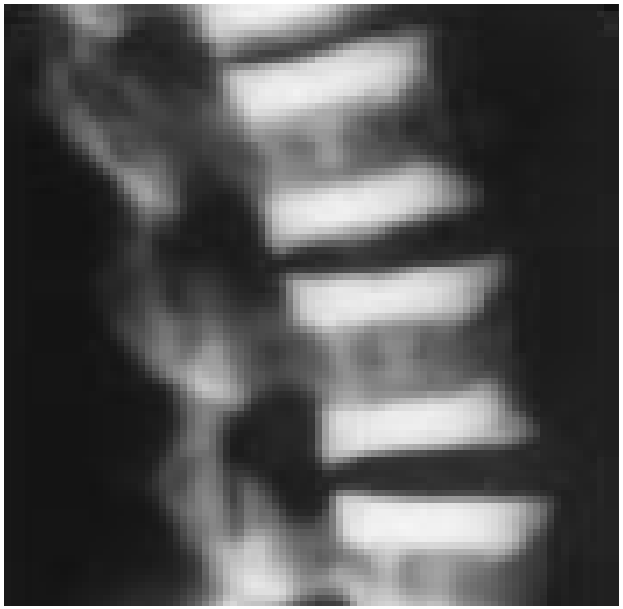
- A genetic bone disorder known as **brittle bone disease**
- Born without the ability to make connective tissue, due to deficiency in type-I **collagen**.
- Influences the molecular nanomechanics of bone through the relationship between the collagen fibrils and hydroxyapatite crystals, causing brittleness

- No cure, current treatments involve
  - Increasing bone strength
  - Corrective surgery with rods to enable walking
  - Physiotherapy to increase muscle strength



Osteopetrosis

- Opposite to osteomalacia
- Rare genetic disorder
- Bones become too highly mineralized → brittle



What makes our skeleton resistant to fractures?

Fracture resistance is “bone strength”

Architecture (Macro-, geometry; micro-, connectivity and shape)

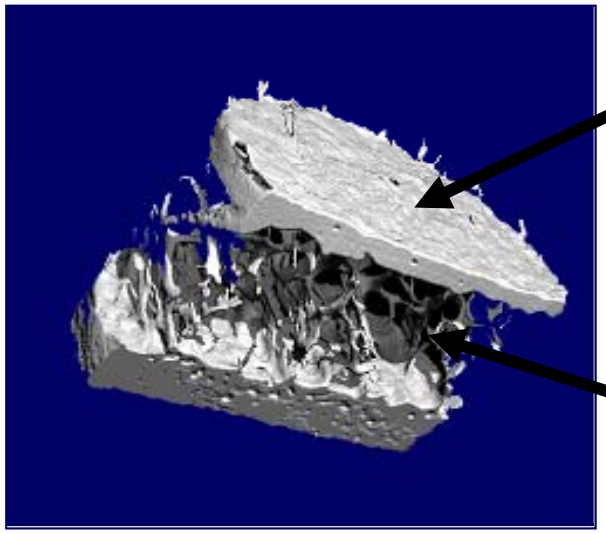
Turnover rate (resorption and formation)

Intrinsic material properties

- Damage Accumulation (microcracks)
- Mineralization (degree and heterogeneity)
- Properties of collagen/mineral matrix (e.g. crosslinking)

NIH Consensus Development Panel on Osteoporosis. JAMA 285:785-95; 2001

Architecture: Cortical and Trabecular Bone



Cortical Bone

- 80% of all the bone in the body
- 20% of bone turnover

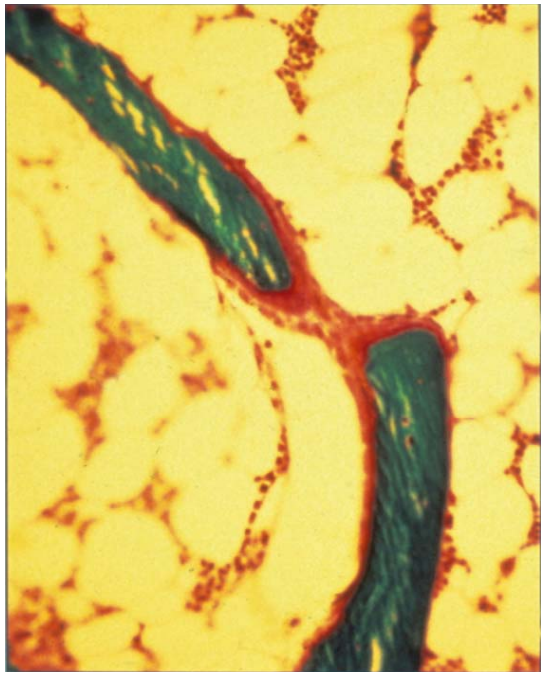
Trabecular Bone

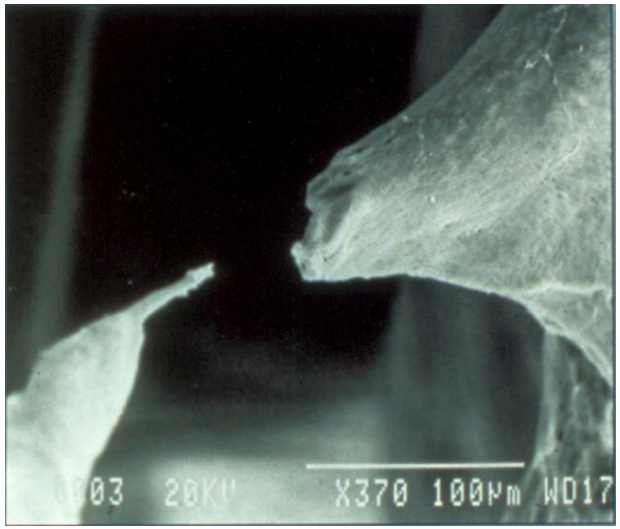
- 20% of all bone in the body
- 80% of bone turnover

Architecture: Trabecular Perforations

Risk of trabecular perforation increases with:

- Increased bone turnover
- Increased erosion depth
- Predisposition to trabecular thinning





Mosekilde L. *Bone Miner* 10: 13-35, 1990
Seeman *Lancet* 359, 1841-1850, 2002.

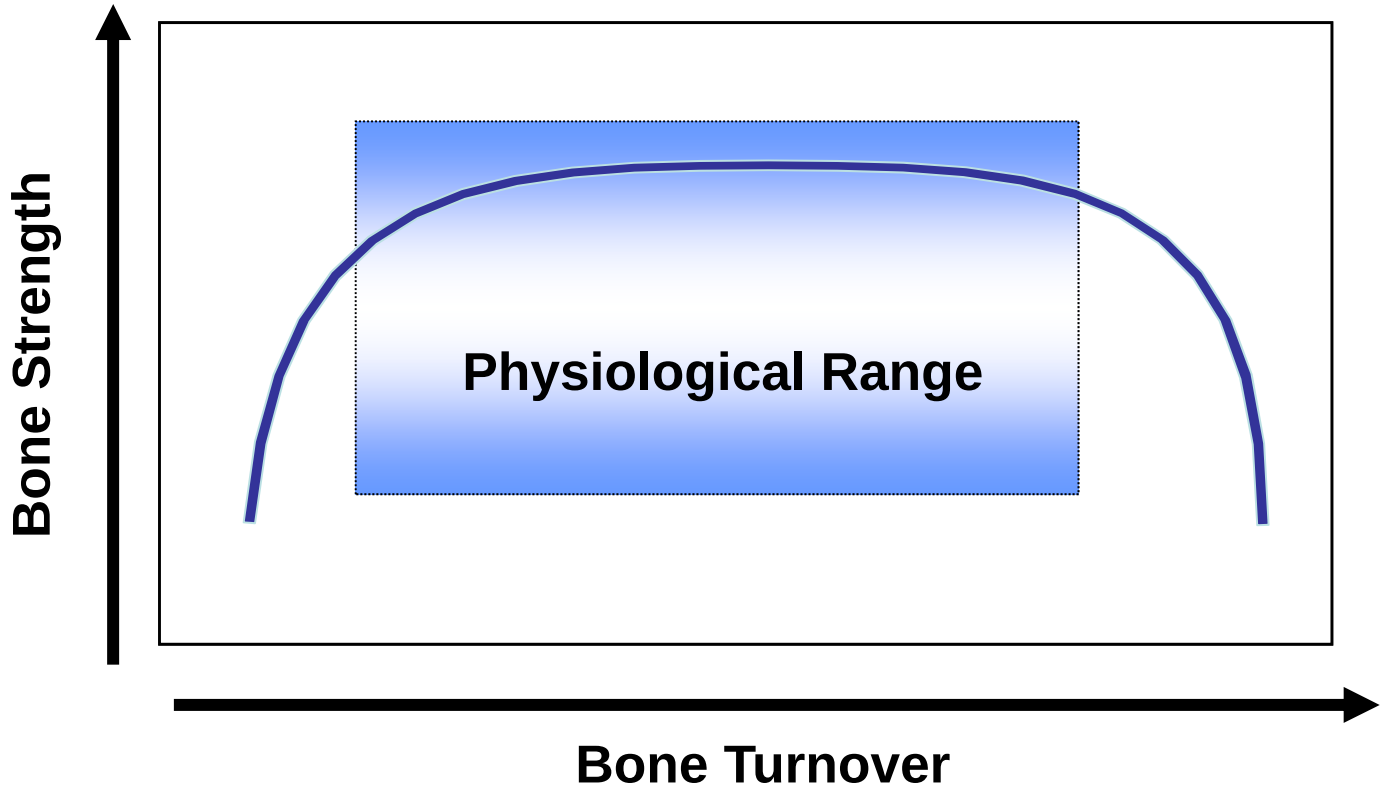
Turnover

Insufficient turnover

- Accumulation of microdamage
- Increased brittleness due to excessive mineralization
- Wide ‘safe zoon’

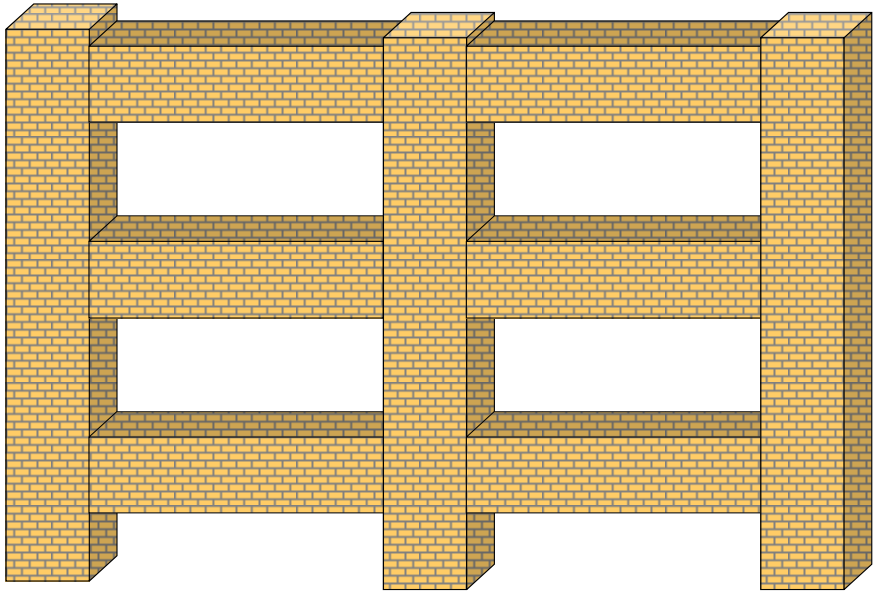
Excessive turnover

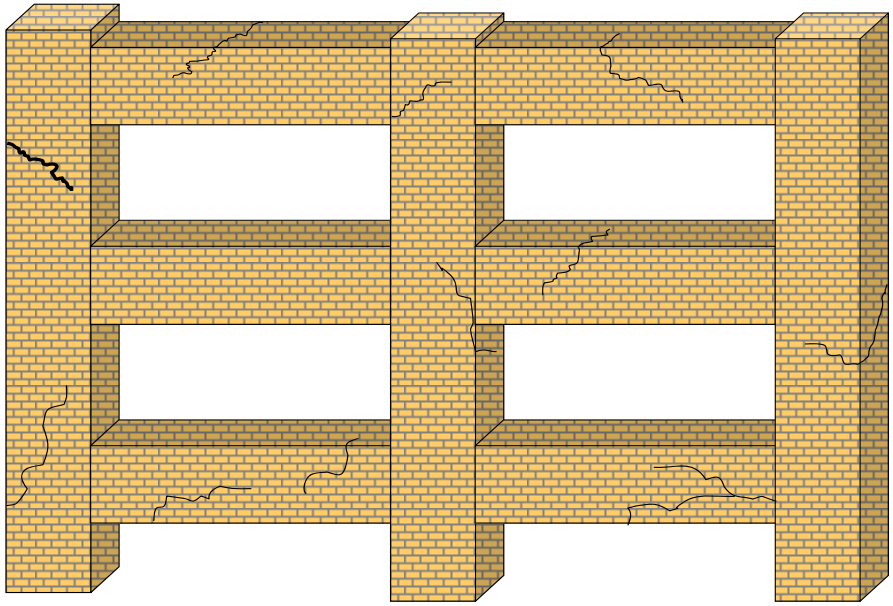
- Osteoid matrix accumulation
- Increase in stress risers (weak zones)
- Increase in perforations
- Loss of connectivity

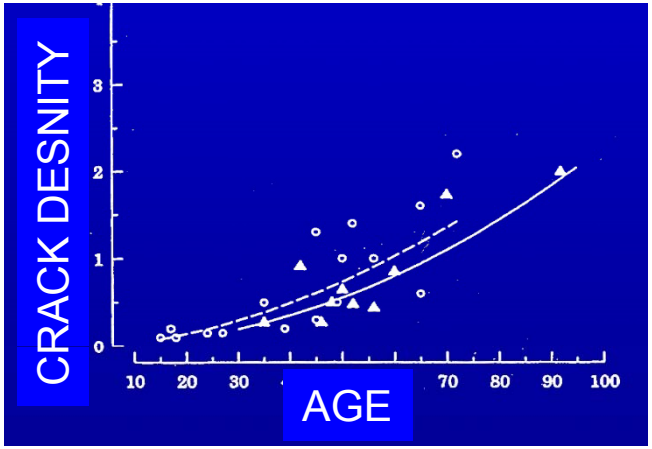


Adapted from Weinstein, *JBMR* 2000

Microdamage (microcrack) accumulation



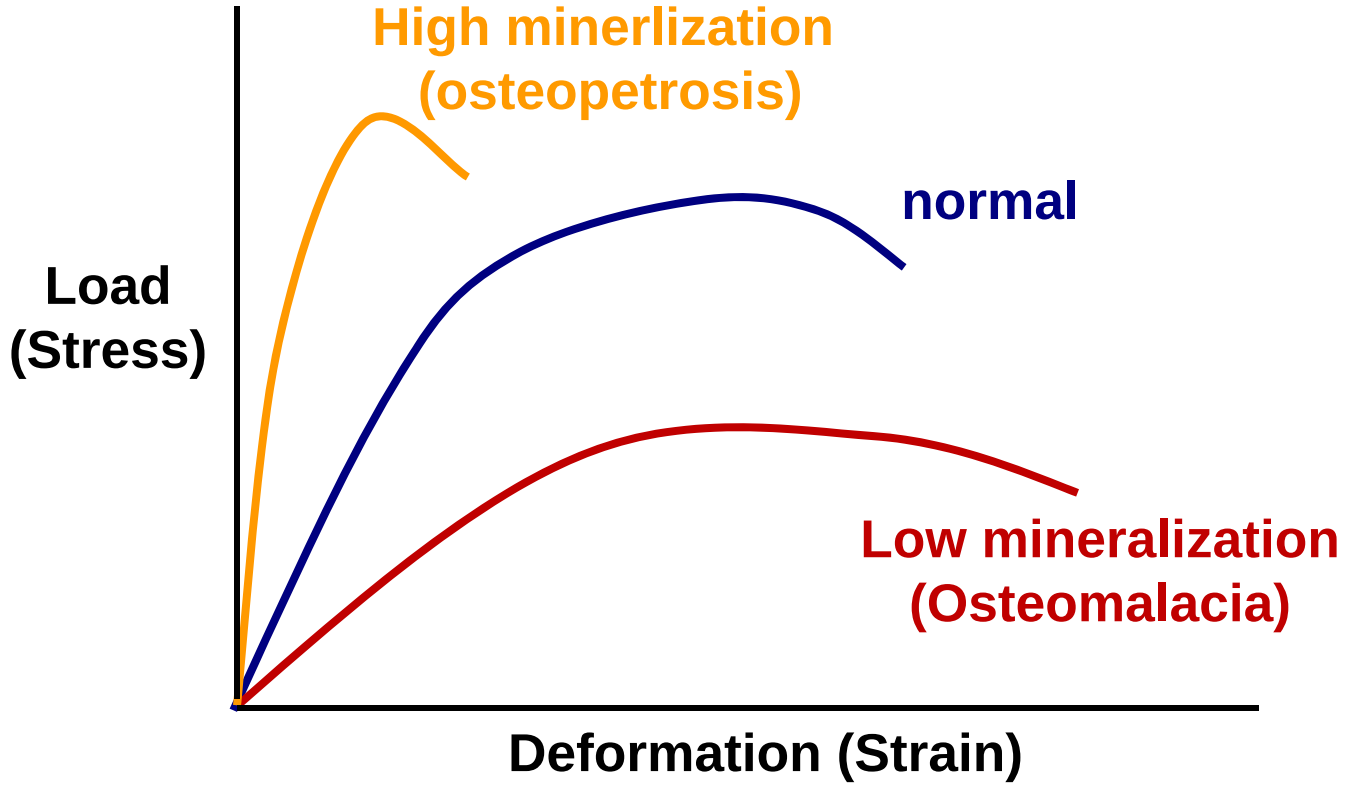




Increases with age!

