Biomechanics of the musculoskeletal system

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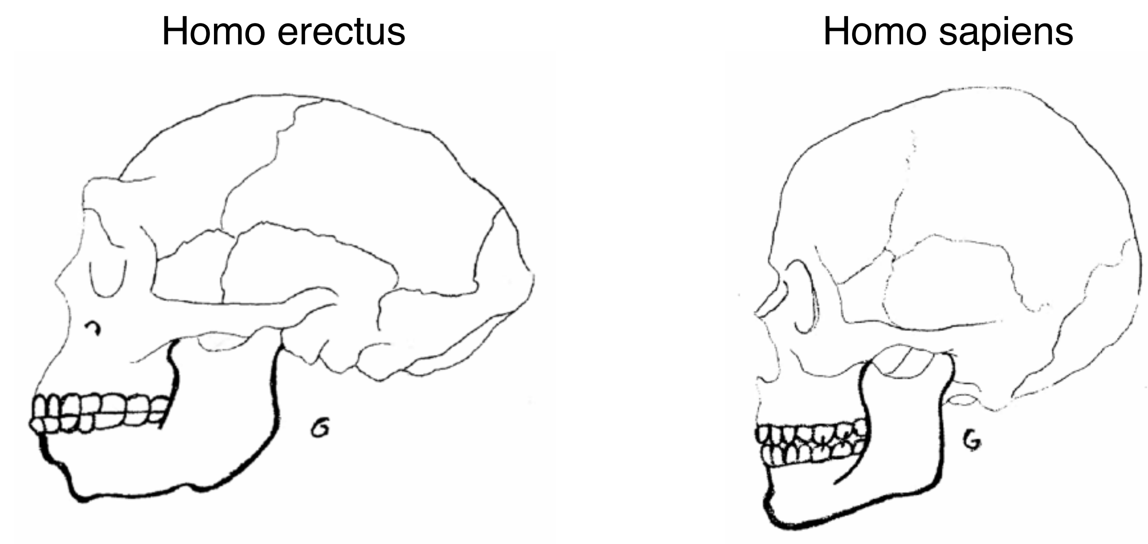
Bone remodeling

i) Mechanical aspect

ii) Hormonal aspect

Bone remodeling can be seen from two different aspects: i) it allows the skeleton to continuously adapting its shape and its density to its (mechanical) function and ii) it participates in the calcium homeostasis in the body (as being the calcium reservoir of our body). It seems then not surprising that bone remodeling can be (partially) under the influence of the mechanical loading exerted on the skeleton. The calcium homeostasis being central for many biological phenomena in our body, its regulation is under hormonal control.

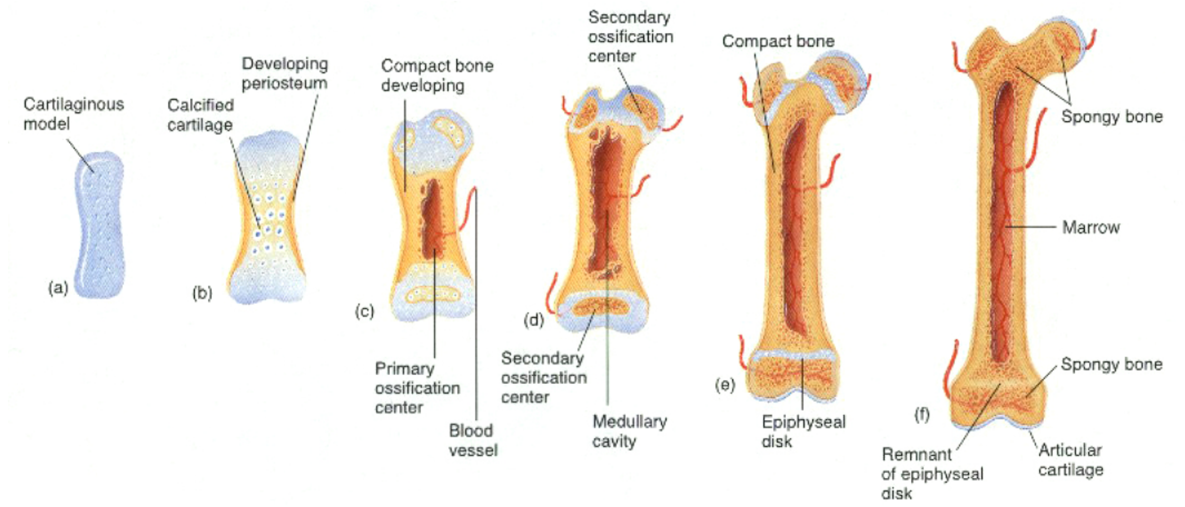
The tissues adapt to their mechanical environment: several time scales



-> thousands of years

If we compared the anatomy of the Homo erectus (extinct around 150’000 years ago) with the one of the homo sapiens, obviously striking differences are present. Specifically if we focus on the jaw, we immediately observe that its size has considerably decreased. This is certainly due to the quality of the food which has a tendency to become softer during the human kind evolution. The shape then adapts to its function. This tissue mechanical adaptation is the results of an evolution over many generations.