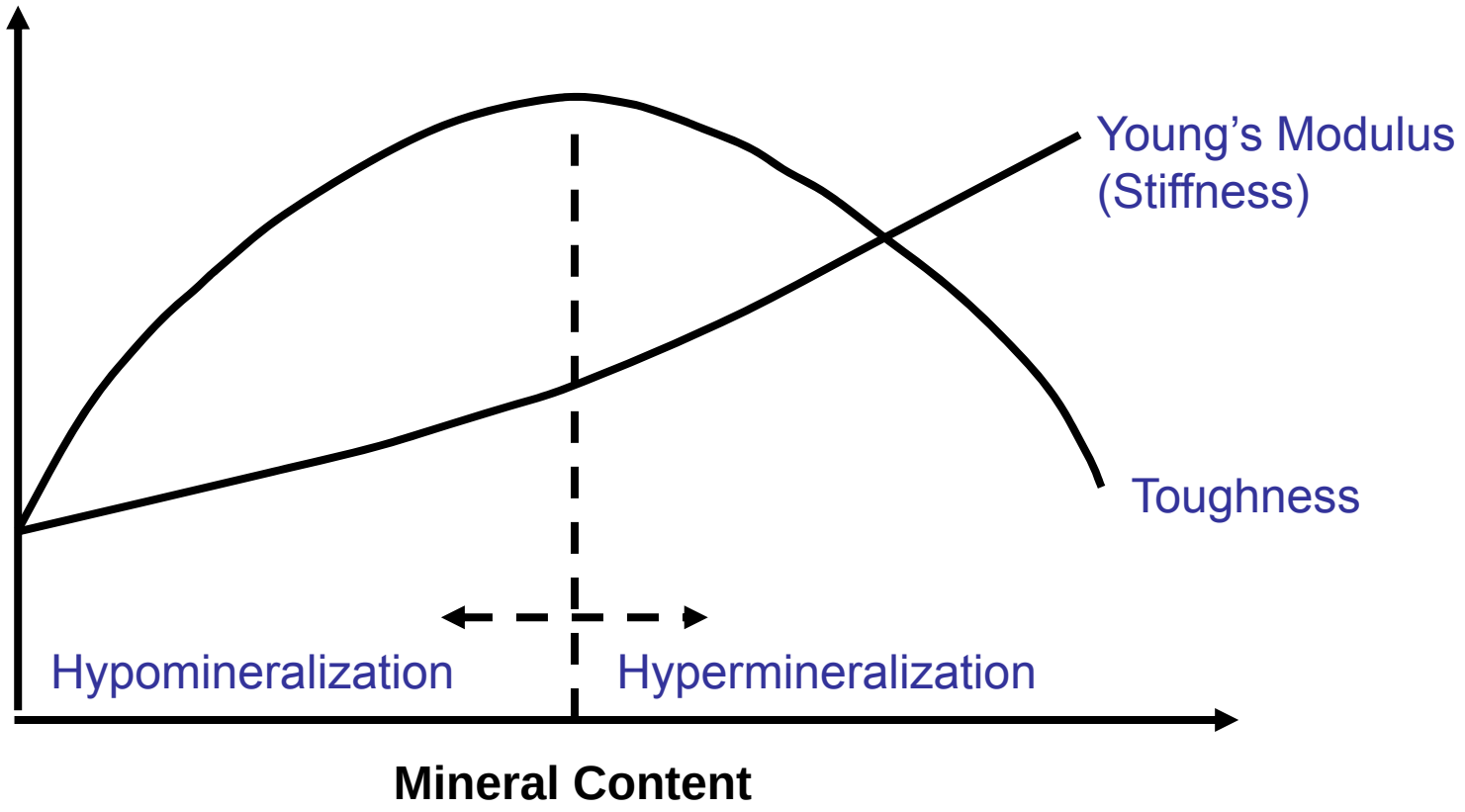
Matrix mineralization

Relationship between mineralization, density and mechanical properties



Turner et al. *Osteoporos Int*; 2002; Bouxsein, ASBMR 2003

Relationship between mineralization and toughness

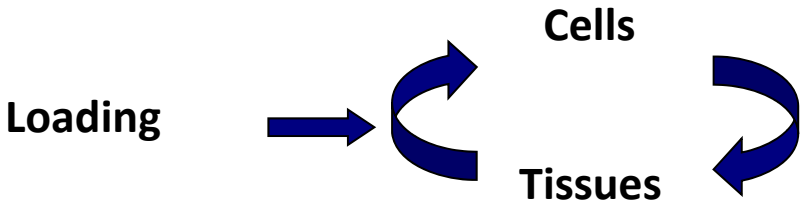


Wainwright, et al., M*echanical Design in Organisms*. Princeton Press, 1976

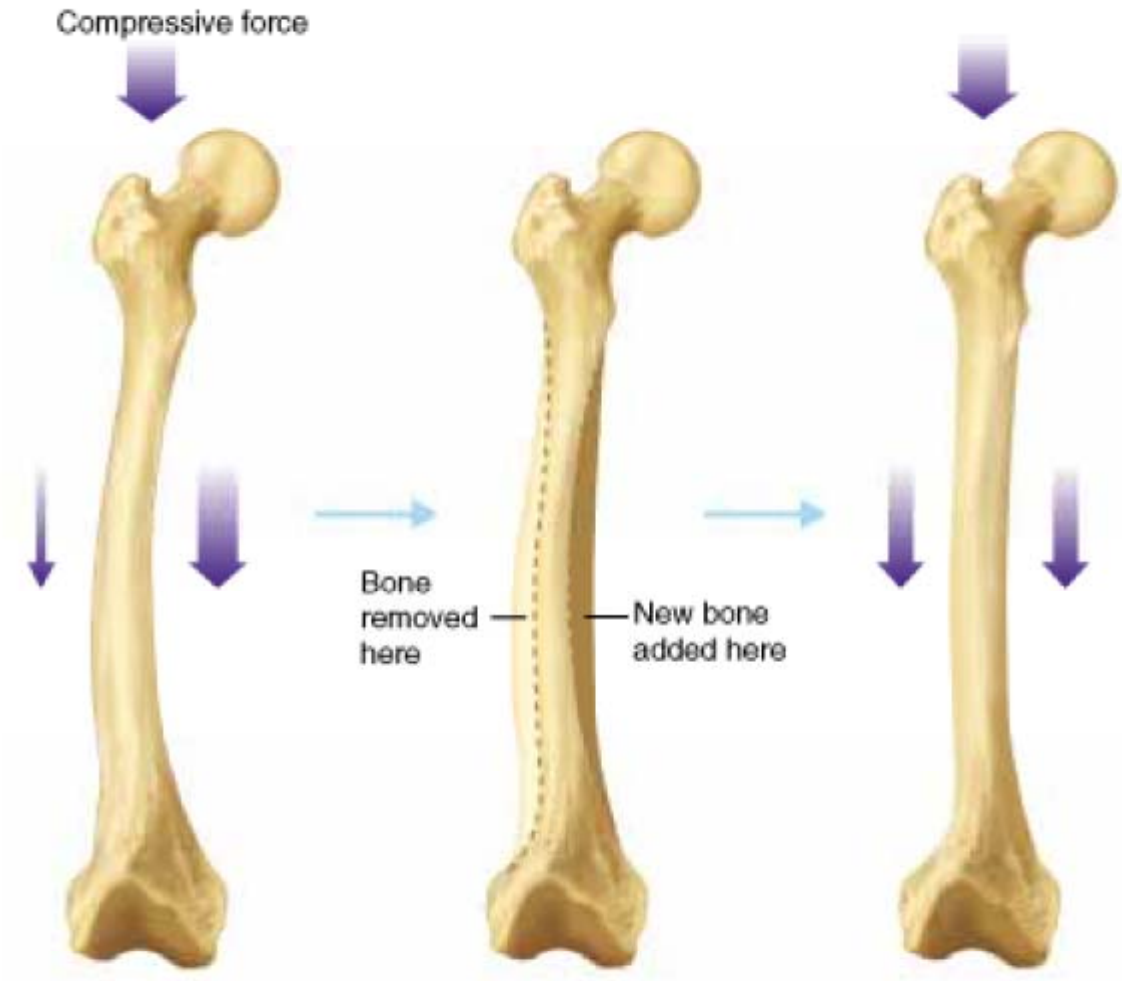
Bone mechanobiology and adaption

Mechanobiology

- When a tissue is exposed to mechanical stresses, the stresses can result in:
  - A change in the tissue phenotype (tissue differentiation). The tissue changes from one class of tissue to another, e.g. cartilage could change into bone.
  - Or the tissue will not change but rather reorganize its internal structure; This case applies mainly to bone, and the process is called bone remodeling.



Bone remodeling



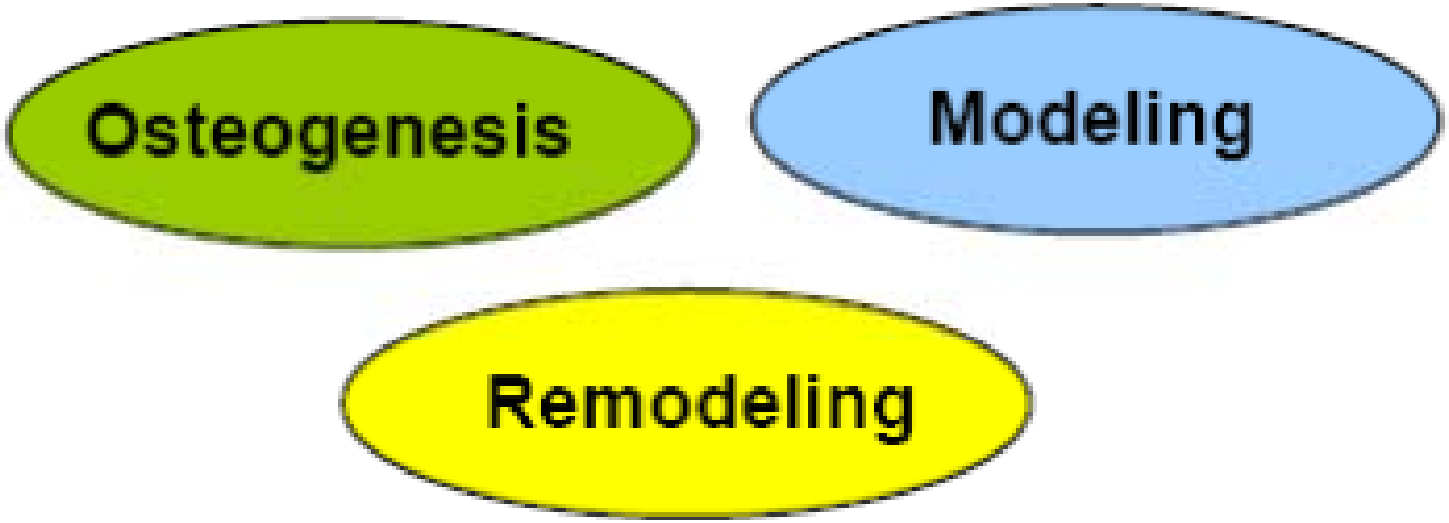
Bone is a dynamic tissue. It adapts!

-What does it mean?

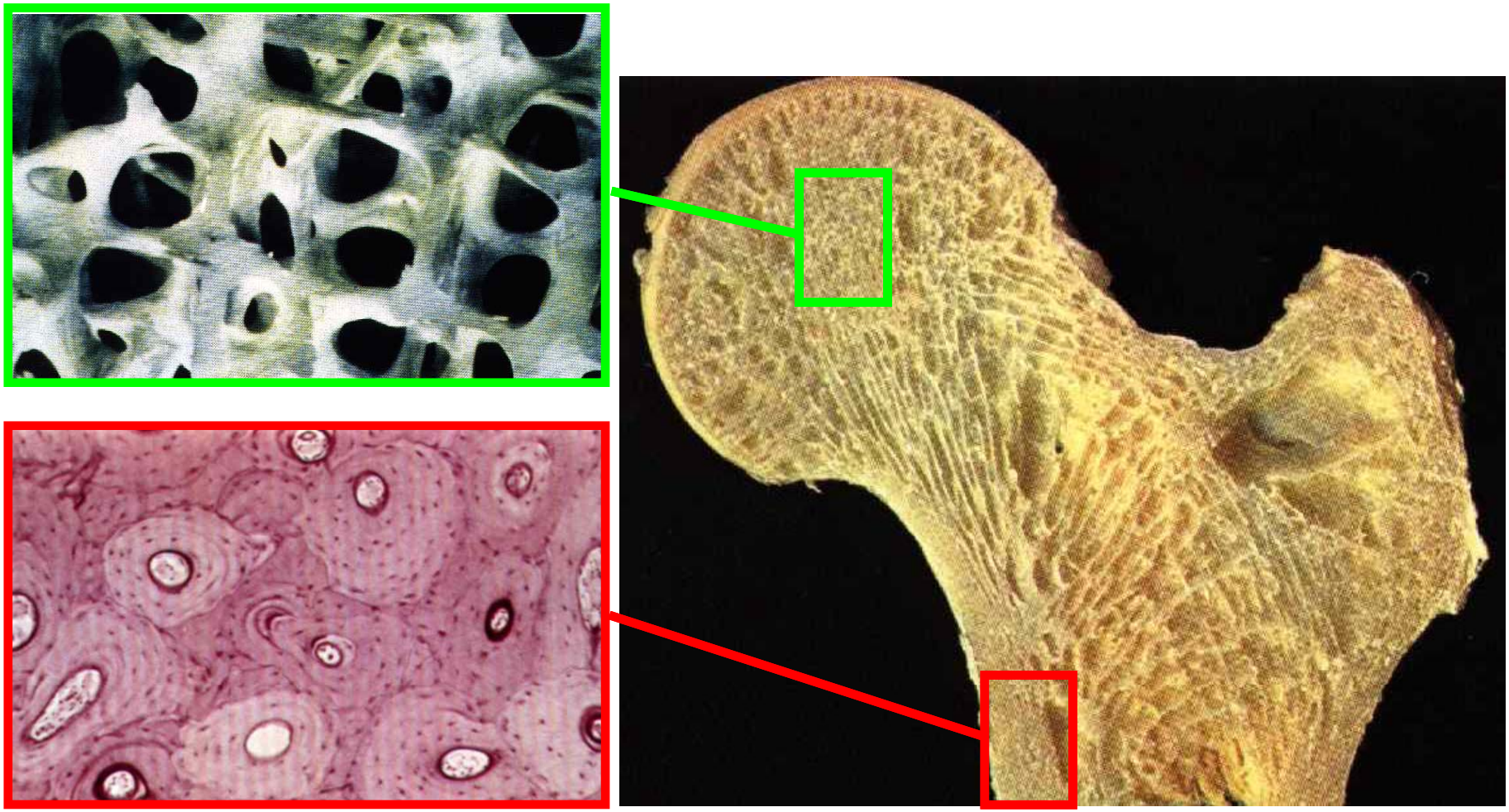
Three major methods of bone adaptation

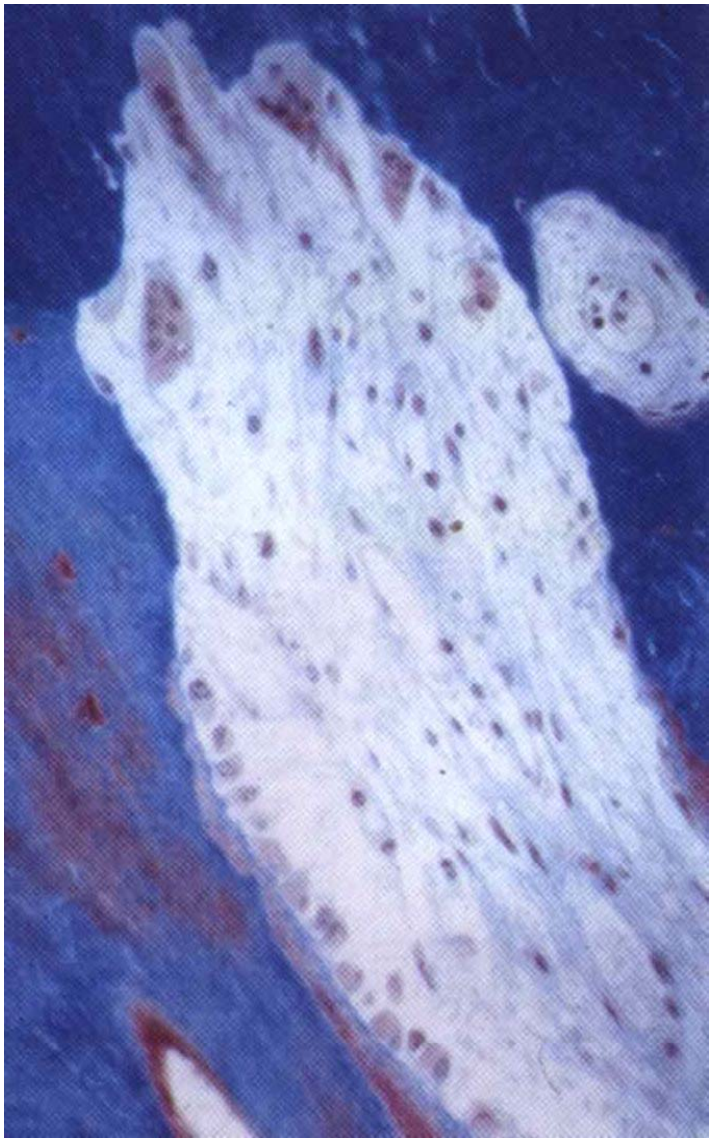
Ossification
Creating bone

Re-shaping,
sculpting
Cells uncoupled

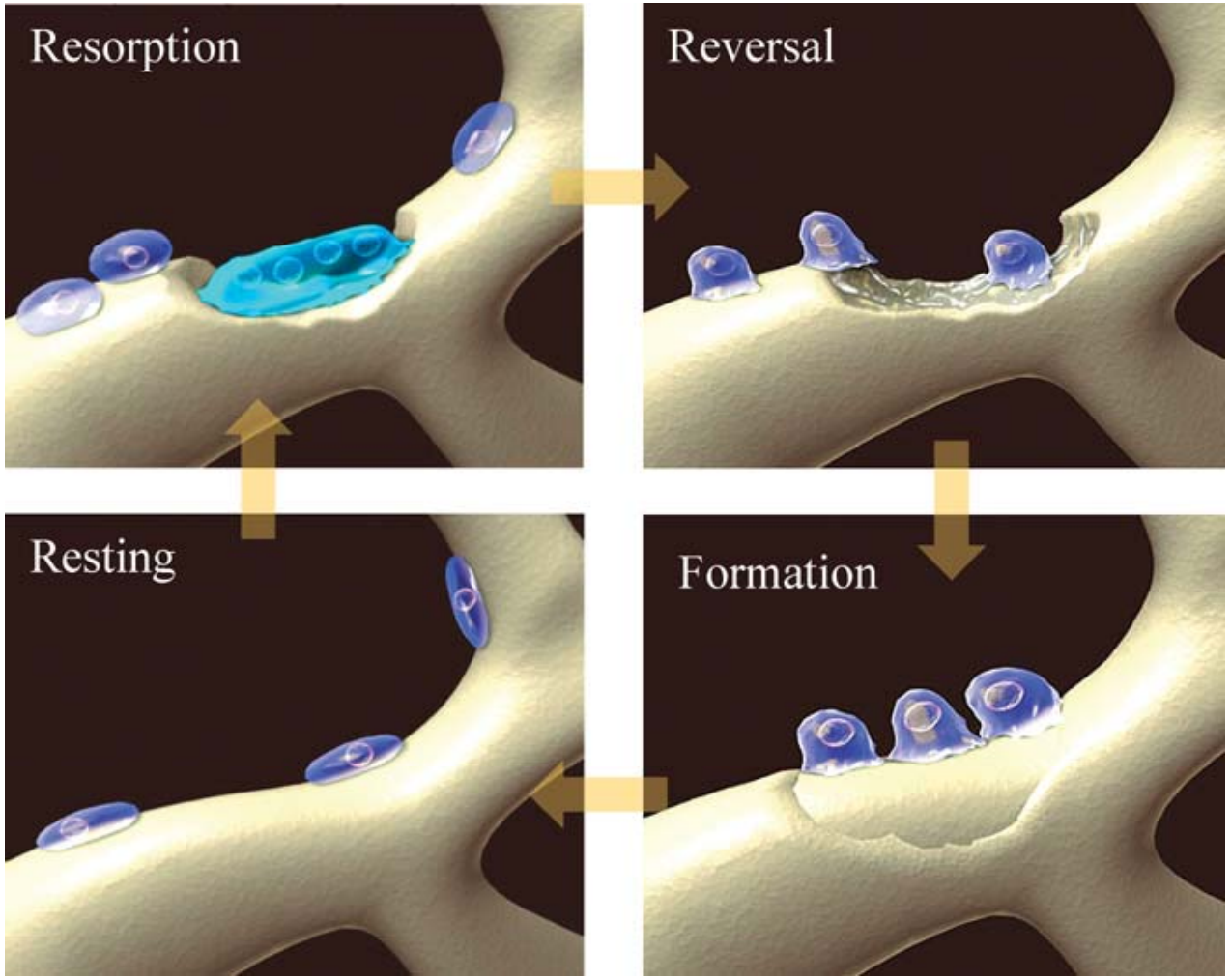


Repair,
microdamage
Cells coupled





Surface remodeling cycle



Remodeling balance

ASBMR Bone biology page

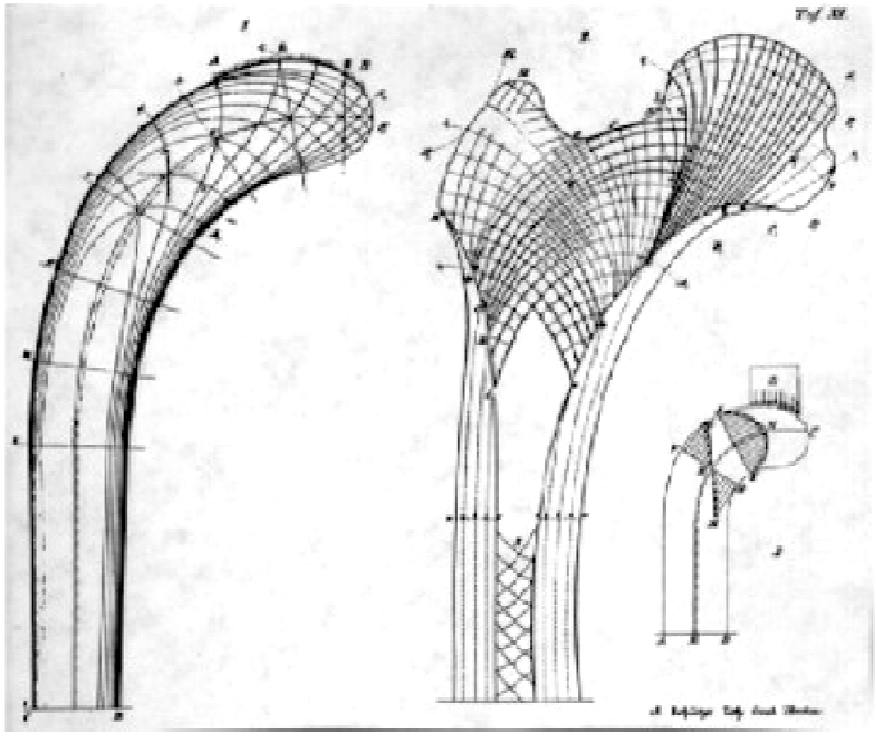
http://depts.washington.edu/bonebio/ASBMRed/growth/newBMUbu.swf