The tissues adapt to their mechanical environment: several time scales



source: http://www.sirinet.net/~jgjohnso/

-> 100 years

Our bones are initially made of soft structure (cartilage) during the foetal period then they become a stiffer and stiffer structure till adulthood. A natural decrease of the bone mechanical properties is finally observed as we aged, starting from around 30 years old (at least for the women, a bit later for the men).

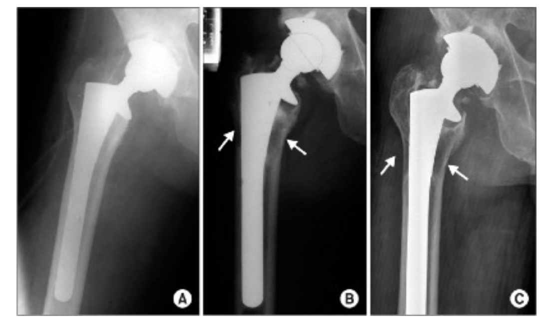
The tissues adapt to their mechanical environment: several time scales

Femur of mouse

Normal W/O mech. constraint

Hip Implant

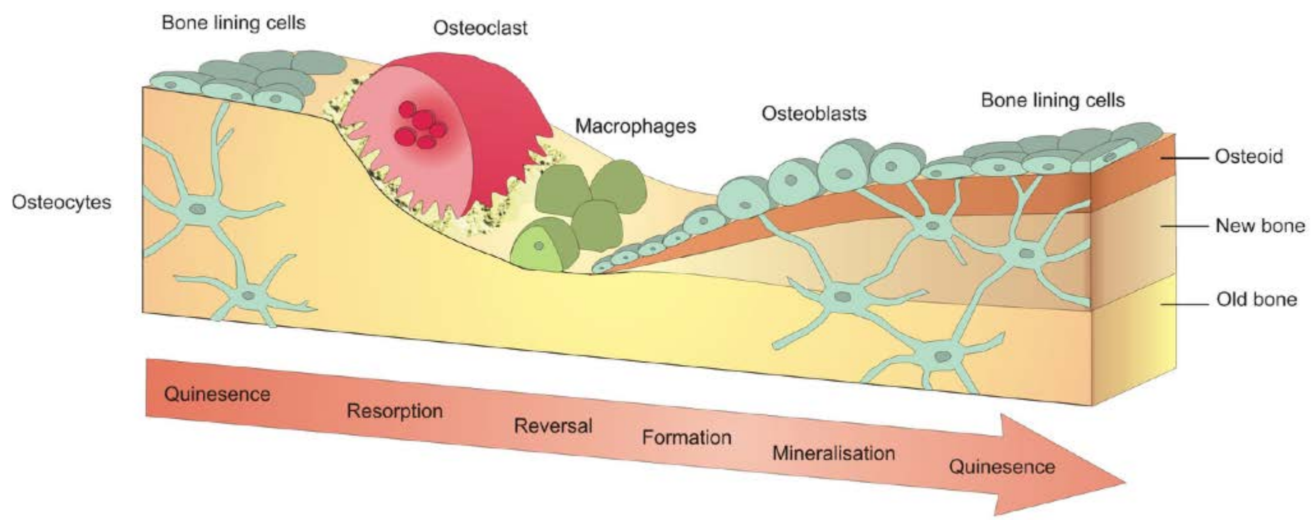
Post-op 2 years 7 years



-> months to years

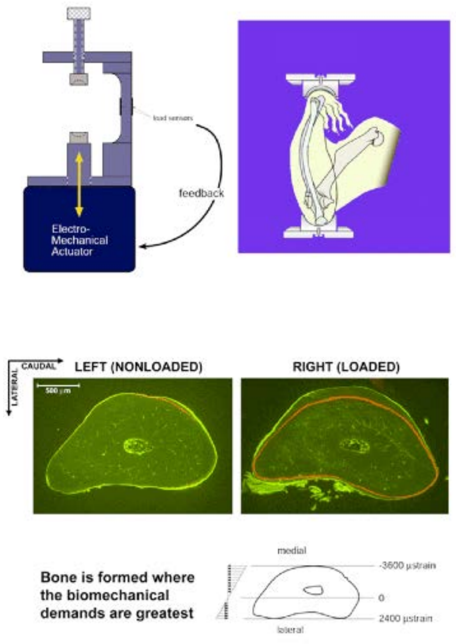
Finally, a tissue mechanical remodeling (or adaptation) can also be observed at a shorter time scale. Indeed, it has been shown that if we deprived the mouse femur from mechanical loading, a bone resorption occurs after several weeks already. Bone resorption around orthopedic implant is a common clinical problem which is related, at least partially, to an absence of adequate mechanical stimulation.

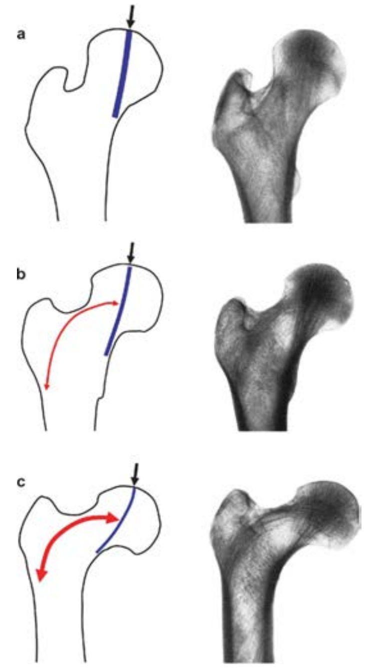
During remodeling, the cells control the structure and composition of the bone



Once the bone has been formed during the modeling process, it will be modified during our entire life (through mechanical and/or hormonal influences), a process called remodeling. The osteoclasts first remove the bone extracellular matrix and are followed by the osteoblasts which deposit an uncalcified extracellular matrix (ECM) (mainly collagen type I) called osteoid. Precipitation of calcium phosphate crystals (mainly in hydroxyapatite crystal form: $Ca_{10}(PO_4)_6(OH)_2$) in the osteoid and expansion of these crystals, a process called mineralization, give the high mechanical properties of the bone in compression.

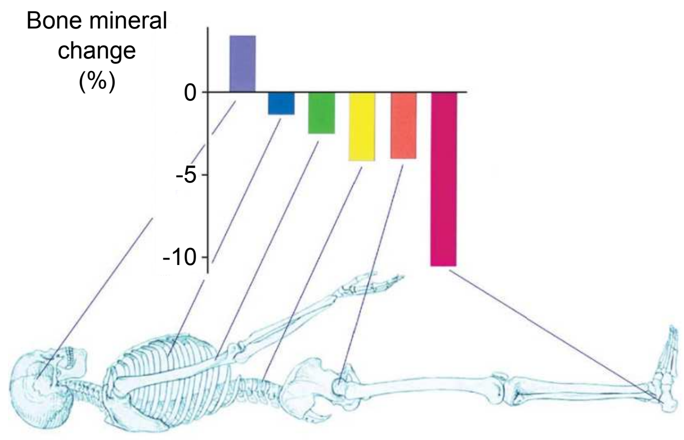
The remodeling affects the shape of the bones (external remodeling), …

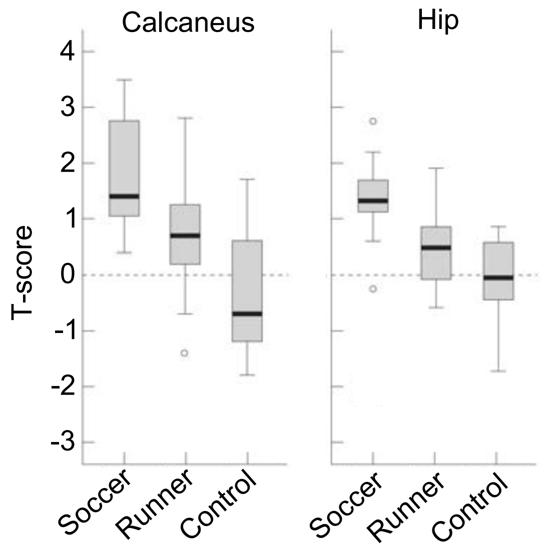




Bone adapts to the mechanical loading they are exposed to by modifying their shape. The diameter of the bone can then change or more drastic changes can be observed as illustrated in this slide.

as well as their density (internal remodeling)