http://depts.washington.edu/bonebio/ASBMRed/normal.swf

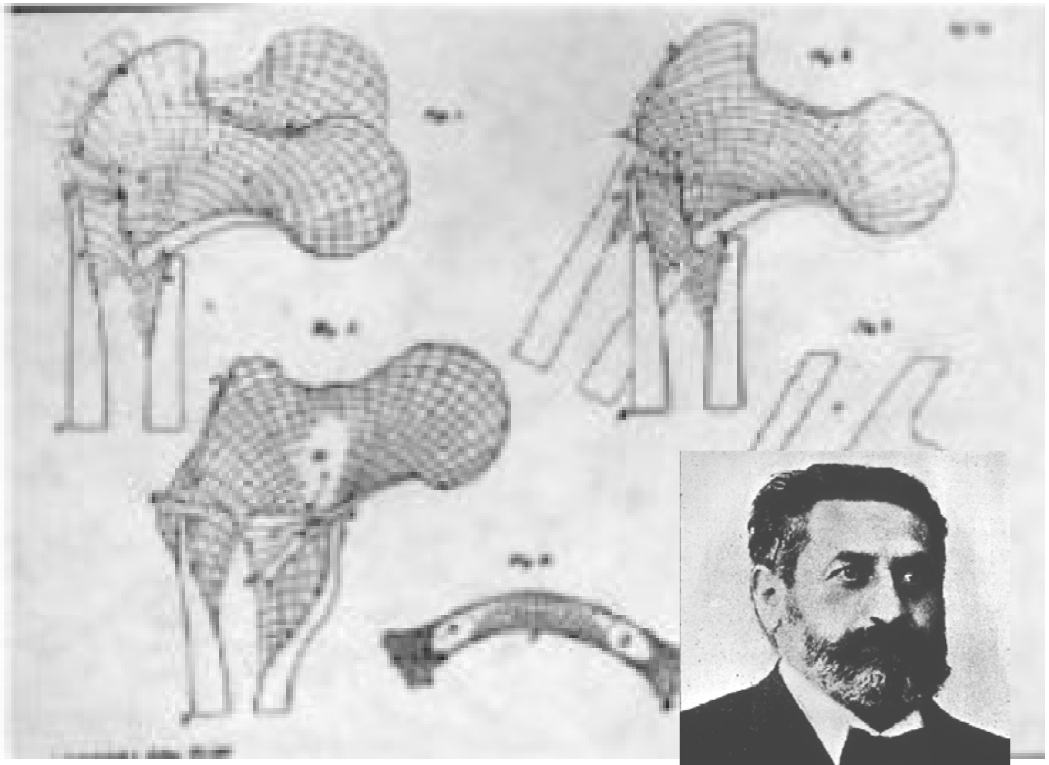
http://depts.washington.edu/bonebio/ASBMRed/growth/BMURemodel.swf

Courtesy of Dr Susan Ott

History of bone adaptation
Mechanically mediated theories (1865 – 1920)



Graphical Statics



Wolff,1892

Julius Wolff, 1870-1894

Wolff's law, 1892

"As a consequence of primary shape variations and continuous loading, or even due to loading alone, bone changes its inner architecture according to mathematical rules and, as a secondary effect and governed by the same mathematical rules, also changes its shape"

Wolff J. D. *Das gesetz der trasformation der knochen* (The law of bone remodeling) Berlin, A. Hirschwald, 1892

History until 1920

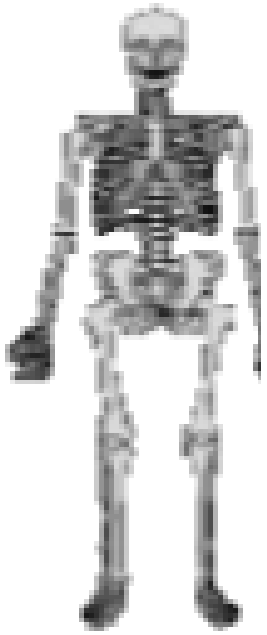
- Bone cells may be regulated by local stress (Roux, 1891)
- Trabecular orientation aligned with principal stresses (Wolff, 1892)
- Bone structure can be adapted to change in load (Wolff, 1892)
- Density is highest in areas of highest shear (Koch, 1917)

- Yet no direct relation between stress and cell activity:
  - Relationship of bone structure to mechanics derived without regards of physiological mechanism.

Bone adaptation 1920- 1970:
General relationships of mechanics to bone physiology

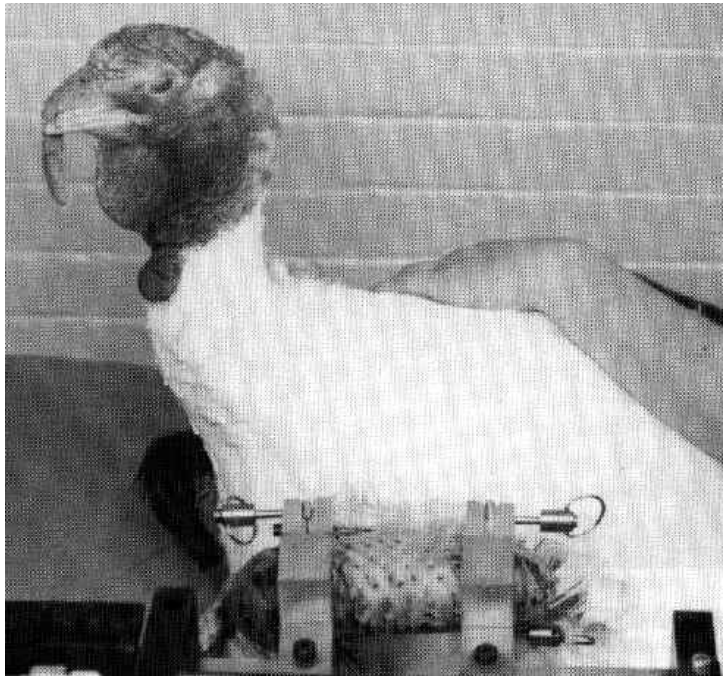
Frost's (1966):

- Determined that bone could be adapted by either **modeling or remodeling** mechanisms
- Determined that **osteoblast** and **osteoclast** activity were coupled during remodeling. No net gain of bone
- Suggested that the relationship between strain and bone mass was different in growing (modeling) and mature (remodeling) bone.

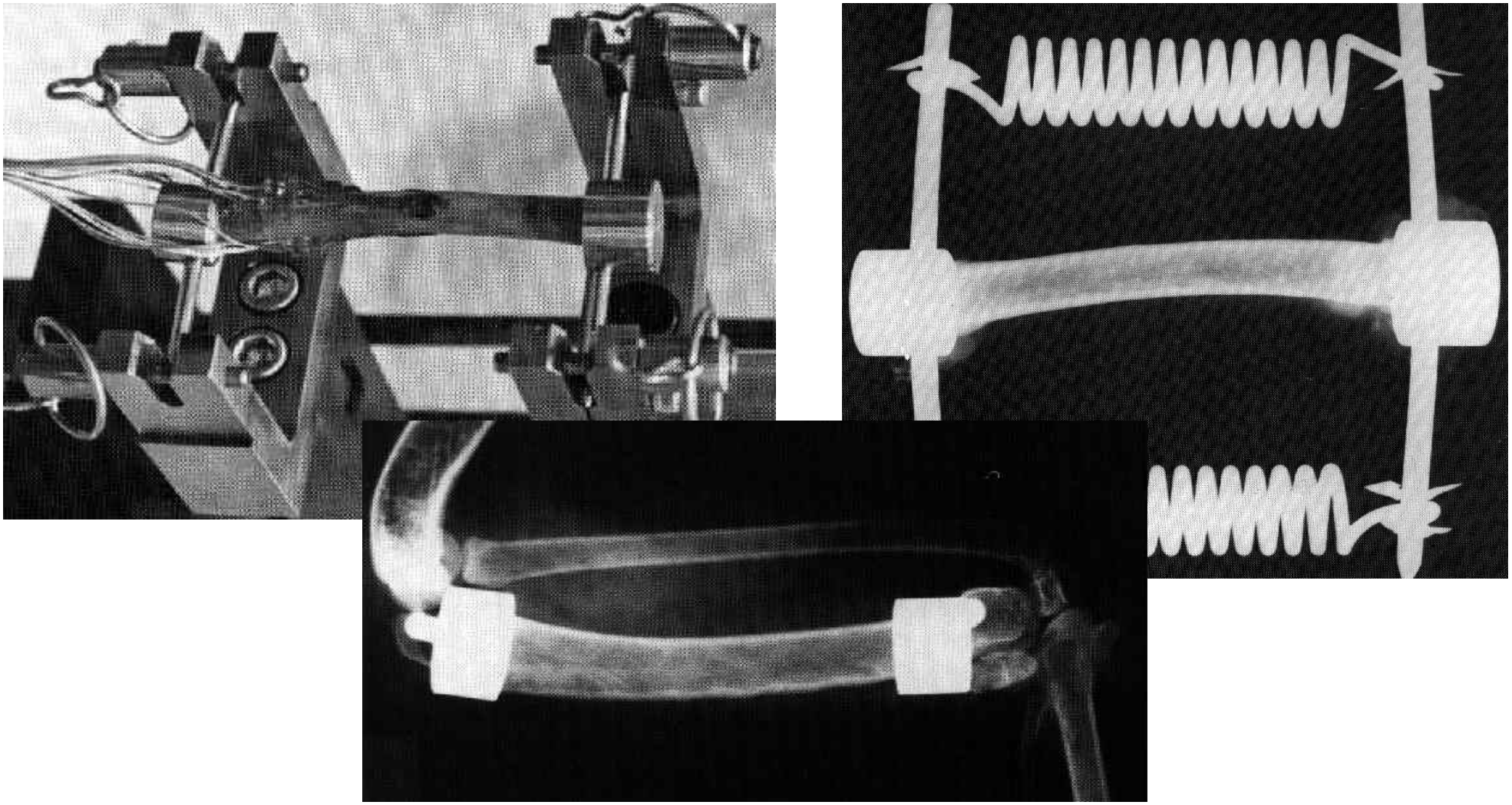


Rubin and Lanyon (1982, 1984, 1987)
Dynamic loading of Turkey ulna

- Imposed controlled dynamic bending strain on the isolated ulna
- Findings:
  - Dynamic strains necessary to maintain bone
  - Static load led to bone resorption
  - 4 cycles per day sufficient to maintain bone

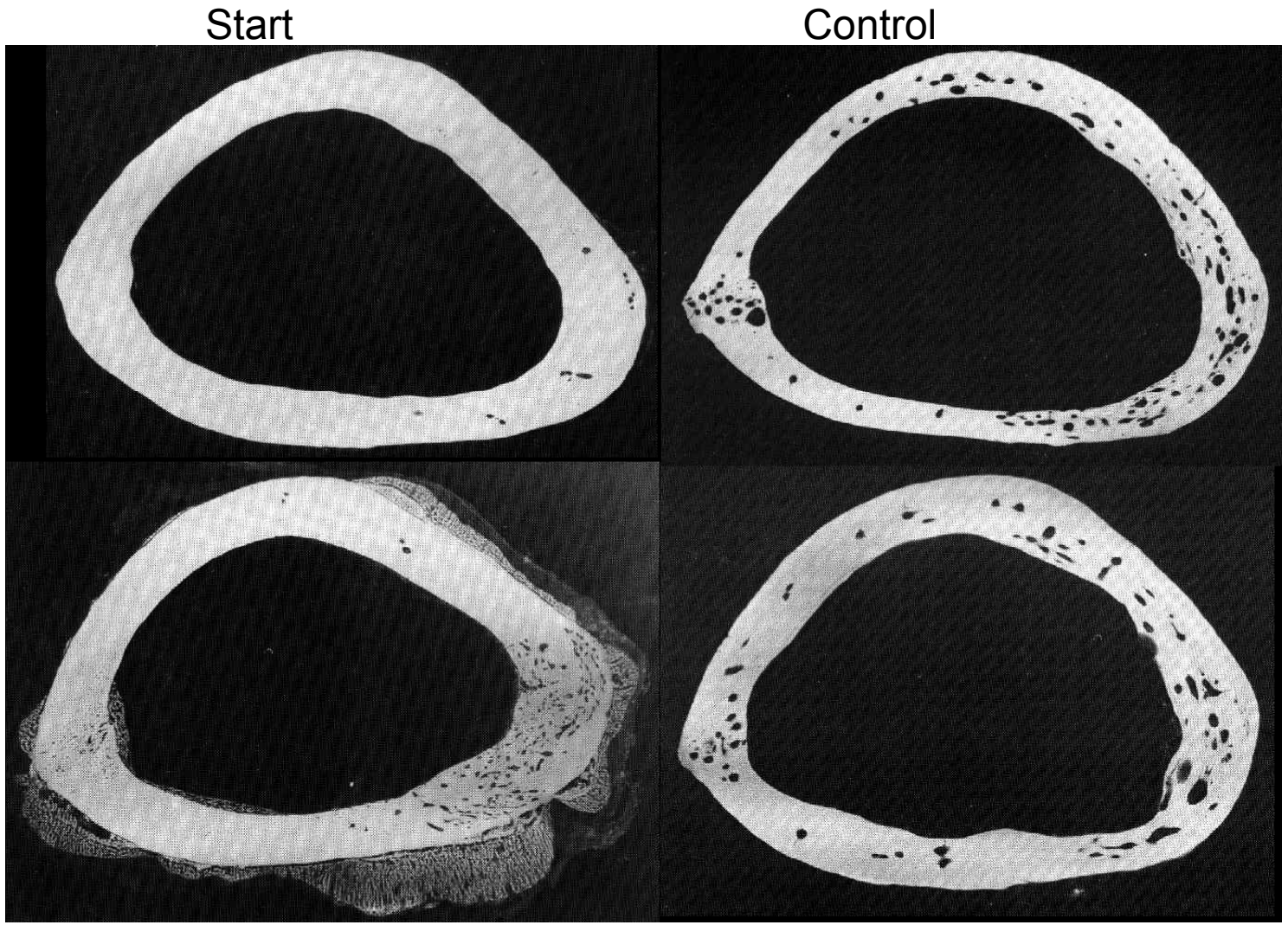


Lanyon and Rubin "Static vs dynamic loads as an influence on bone remodeling" *J. Biomechanics*, 17(12):897-905, 1984



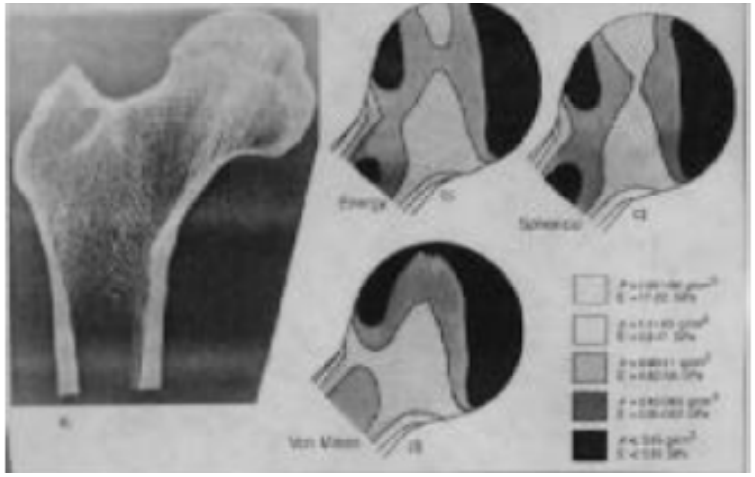
Rubin and Lanyon "Osteoregulatory nature of mechanical stimuli: function as a determinant for adaptive remodeling in bone" *J. Orthop. Res.* 5(2):300-310, 1987

Lanyon and Rubin "Static vs dynamic loads as an influence on bone remodeling" *J. Biomechanics*, 17(12):897-905, 1984



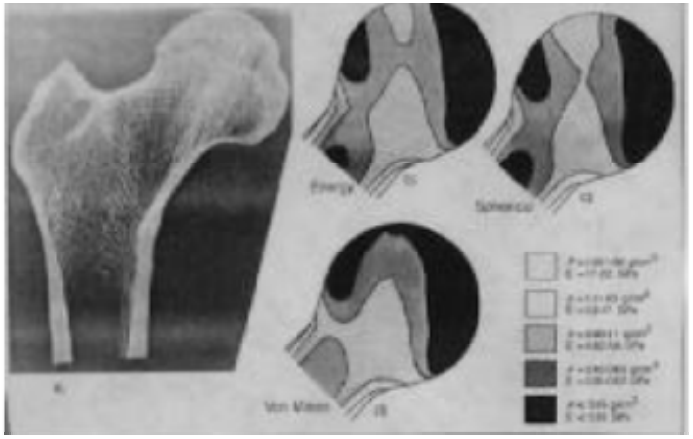
Bone adaptation theories (1985 – 2000): Numerical simulations!

- **Cowin** proposed idea of adaptive elasticity 1976
- **Hart** performed computational FE implementation 1983
- Separates surface and external remodeling
- Rate of change of bone volume fraction related to strain
- Qualitative results good, but no accurate validation.



Recent development
From in-vivo to in-silico analysis

- First computational implementation of bone adaptation in 1983



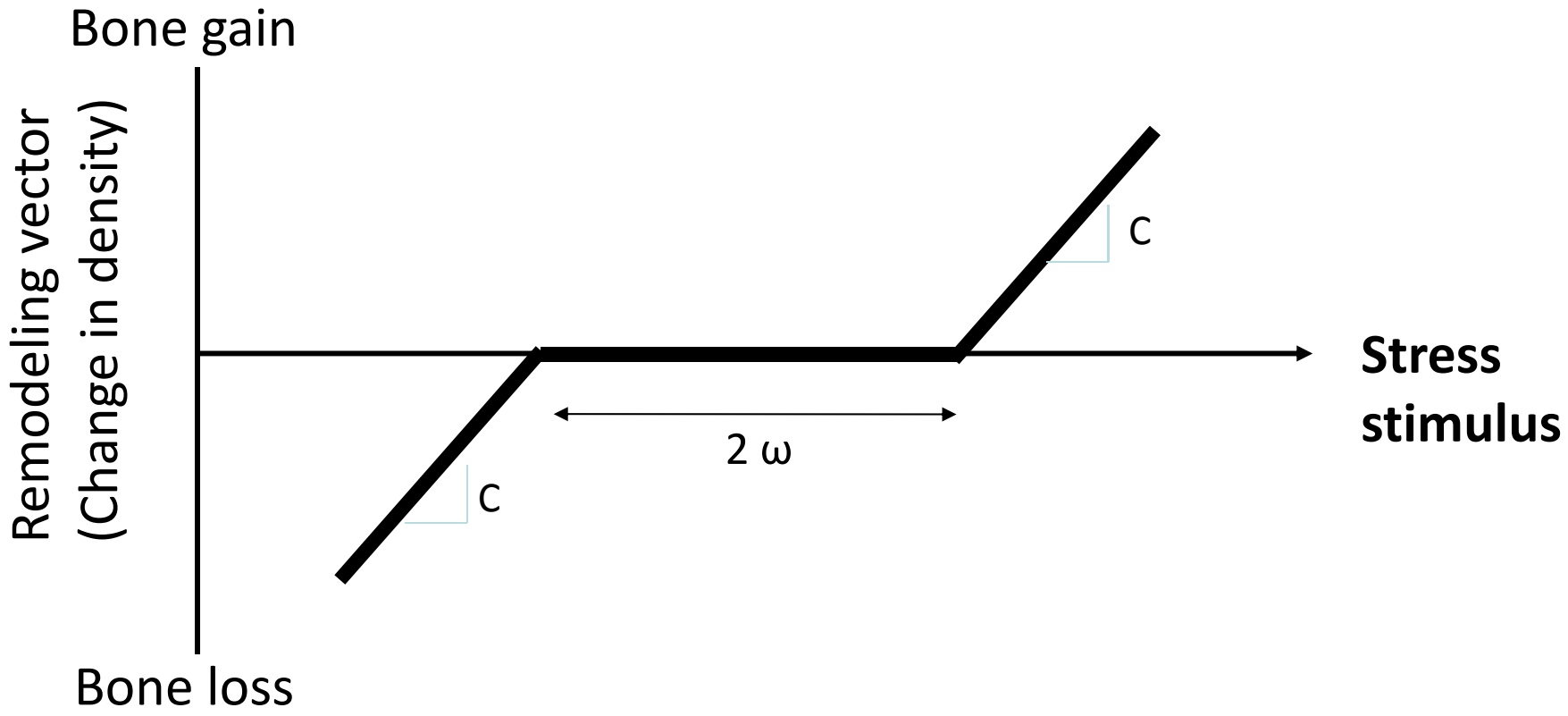
Computer models can help us to

- Understand and quantify bone optimality
- Improve the diagnosis of bone strength
- Understand bone remodeling processes
- Help us to develop optimal drug strategies
- Help us to define (animal) experiments

However, results are only as good as the theory they are built on
→ Validation!