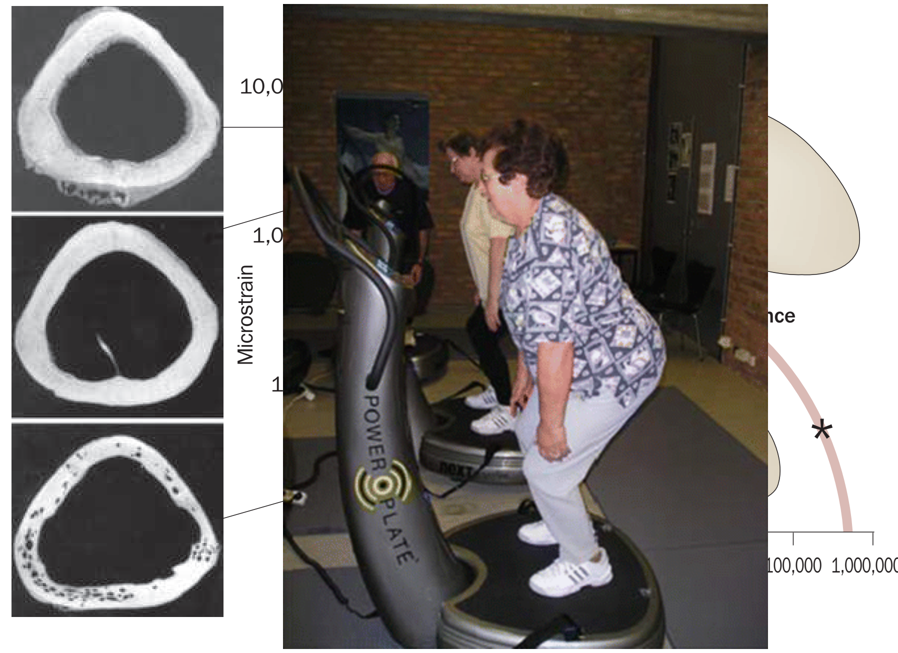




As we have previously shown that the mechanical properties of bone are related to their density, it is then not surprising that the bone density also varies according to the mechanical stimulation. As example, it can be seen on the left that bone mineral content varies after 17 weeks of bed rest (adapted from Robling et al. (2006)). On the right, T-score of calcaneus and hip in runners and soccer players compared to controls (adapted from Fredericson et al. (2007)).

(definition of T-score in bone physiology: your bone density test results are compared to the ideal or peak bone density of a healthy 30-year-old adult, and you are given a T-score. A score of 0 means your BMD is equal to the norm for a healthy young adult.)

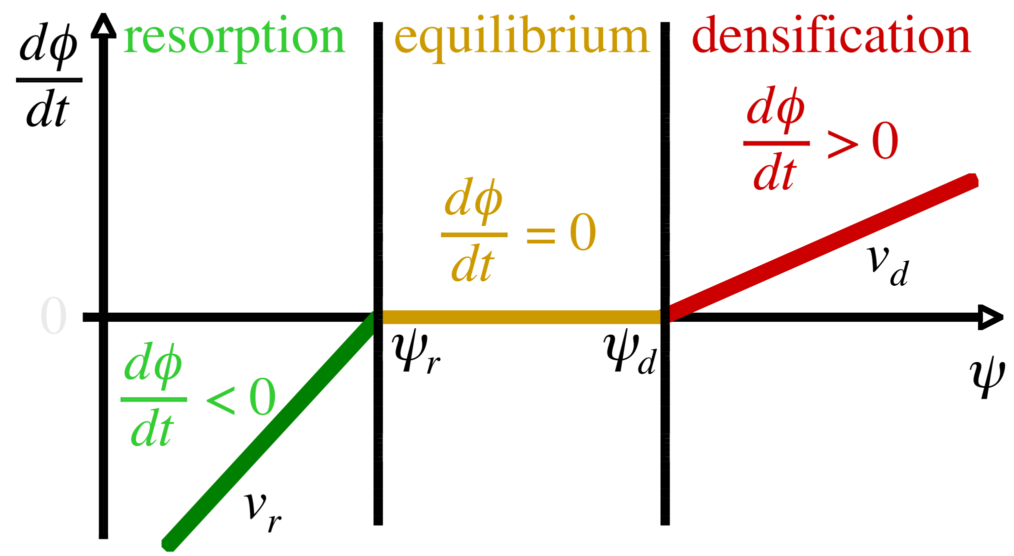
Differential effects of mechanical loading on bone remodeling



Ozcivici et al, Nat. Rev. Rheumatol., 2010

One of the most clear demonstration of the influence of the mechanical stimulation on bone remodeling has been obtained by precisely correlating bone remodeling (formation/resorption) to a controlled mechanical stimulation applied on turkey ulna. A very interesting finding is that it is not only the amplitude of the strain which affects bone formation, but also its frequency.

“Mechanical stimulus” has been proposed to drive the bone density evolution

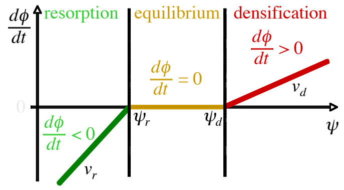


Ψ: mechanical stimulus (scalar invariant)

Already Wolff in 1886 and Roux in 1895 postulated the existence of mathematical laws driving the bone biological adaptation as a function of the mechanical environment. Indeed, for the density evolution, it has been observed that there are basically three possibilities: resorption, equilibrium, and densification. A trilinear function (so 4 parameters) can adequately describe the three possibilities for the density evolution. The graphical representation of this trilinear function is given here, with the concept of “mechanical stimulus”.

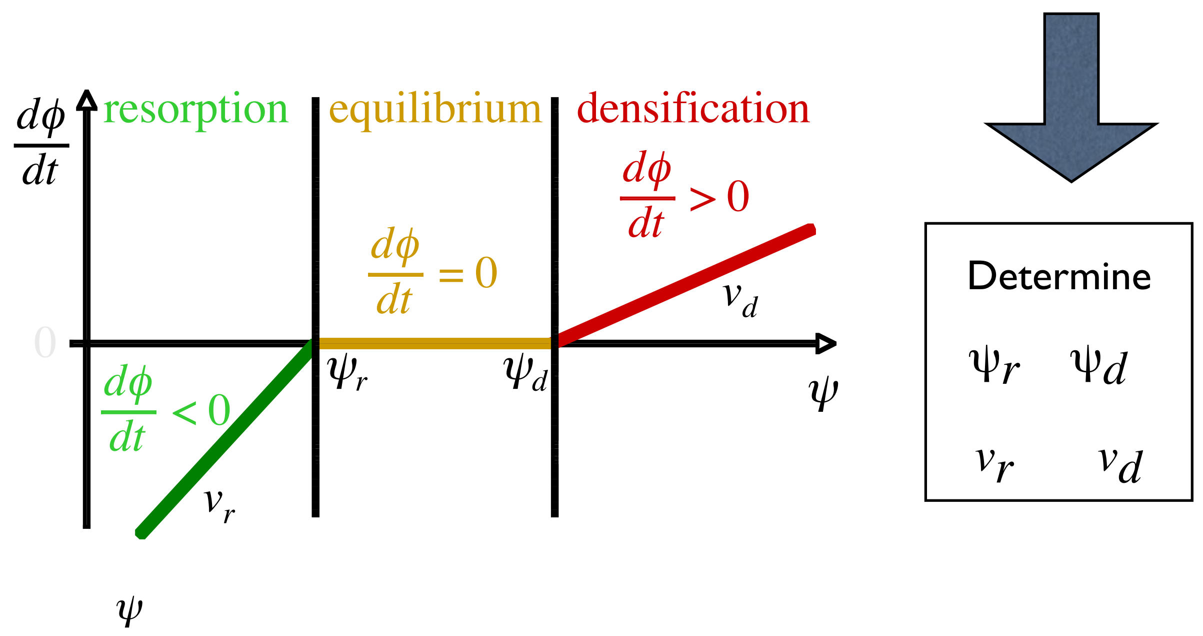
A mathematical formulation between the evolution of density and the mechanical stimulus can be proposed

$$\frac{d\phi}{dt} = \begin{cases} v_r[\psi - \psi_r] & \psi < \psi_r \\ 0 & \psi_r \leq \psi \leq \psi_d \\ v_d[\psi - \psi_d] & \psi > \psi_d \end{cases}$$



The trilinear function takes the mathematical form given here. Basically, if the mechanical stimulus is below the resorption threshold value, the density rate (which is negative here) is given by v_r that we call “resorption rate”. If the mechanical stimulus is comprised between the resorption and densification threshold values, the density rate is trivial, no bone is resorbed or produced. If the mechanical stimulus is above the densification threshold, the density rate (which is positive here) is given by v_d that we call “densification rate”. Note that the values of v_d and v_r are not identical.