Huiskes et al's 1984, 1987 ★

Describing the **change in bone density** with respect to the mechanical stimulus of **strain energy density (U)**



Huiskes et al., 1984, 1987 etc

Huiskes et al, 1984, 1987
Mathematical formulation

Density-stiffness relation:

$$E = \alpha\rho^{3}$$

$$\alpha = 2875 \text{ MPa cm}^3/\text{gr}$$

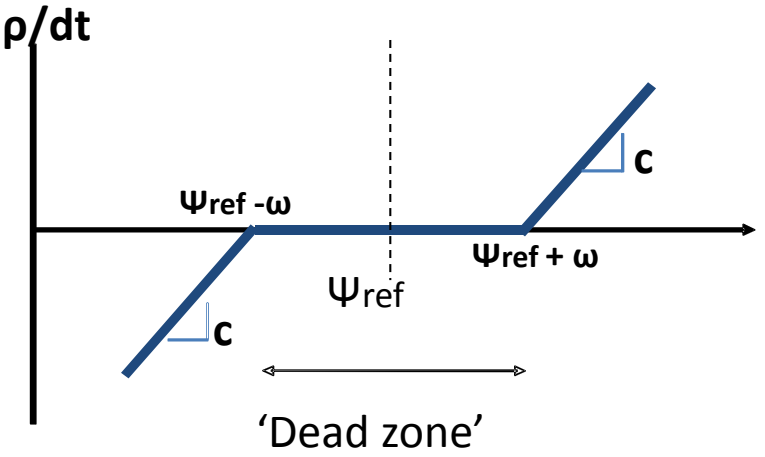
(Carter and Hayes, 1977)

Stress stimulus for bone remodeling:

$$\psi = \frac{U}{\rho}$$

$$U = \frac{1}{2}\varepsilon \cdot \sigma$$

(van Reitbergen *et al.*, 1993)

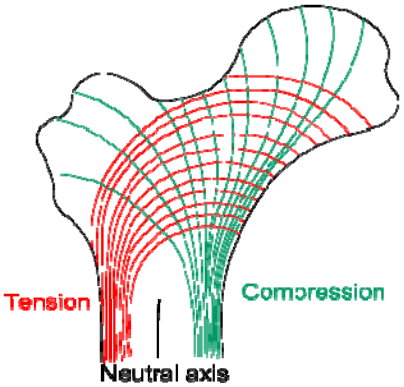


Remodeling rule:

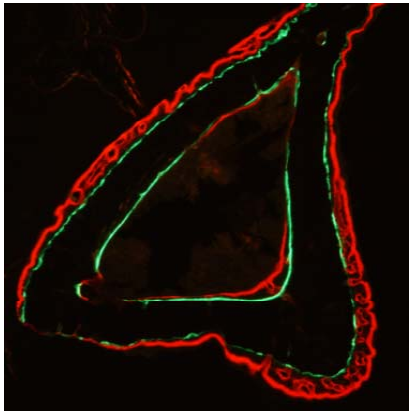
$$\frac{d\rho}{dt} = \begin{cases} c\cdot(\psi - \psi_{ref}) + c\omega & (\psi - \psi_{ref} < -\omega) \\ 0 & -\omega \le \psi - \psi_{ref} \ge +\omega \\ c\cdot(\psi - \psi_{ref}) - c\omega & (\psi - \psi_{ref} > +\omega) \end{cases}$$

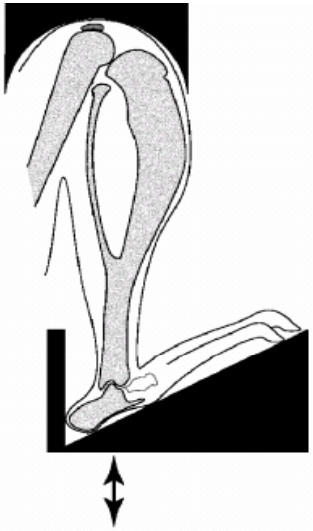
Use in A1 !!!

Current 'truth':
Evidence in animals



- Cyclic loading is required to induce bone apposition - both to maintain and to increase bone mass
- Necessary strain to maintain bone or to cause apposition is small
  - Maintain: 1000 to 3000 microstrain (e = 0.001 to 0.003)
  - Apposition: microstrain > 3000 (e > 0.003)
- 'Ideal' strain levels are site dependent:
  - Minimally loaded bones, e.g. skull & inner ear bones do not resorb
- Animal limb compression show increased cross-sectional area by adaptation at locations with high amount of stress due to natural bending

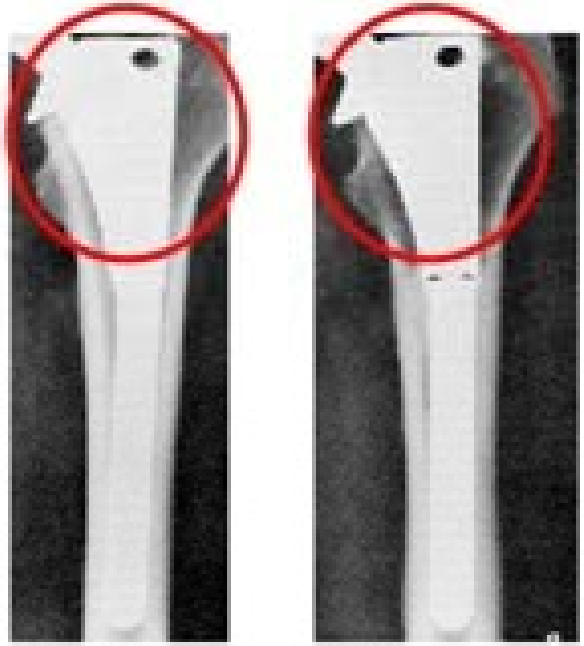




Current 'truth':
Evidence in humans

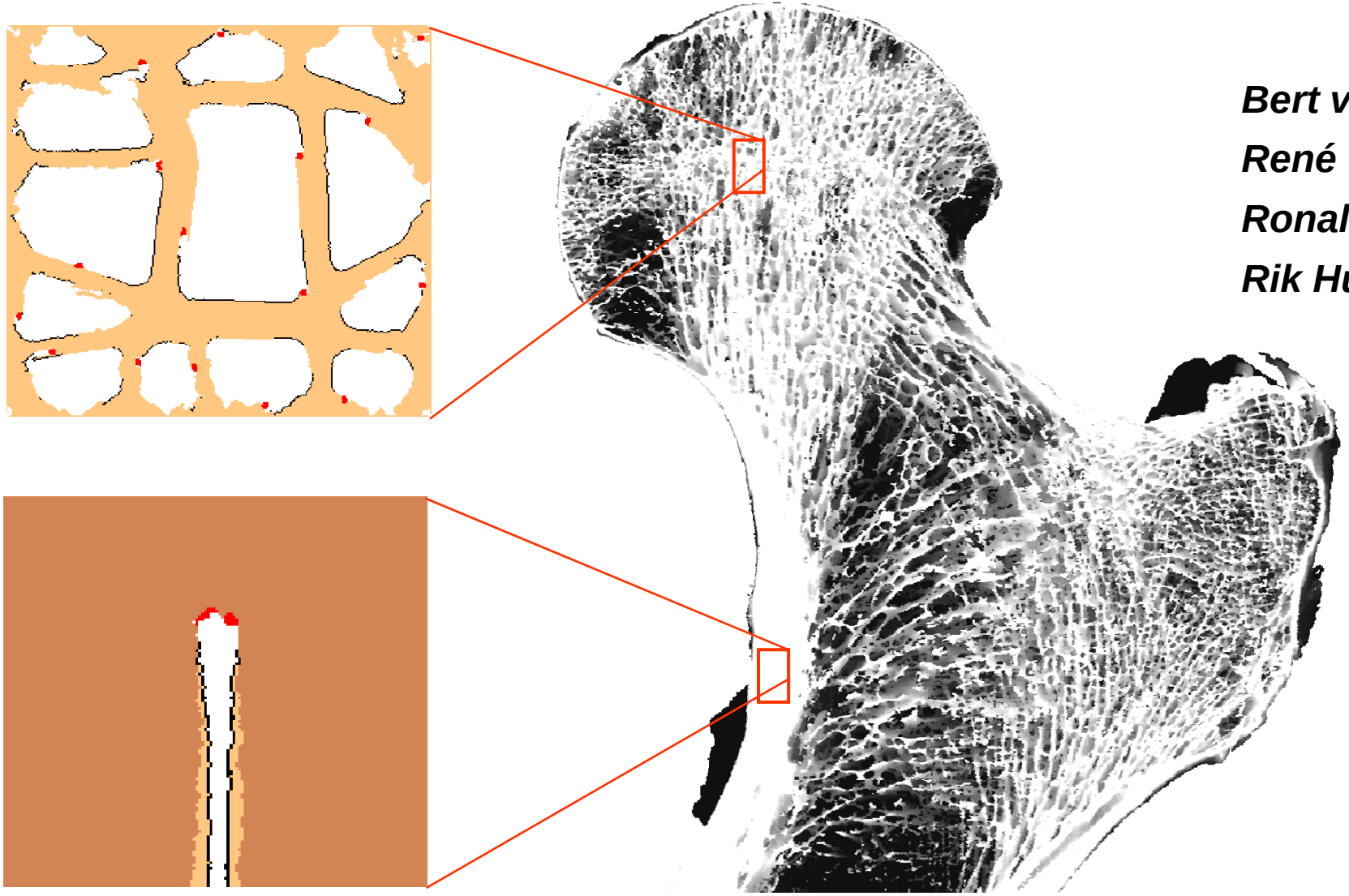
- Bone is lost after extended immobilization or time in a zero-gravity environment
  - 15% BMD loss after 6 months in space
  - Partial recovery 12 months later
    (Collet et al. 1997; Keyak et al., 2009)

- Bone is lost around mechanical implants of high stiffness, as a result of stress shielding.



Post-op x-ray 10 year x-ray

Example of current theory:
Bone remodeling by finite elements



Bert van Rietbergen

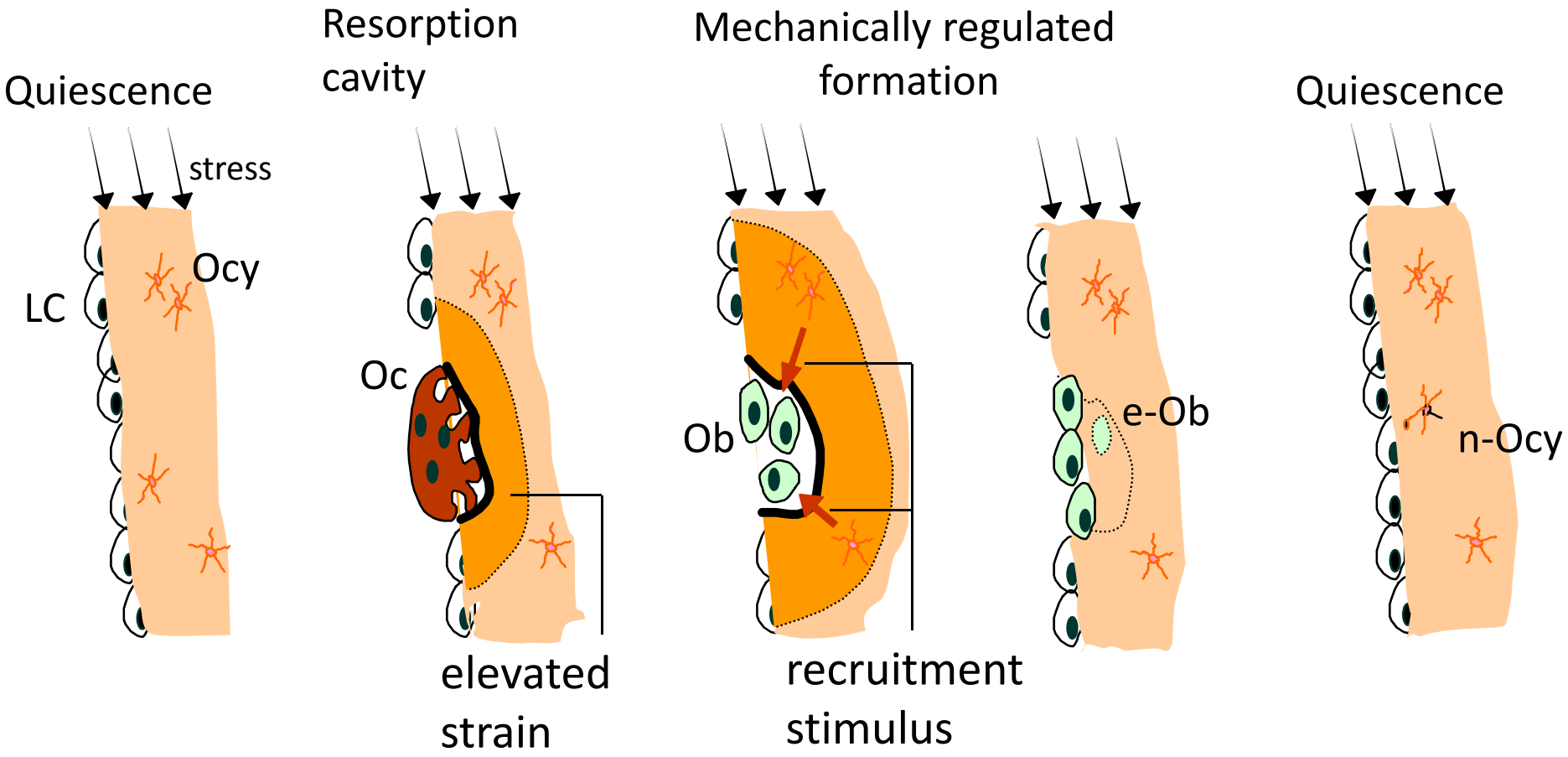
René van Oers

Ronald Ruimerman

Rik Huiskes

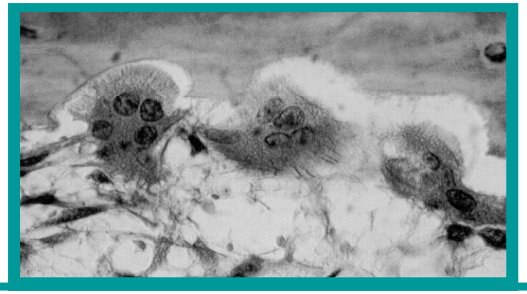
Recent models of bone remodeling

Mechanism: Strain as the coupling factor?



(Huiskes et al., Nature, 2000)

Test theory by computer simulation

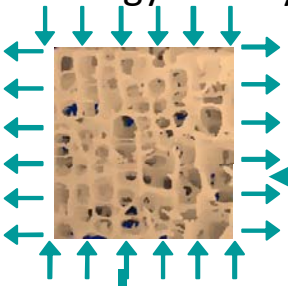


Osteoclasts attracted by microcracks

Osteoclast resorption

SED rate

Strain energy density



Architecture

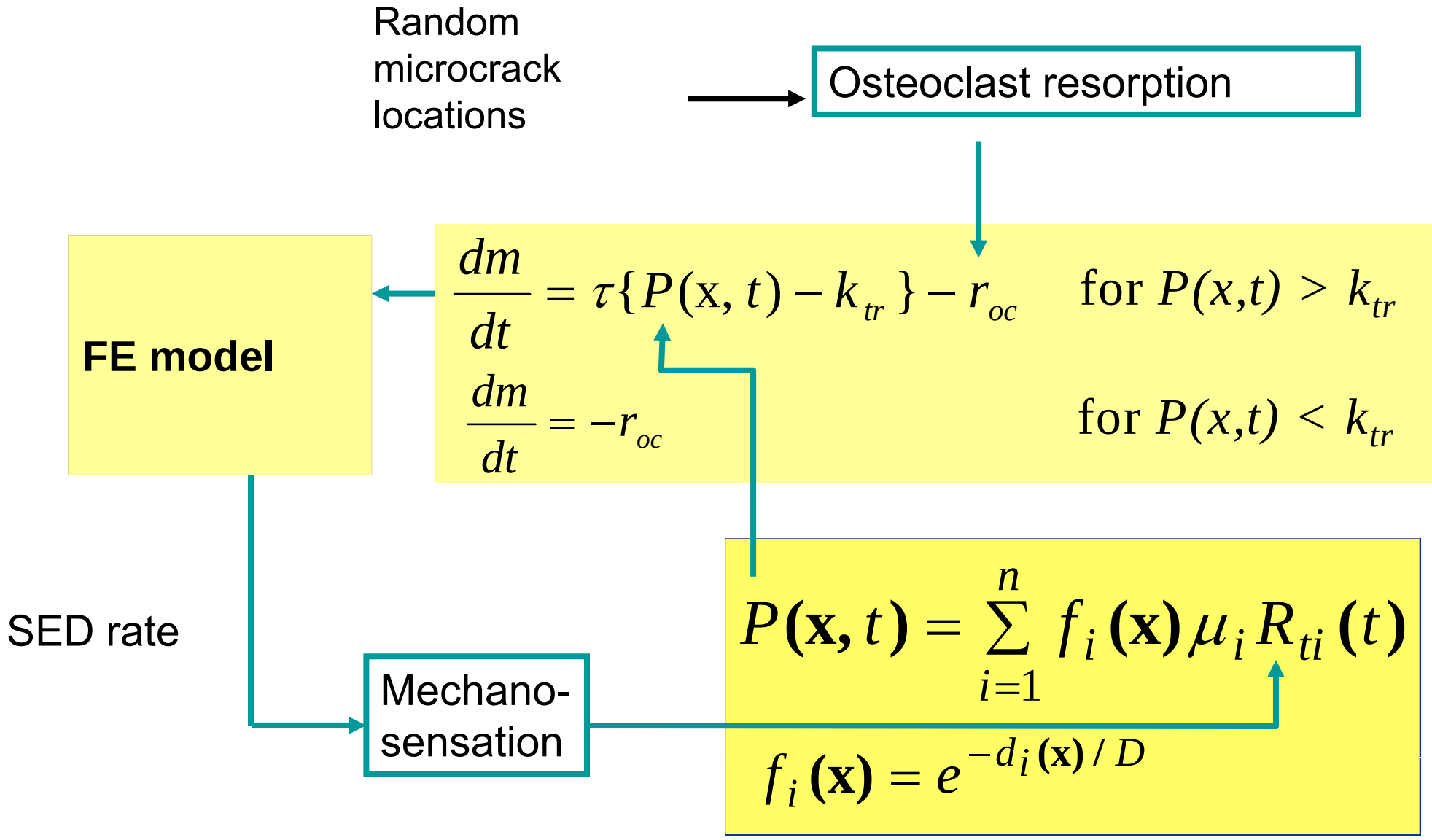
\- +

Summarized in mathematical equations

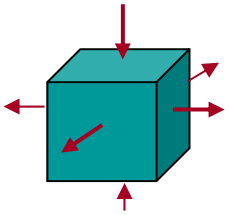
Osteoblast formation

Mechano-sensation

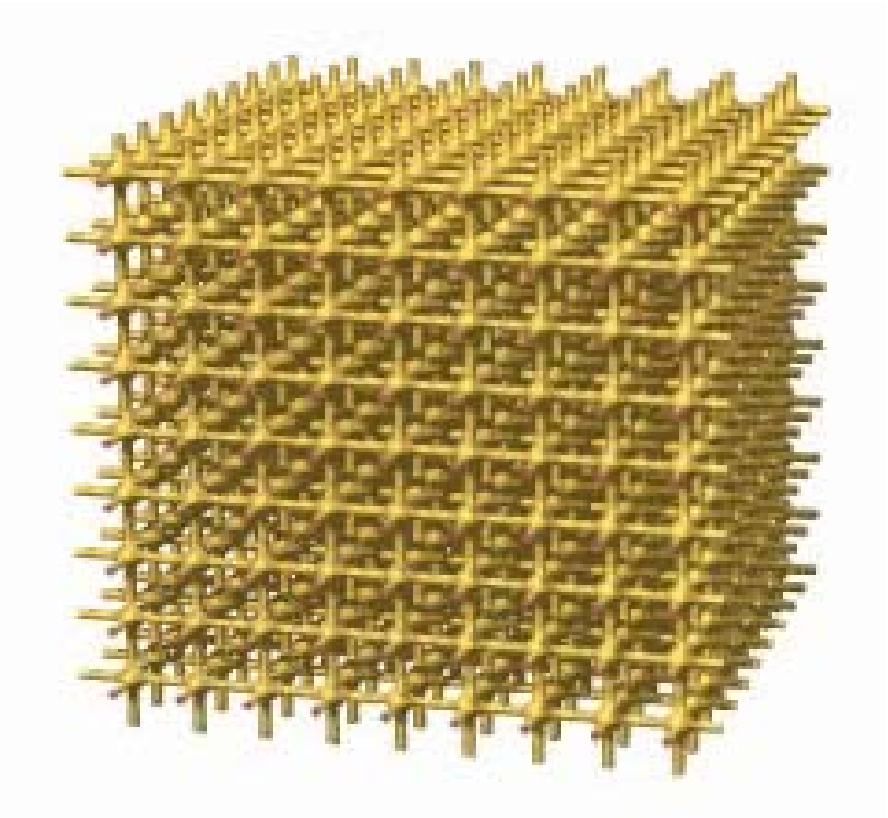
Mechano-transduction


Random microcrack locations
Osteoclast resorption
$\frac{dm}{dt} = \tau\{P(x,t) - k_{tr}\} - r_{oc}$ for $P(x,t) > k_{tr}$
$\frac{dm}{dt} = -r_{oc}$ for $P(x,t) < k_{tr}$
FE model
SED rate
Mechano-sensation
$P(\mathbf{x},t) = \sum_{i=1}^{n} f_i(\mathbf{x})\,\mu_i\,R_{ti}(t)$
$f_i(\mathbf{x}) = e^{-d_i(\mathbf{x})/D}$