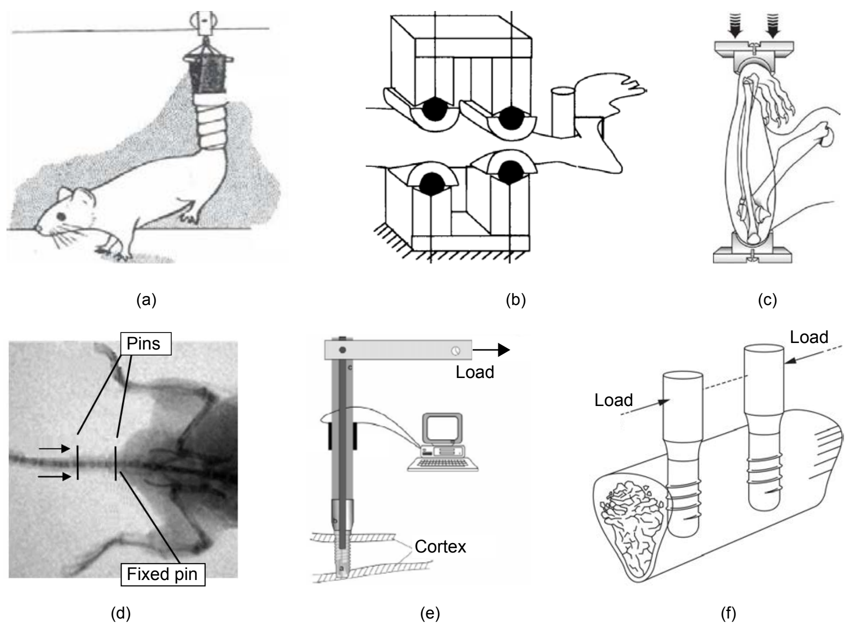
It is necessary to identify the parameters appearing in the evolution law



Ψ: mechanical stimulus (scalar invariant)

The trilinear function needs to be identified with experimental data to determine the value of the 4 parameters.

A clinical or an animal study is necessary to determine the parameters of the evolution law



Different in vivo models have been used to correlate mechanical loading and bone remodeling.

A clinical or an animal study is necessary to determine the parameters of the evolution law

The rat’s fitness room!

A clinical or animal study is necessary to determine the parameters of the evolution law

Measure… months)