Bone modeling and remodeling



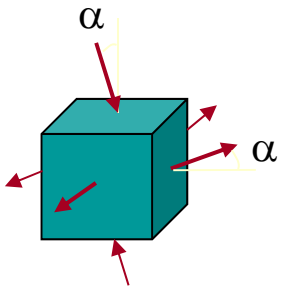
2 Mpa external stress, cycling at 1.0 *Hz*

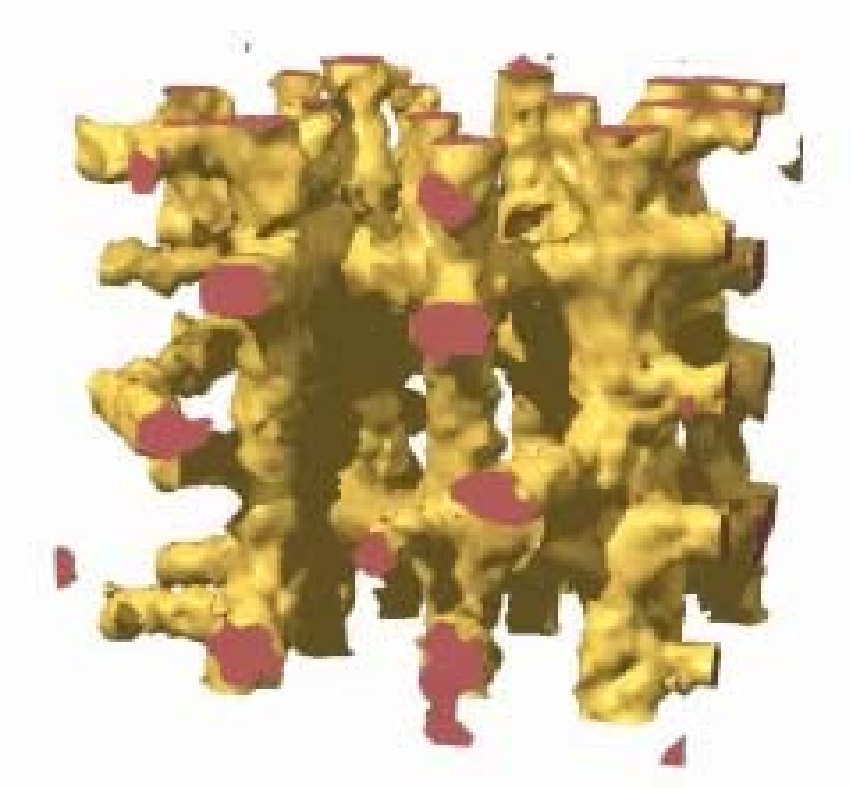


$(1.5\ mm)^3$

Ruimerman et al, *J of Biomechanics*, 2005

Adaptation to loading direction





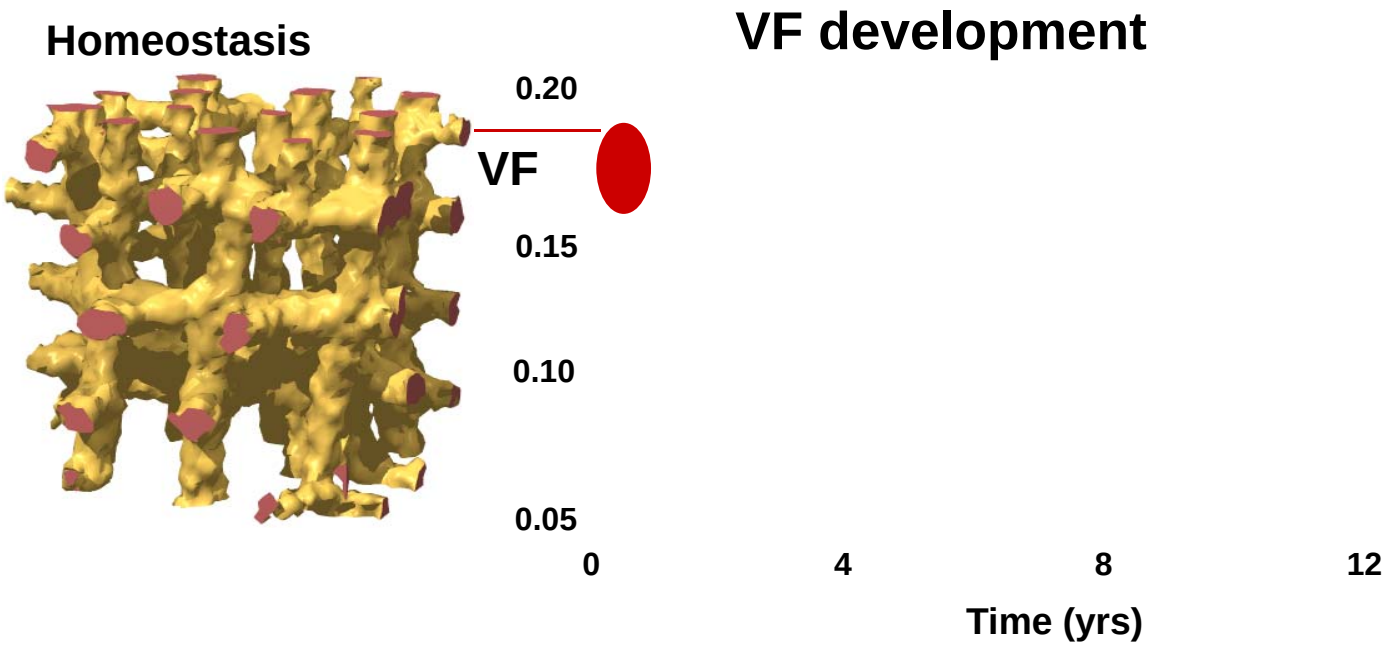
Ruimerman et al, *J of Biomechanics*, 2005

Theory explains modeling (growth and adaptation) as well as remodeling (maintenance) of trabecular bone

Can it also explain:

- **Osteoporosis?**
- **Medical intervention (anti-resorptive drugs)?**

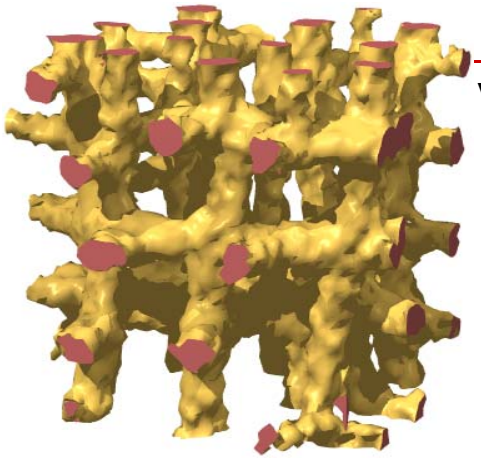
Disuse osteoporosis

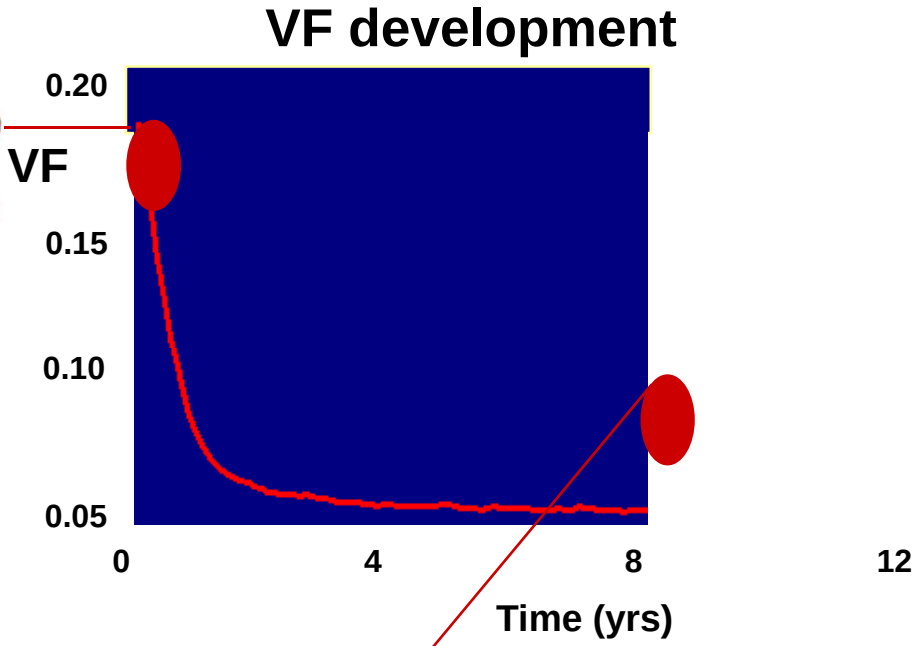


Ruimerman et al., ASBMR 2004

Disuse osteoporosis

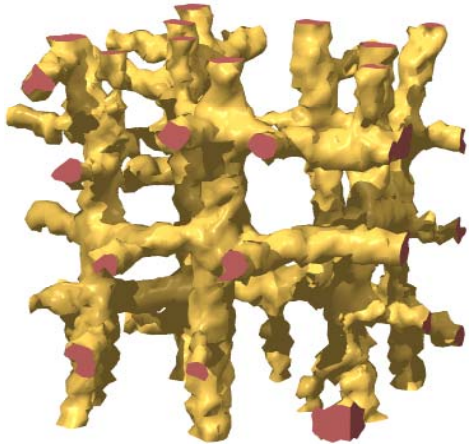
Homeostasis





Osteoporosis

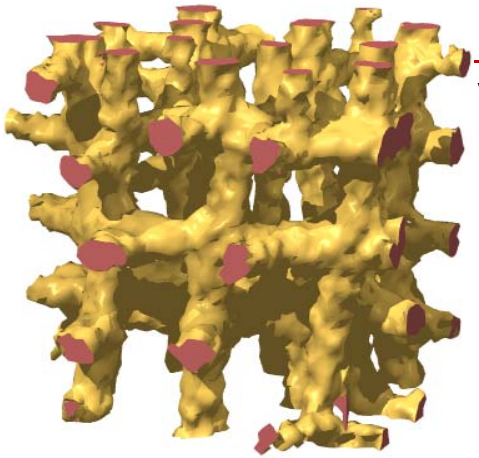
50% reduced loads



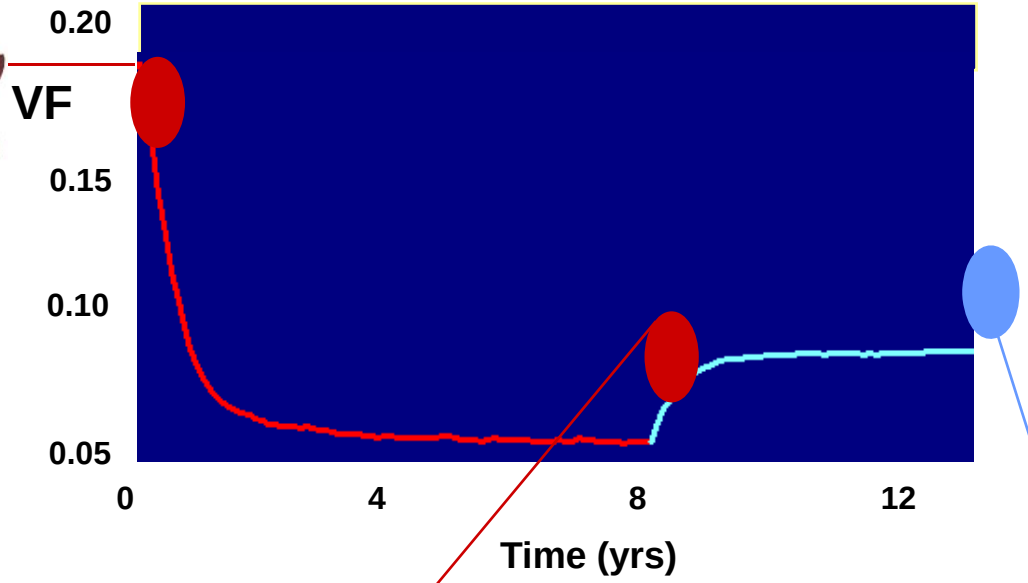
Loss of bone tissue and trabecular connectivity