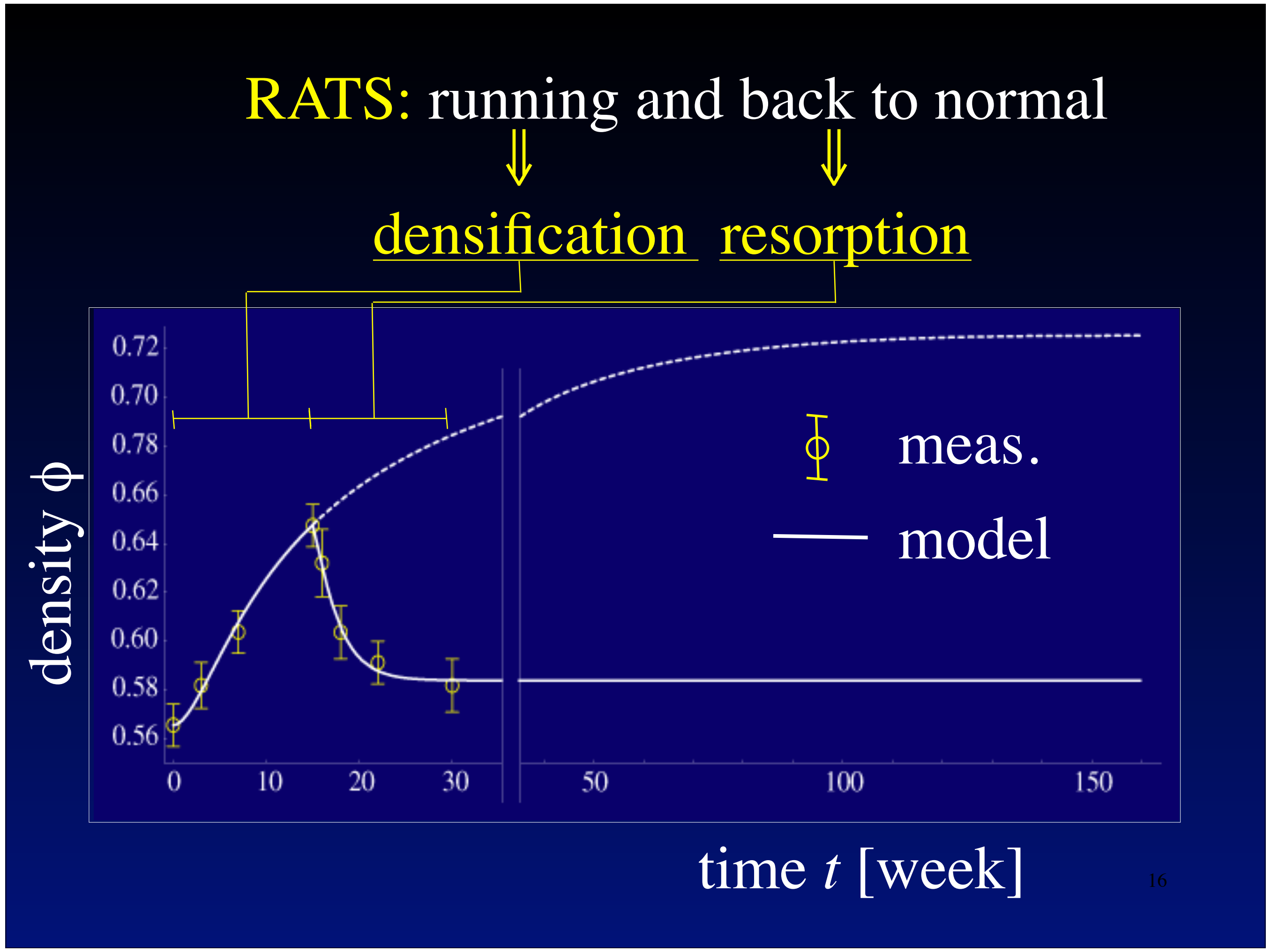
4 mont…

…on

4 mont… …n cage)

…n

As mentioned early, evolution laws have inherently the time as variable. We can then not use standard mechanical data, but we need to evaluate the evolution of the density. A controlled mechanical environment has then to be designed for an in vivo experiment.



At different time points, the density in the rat tibia is measured. A curve density/time is obtained. We have then to identify the differential equation (dΦ/dt) with the chosen mechanical stimulus on the data to obtain the two densification parameters (on the densification part) and the two resorption parameters (on the resorption part).

After identification, the values of the remodeling model parameters are obtained

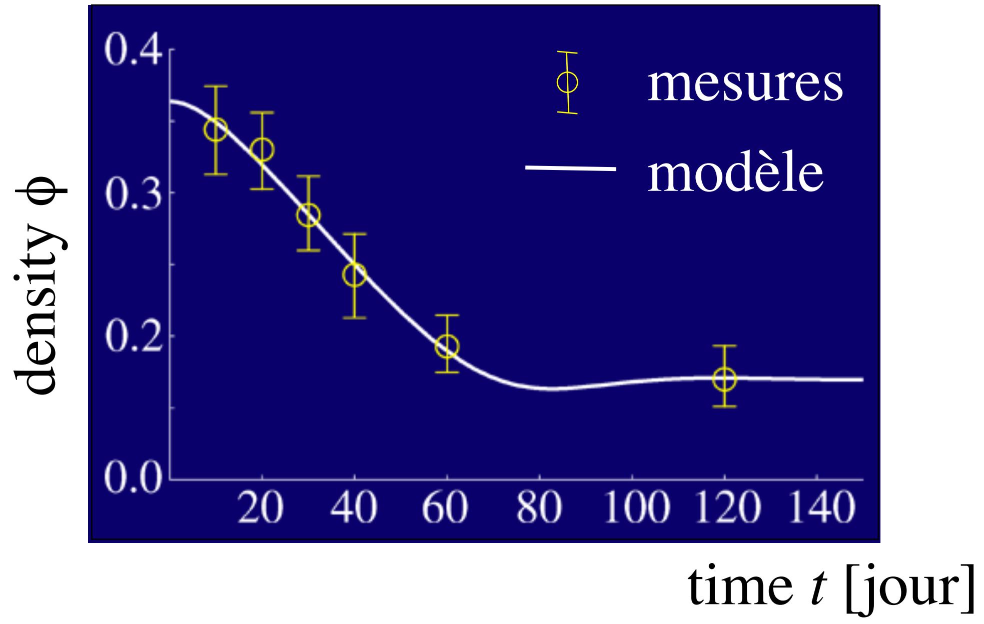
$$\psi_r = 6.62x10^{-3} \qquad \psi_d = 7.52x10^{-3}$$

$$v_r = 9.4 \;\; week^{-1} \qquad v_d = 0.7 \;\; week^{-1}$$

We can verify that the slope of resorption is higher than the slope of formation.