Anti resorptive drugs

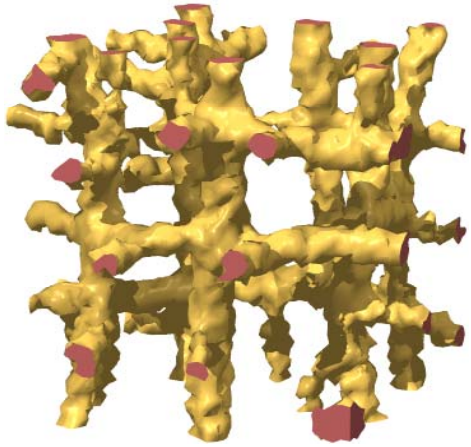
Homeostasis



VF development

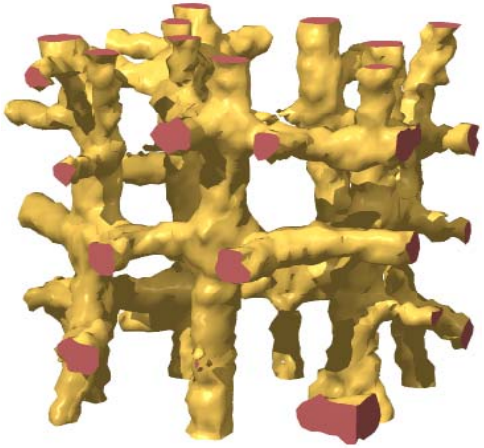


Osteoporosis



70% inhibited resorption

Late treatment

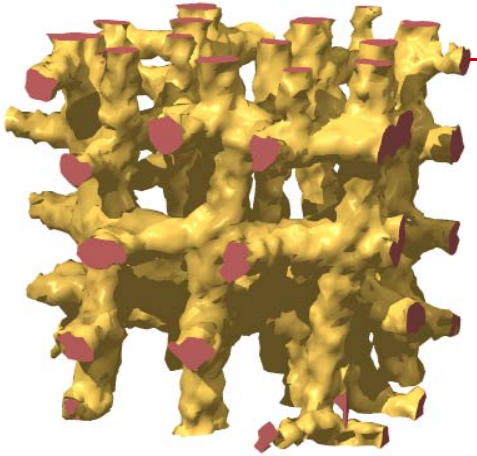


Trabecular thickening

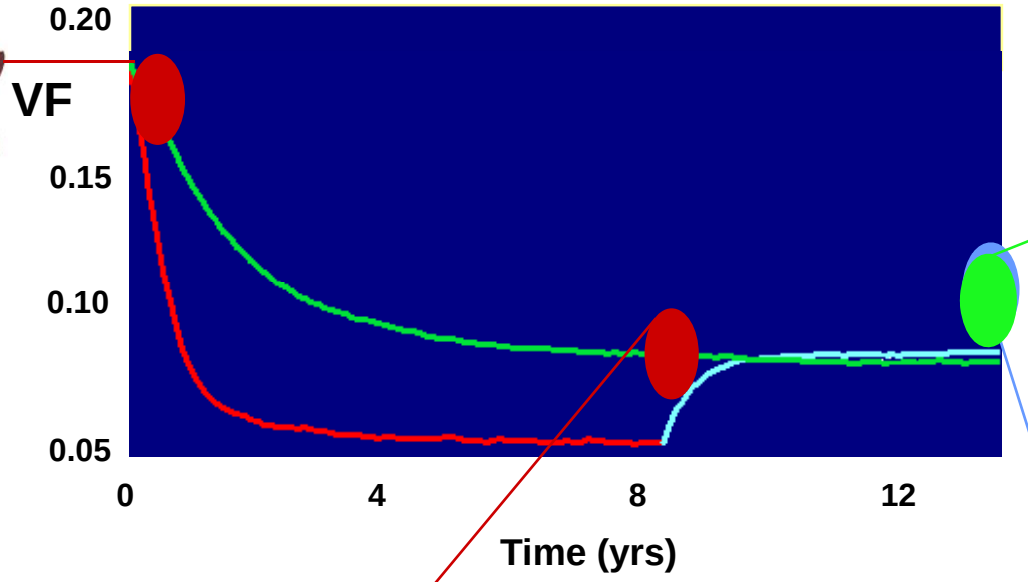
No new trabeculae

Anti resorptive drugs

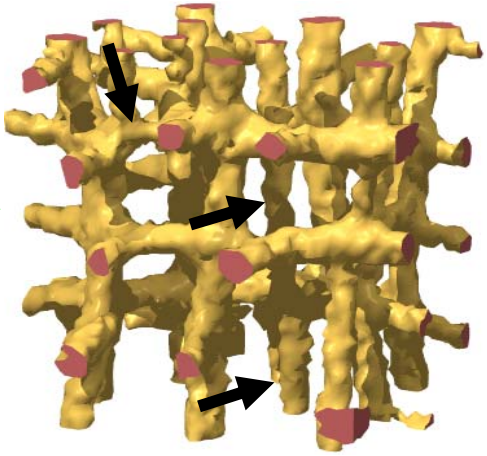
Homeostasis



VF development

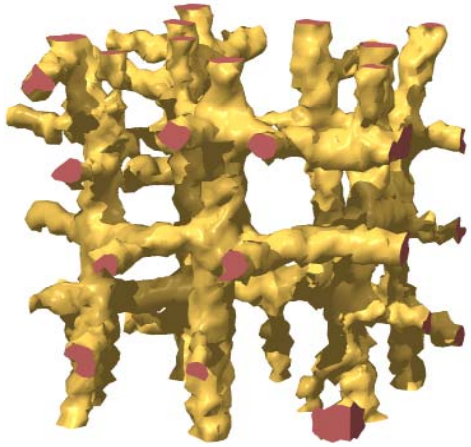


Early treatment

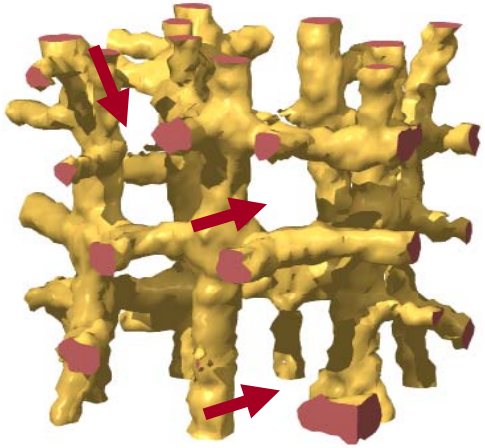


Early treatment preserves bone quality

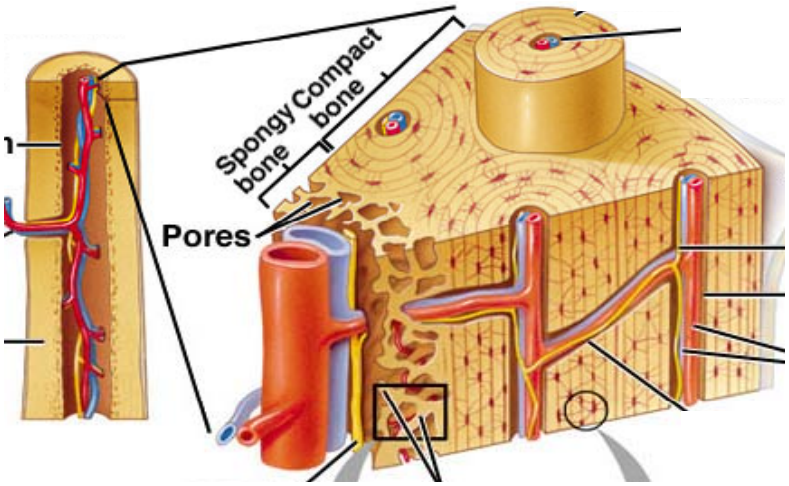
Osteoporosis

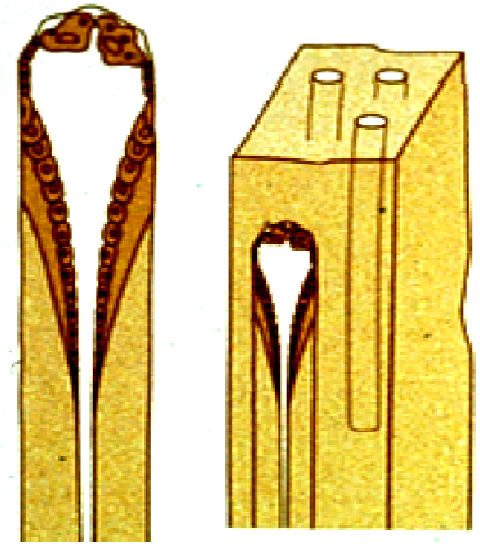


Late treatment



Bone remodeling in cortical bone





Osteon

Haversian system

What guides resorbing osteoclasts in load direction?
Why do osteoblasts follow (coupling mechanism)?

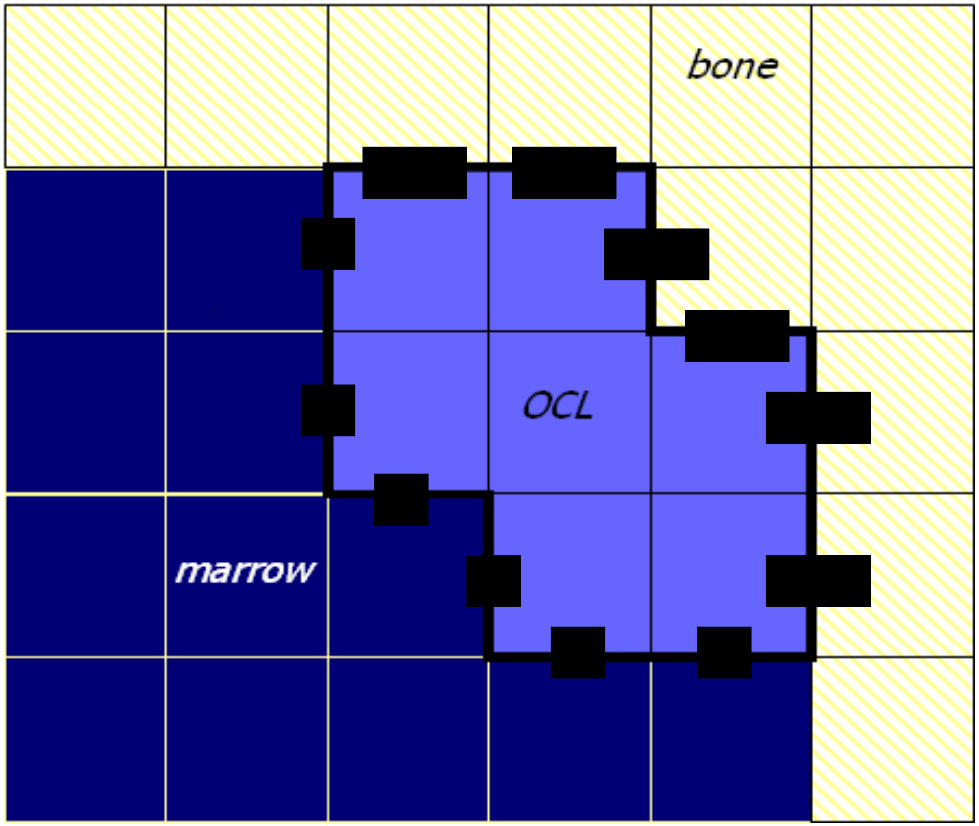
Theory: Strain-induced osteocyte signals …
…*initiate* osteoblast bone formation and
… *inhibit* osteoclast attachment and resorption.

Osteoclast model

Differential cell adhesion

Energy minimization

(Glazier & Graner, 1993)



'Energy' function

$$H_\sigma = H_{surf} + H_{vol}$$

Surface energy $$H_{surf} = \int_{surf} h_M(A)dA$$

$$h_b(P) = \gamma(P - P_{ocl})$$

Volume energy $$H_{vol} = \lambda(V - V_0)^2$$

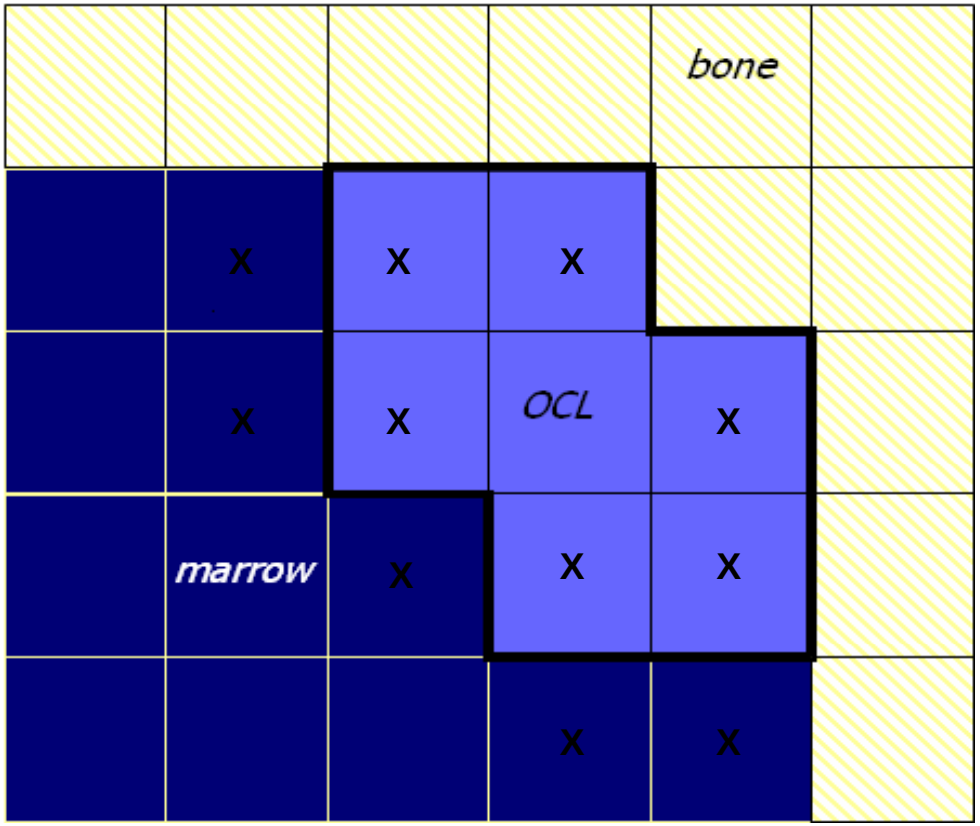
Osteoclast model

Movement:

Evaluate all possible movement options (changes in cell shape)

Choose one option

preferring 'low energy‘ moves

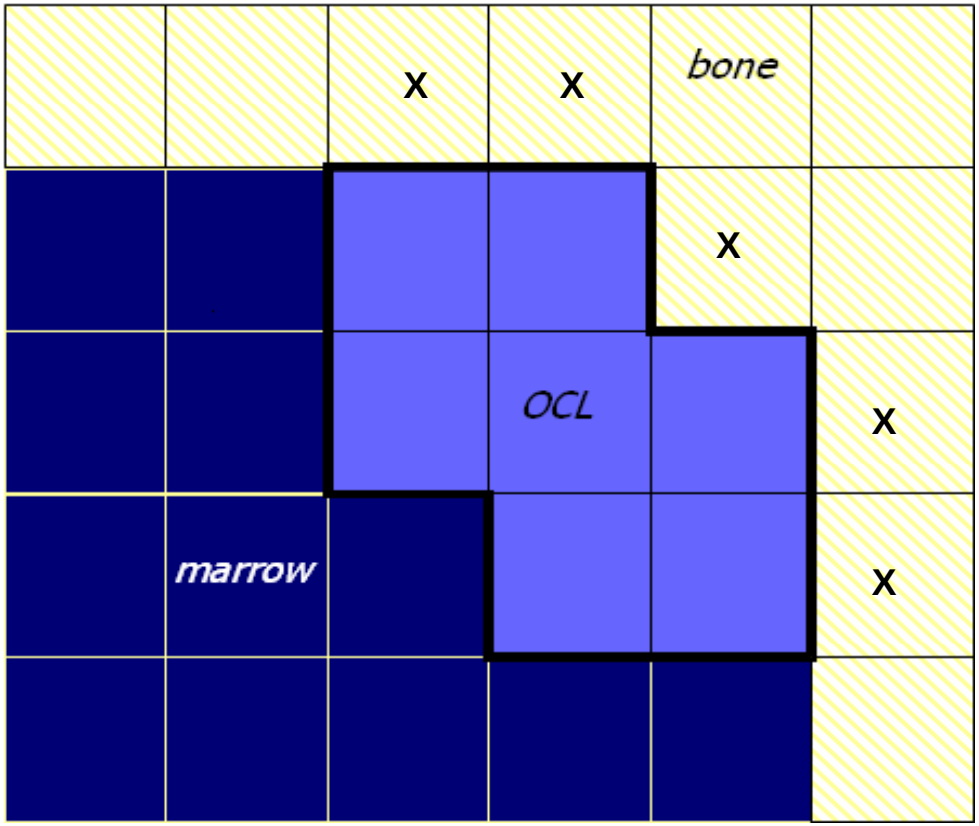


This cell-model
- prefers a rounded shape
- retracts from bone with strong osteocyte signal
- attaches to bone with weak osteocyte signal

Osteoclast model

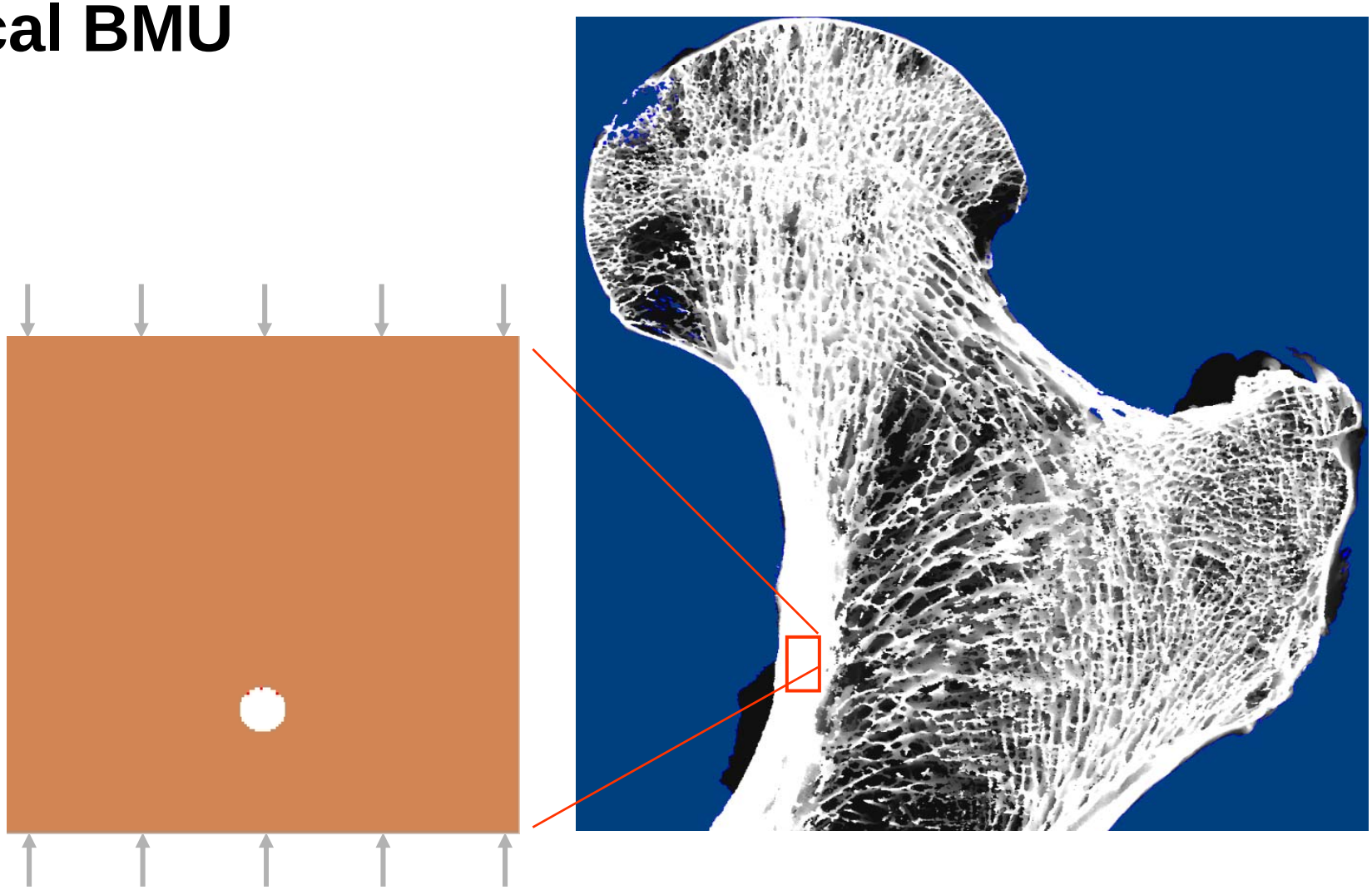
Resorption:

Choose one option, where adhesion is good



This cell-model resorbs bone with weak signal

Cortical BMU

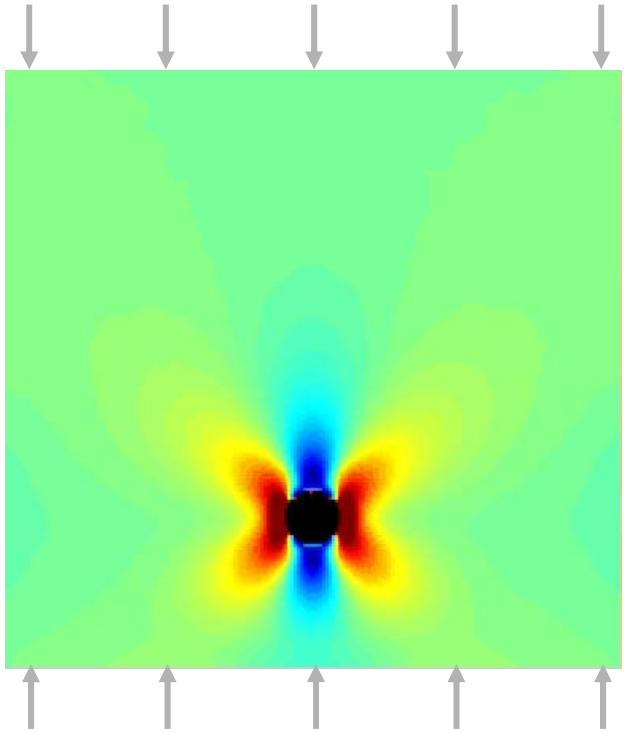


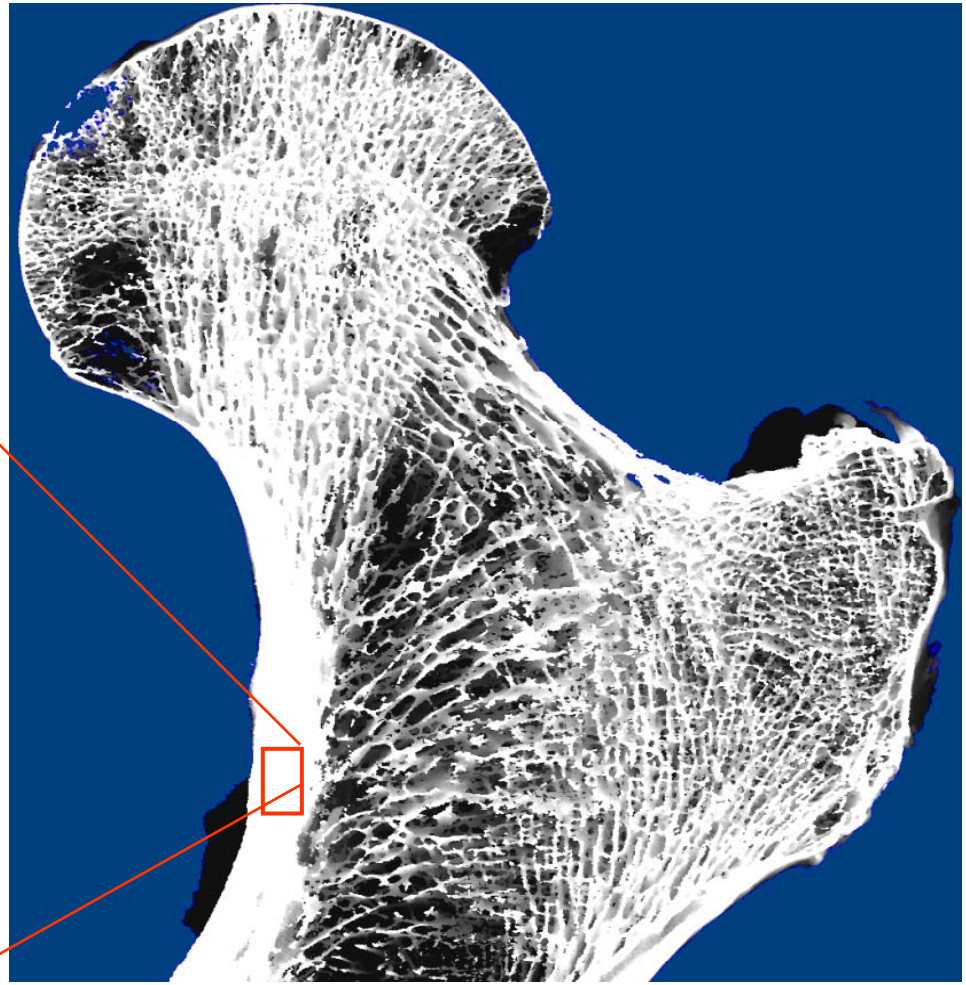
2x2 mm^2

Osteocyte density 1600 mm^{-2}

Cortical BMU

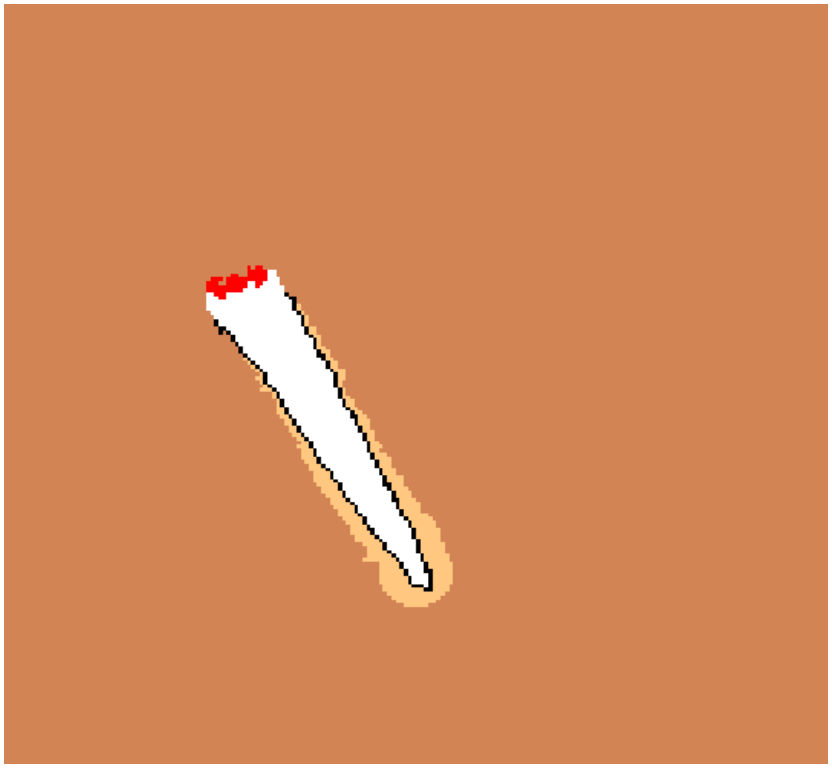
Strains



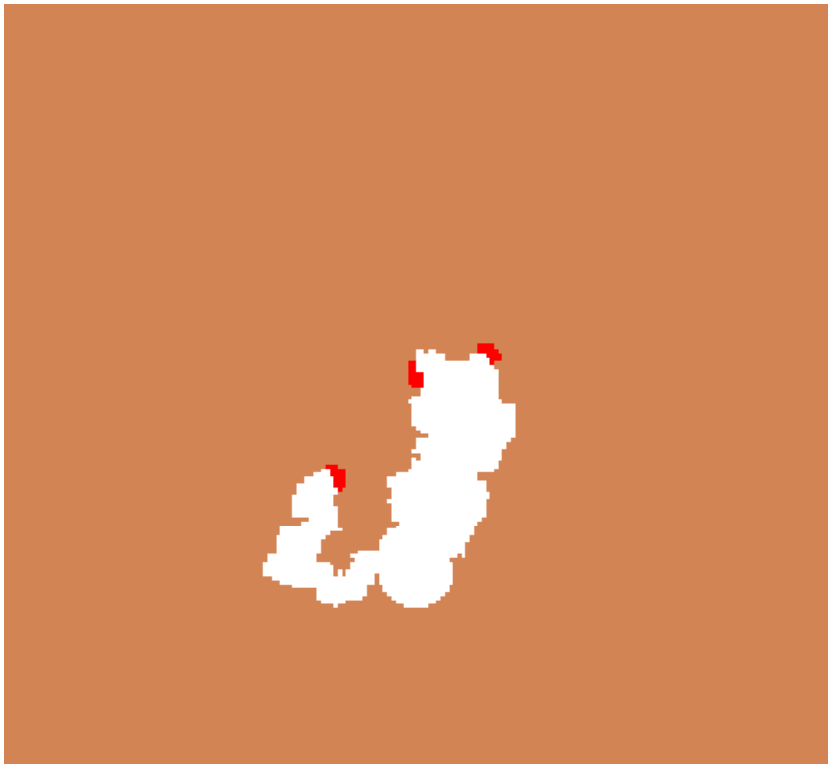


2x2 mm²

30 degrees rotated load

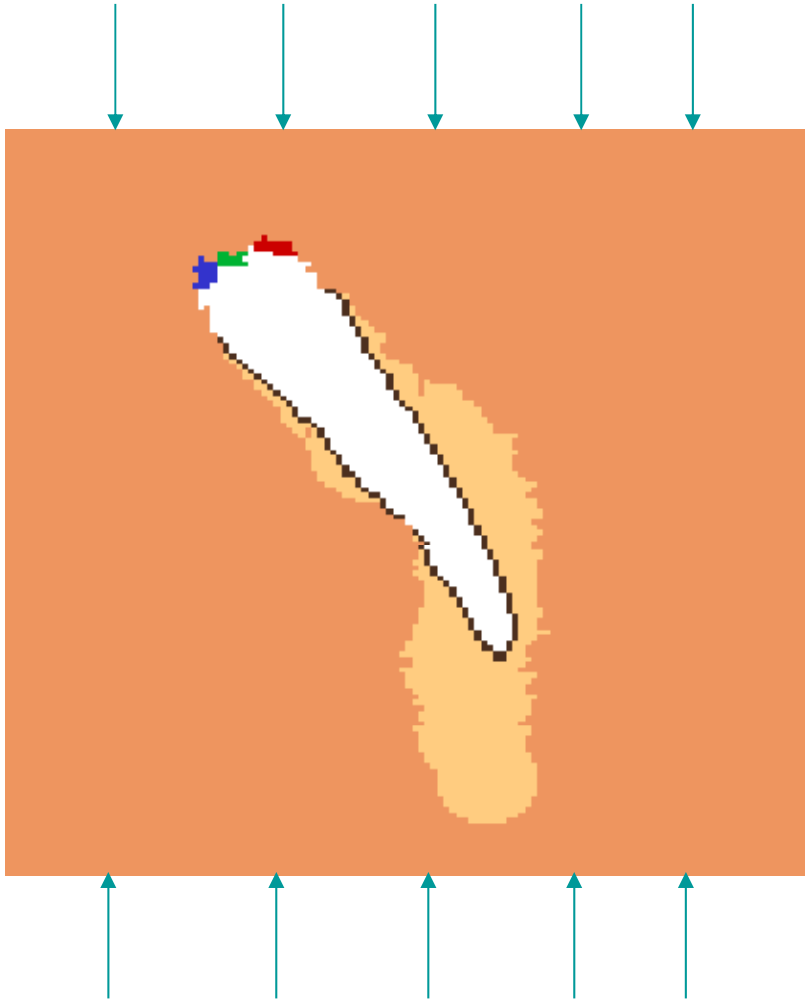


no load

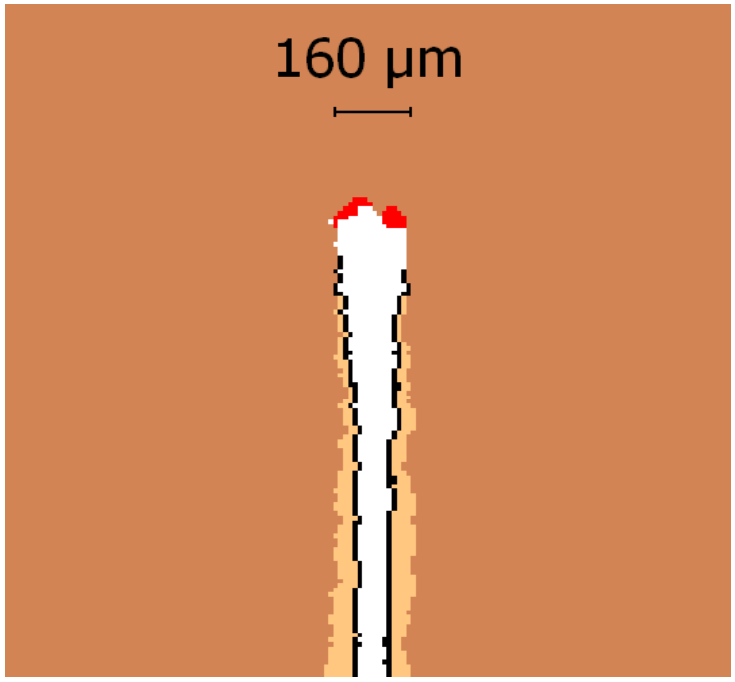


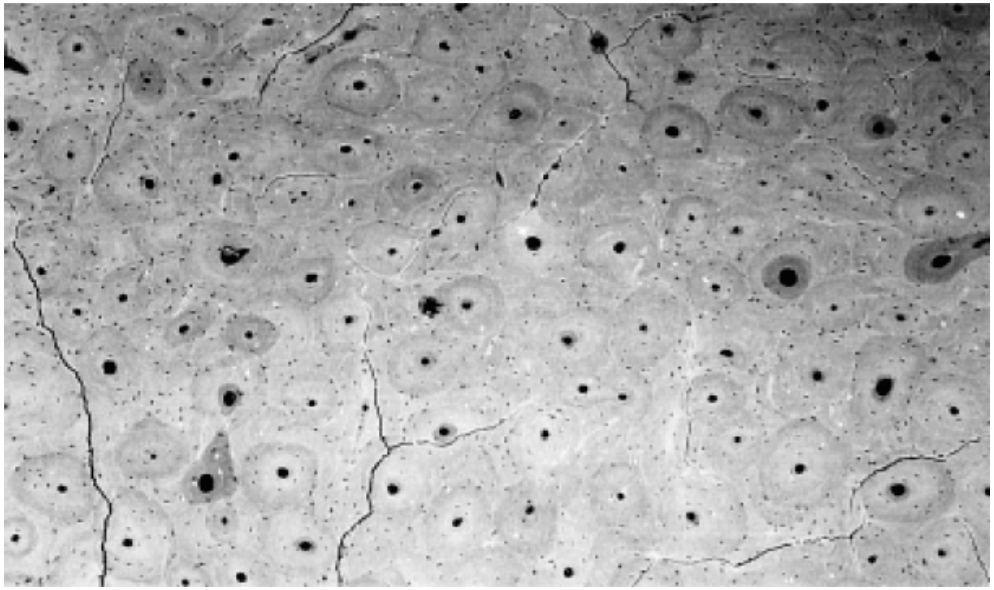
Loading direction

Gradual change in loading direction

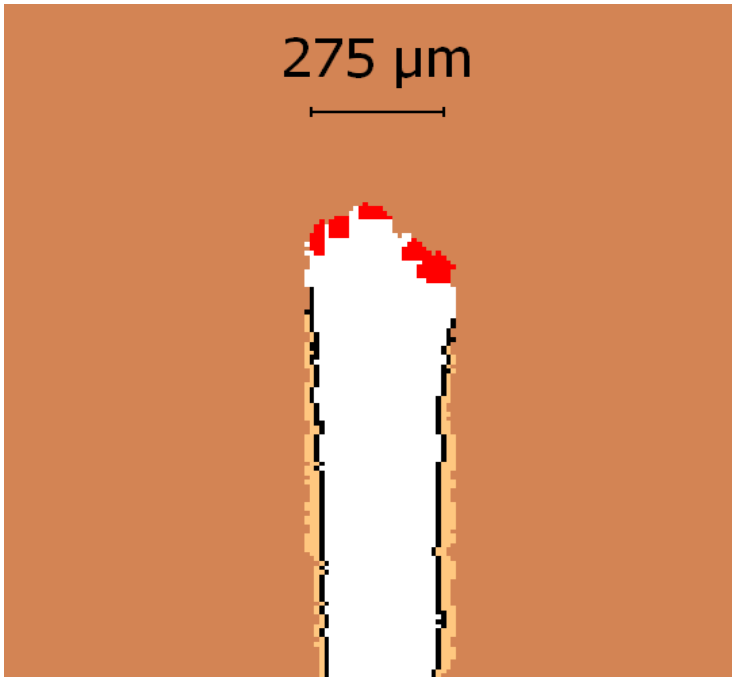


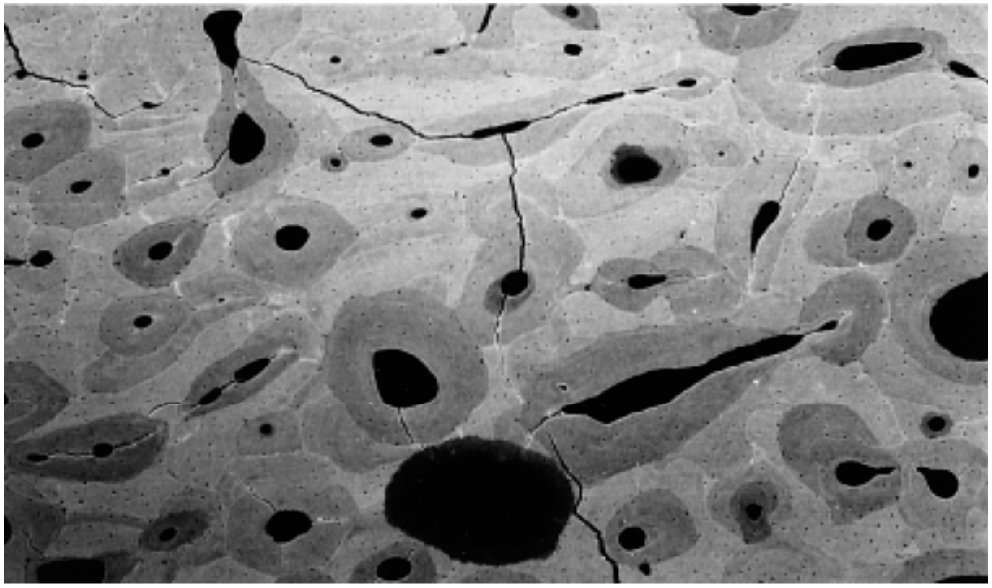
Increased load





Reduced load

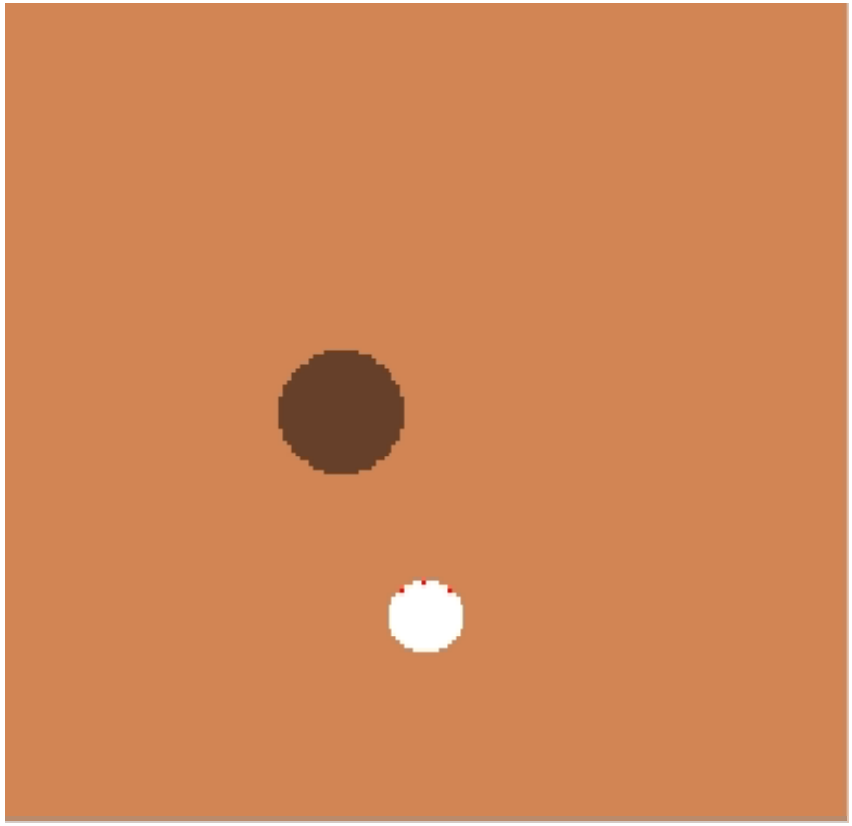




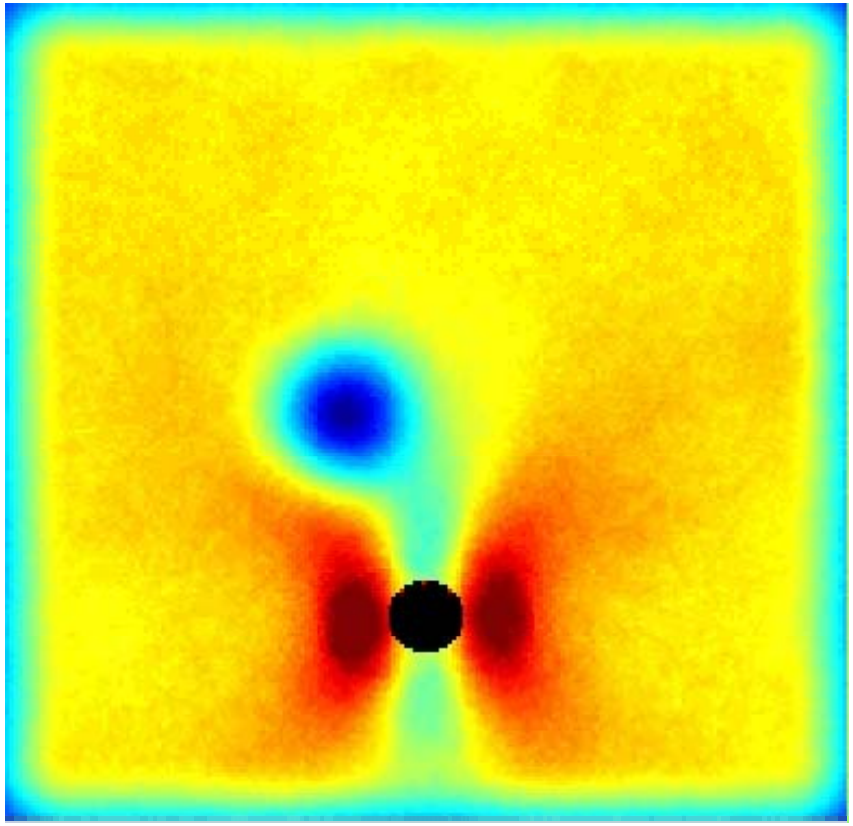
Drifting or waltzing osteon

dead osteocytes

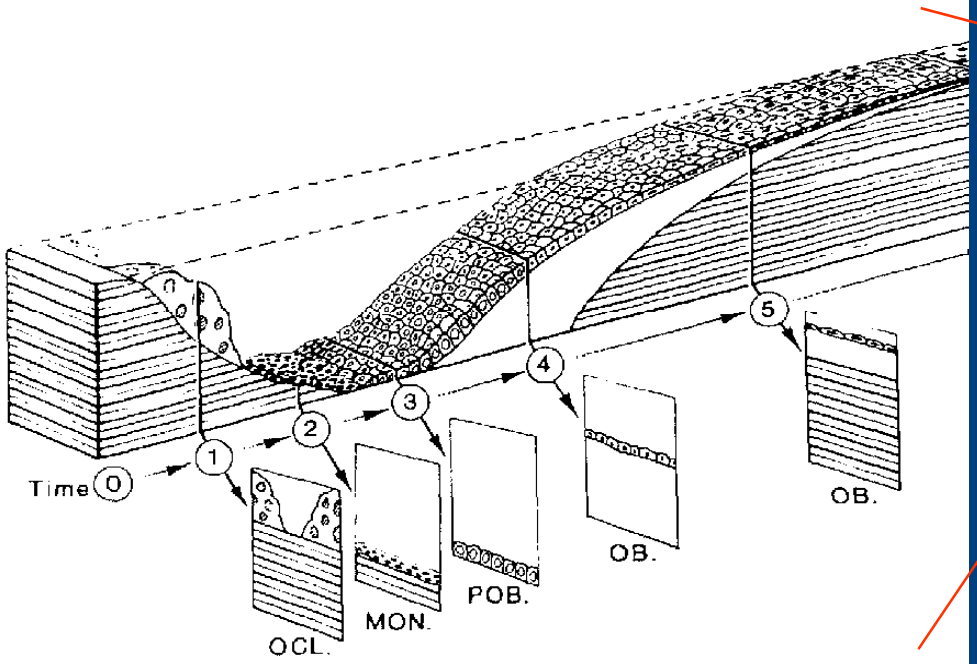
(~microdamage?)



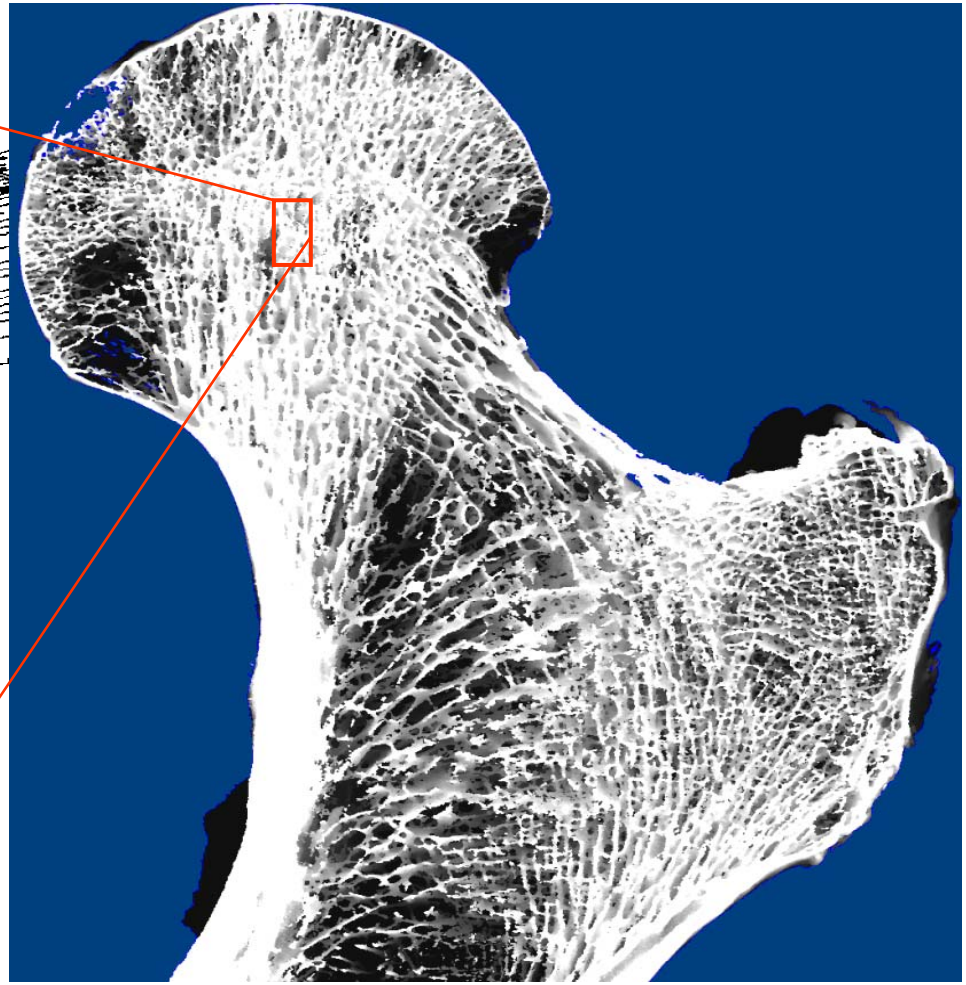
osteocyte signal



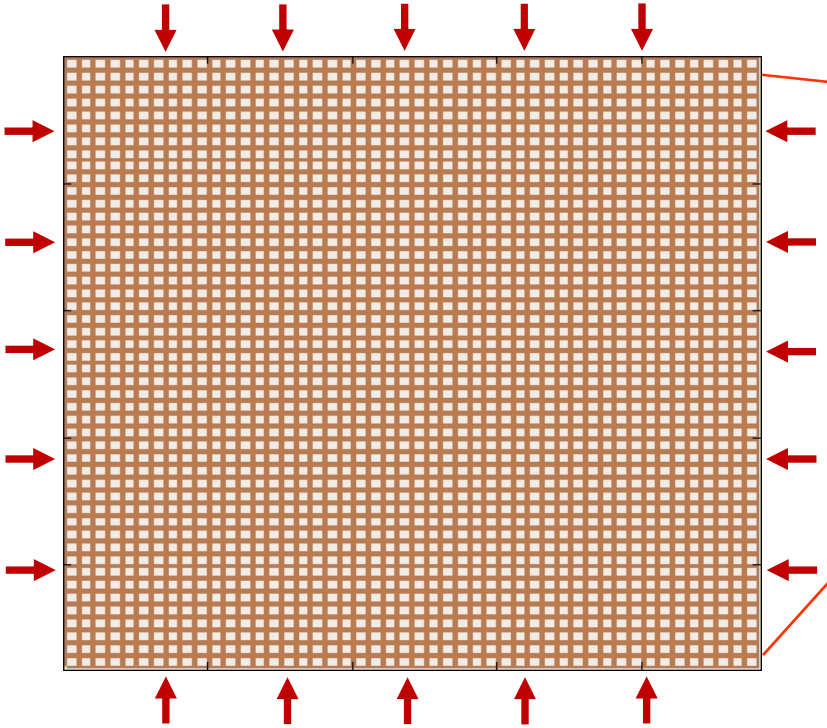
Trabecular BMU

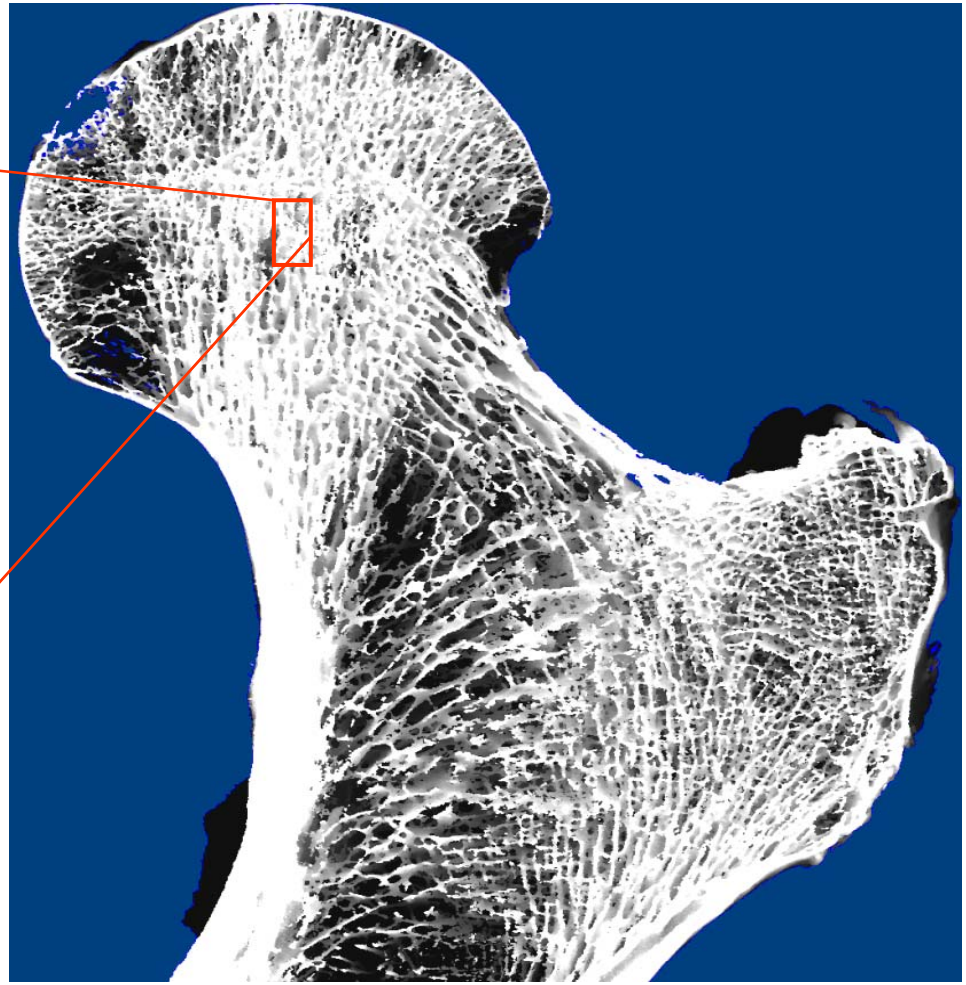


Eriksen, *Endocr. Rev.* 1986



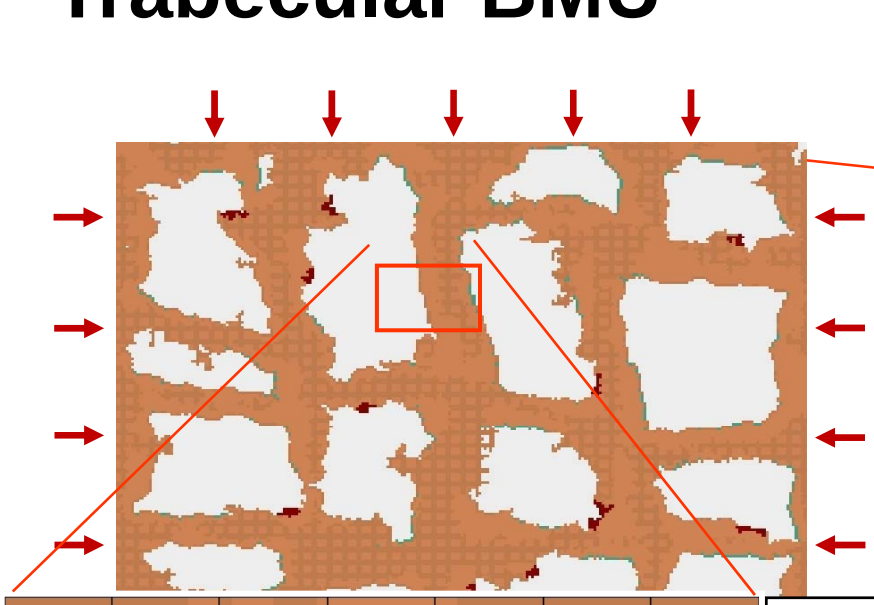
Trabecular BMU

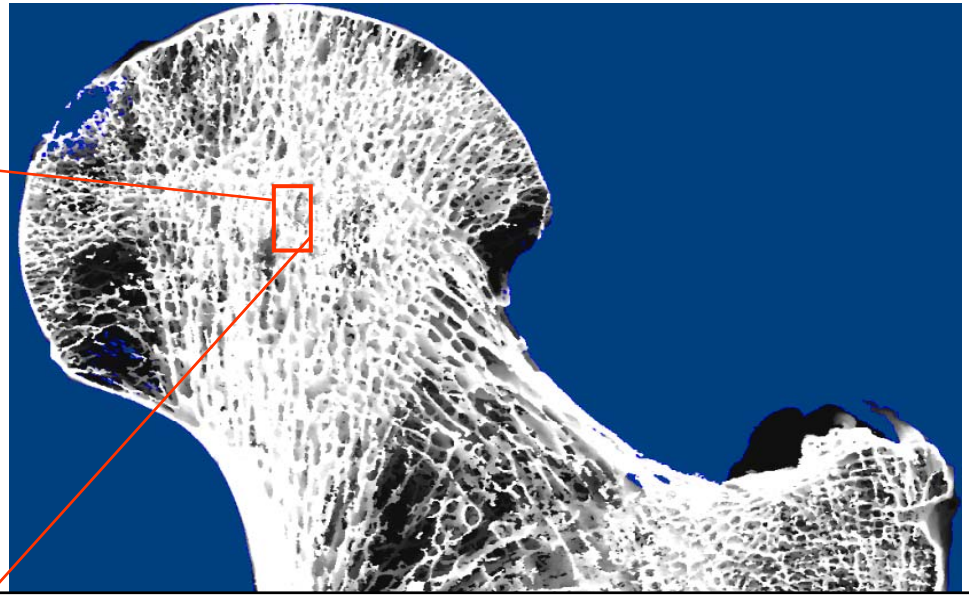


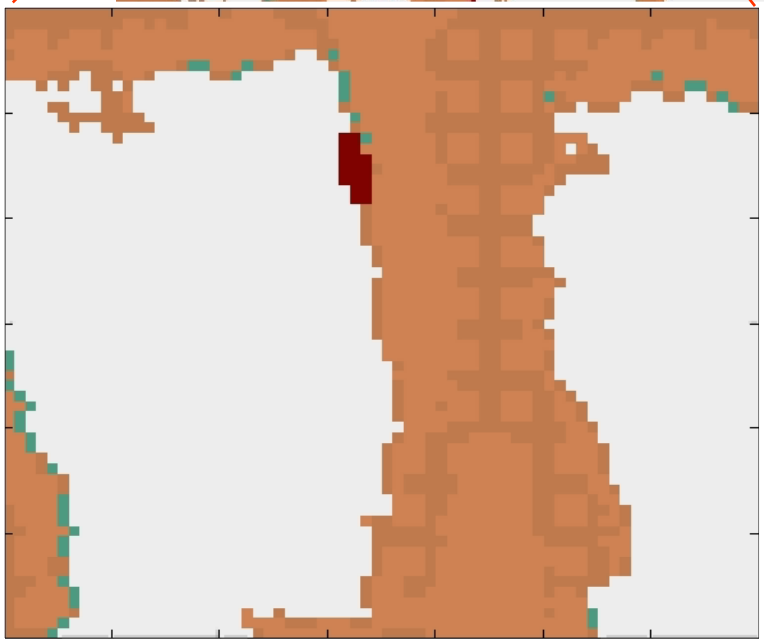


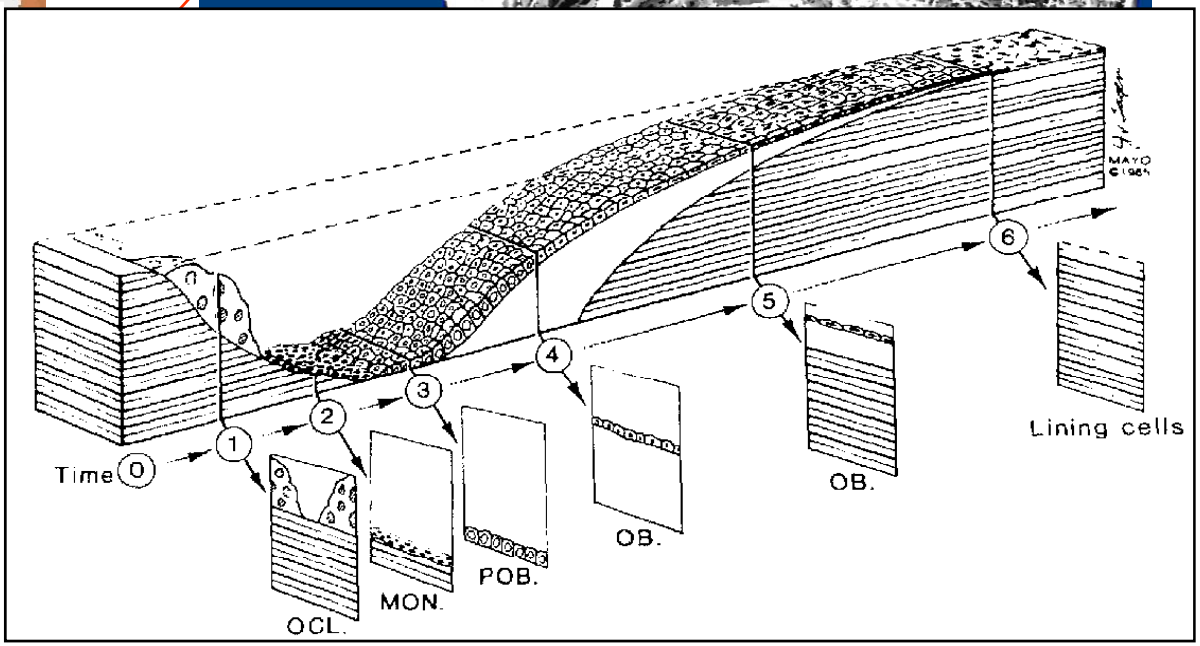
3x3 mm²

Trabecular BMU



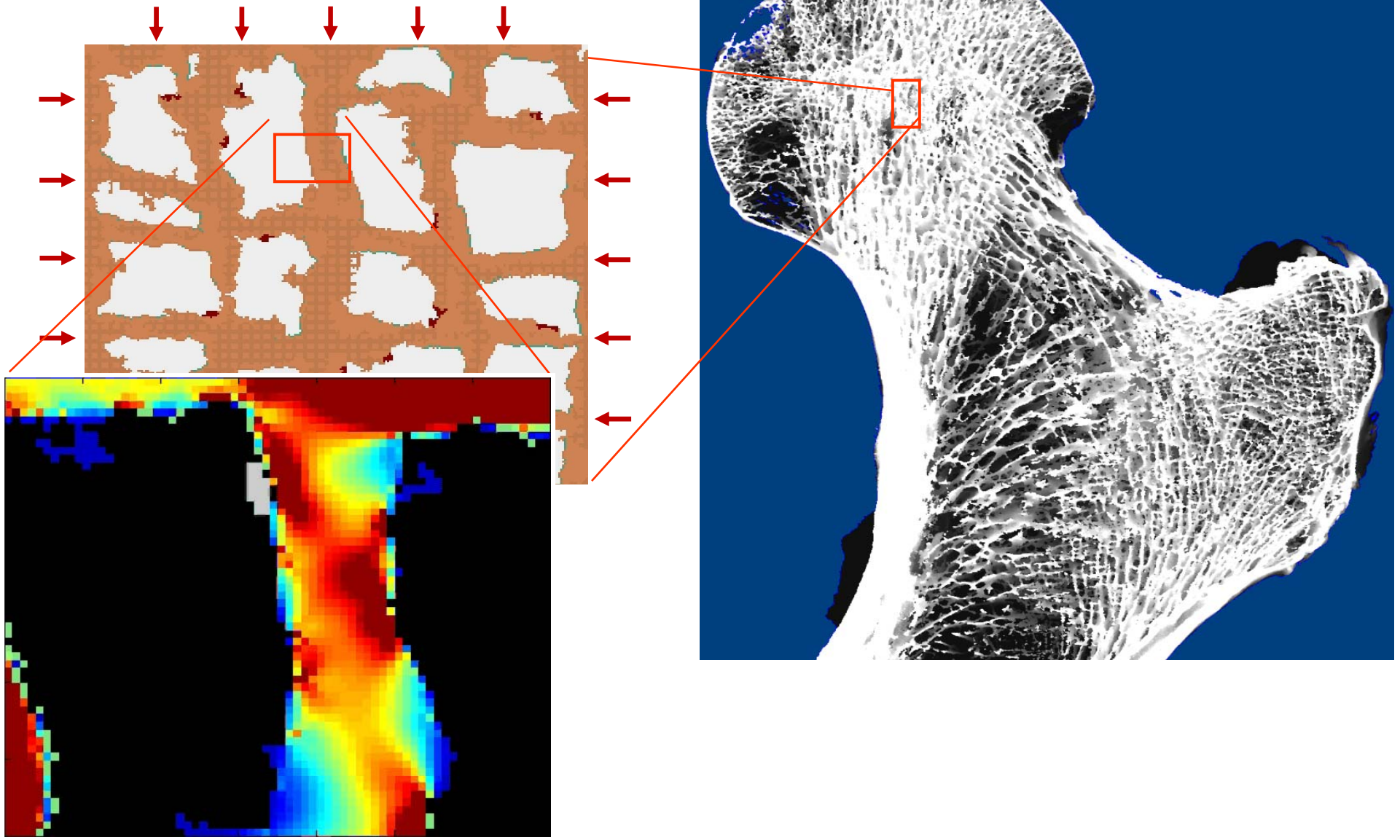






Eriksen, *Endocr. Rev.* 1986

Trabecular BMU



Summary L3

- Osteoporosis and other metabolic bone diseases affects the bones fracture resistance
- **Mechanical stimulation is a major factor influencing bone modelling and remodelling.**
- Continued debate on what is the driving force behind remodeling? And what is the mechanism by which mechanical data is transferred to the bone cells to produce remodeling?
- Bone remodeling simulations are effective tools for evaluating design parameters of new implants and screws, such as geometry, material charactersitcs etc