Human: immobilisation of the tibia

⇒ resorption



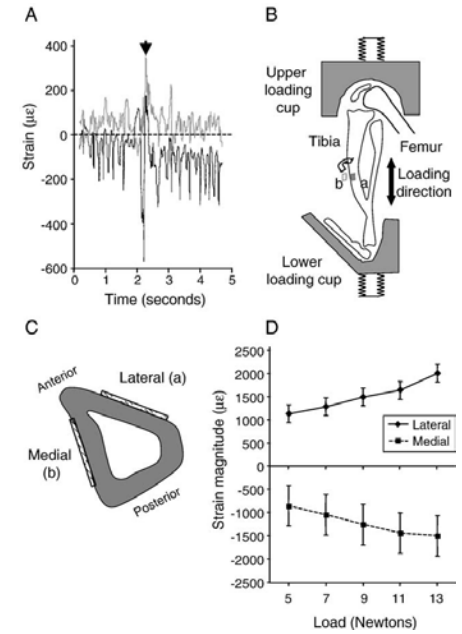
Using available clinical data (mainly resorption), an order of magnitude for the parameters can be obtained.

Comparison of the obtained parameters

Rate of resorption	>	Rate of densification
Delay of resorption	<	Delay of densification
Rate of human adaptation	<	Rate of rat adaptation

We can observe that the bone remodeling is different for rat and human. The data obtained from in vivo study needs then to be corrected for the human situation.

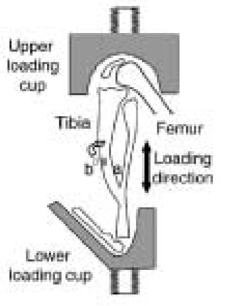
What is the meaning of “mechanical stimulus”?



source: De Souza, Bone, 2005.

(A) Representative strain gauge recordings taken from the lateral (grey line) and medial (black line) surface of the diaphyseal mid-shaft of the 12 weeks mouse tibia during 5 s of normal locomotion encompassing a jump from 30 cm (arrow represents landing phase of the jump; n = 6 animals). (B) Diagrammatic representation of the flexed mouse right hind limb in position in the loading apparatus. (C) Diagrammatic representation of a cross-section of the tibial mid-shaft showing the location of the attached strain gauges on medial and lateral surfaces of the tibia. (D) Ex vivo load: strain calibration profile, showing load magnitude-related increases in tensional (lateral) and compressive (medial) strains (με) at five different loading magnitudes applied to 12 week tibiae. Data shown are mean ± SEM for four animals.

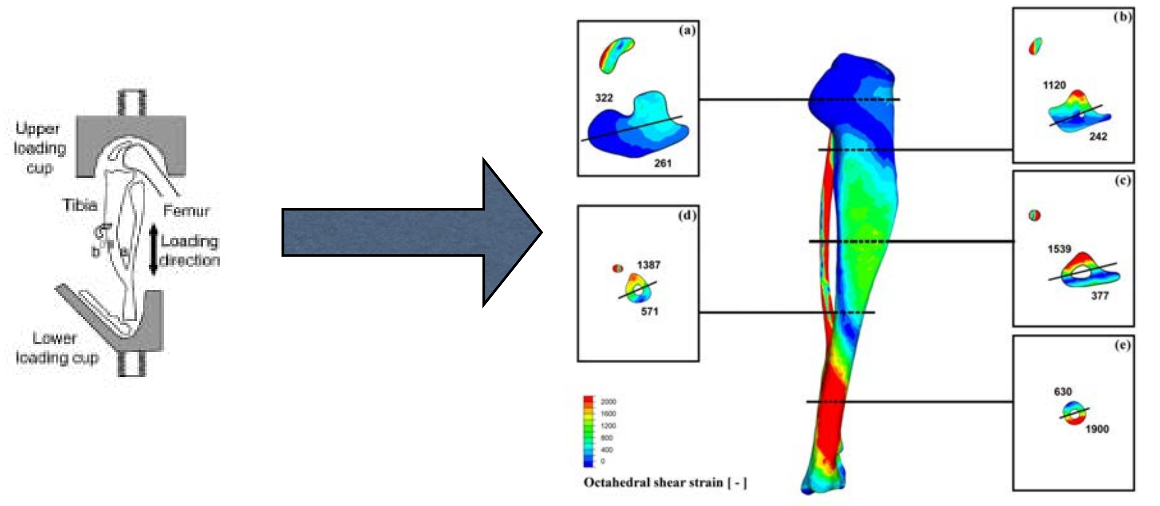
How the external loading can be correlated to internal mechanical stimulus?



Cyclic constant force ?

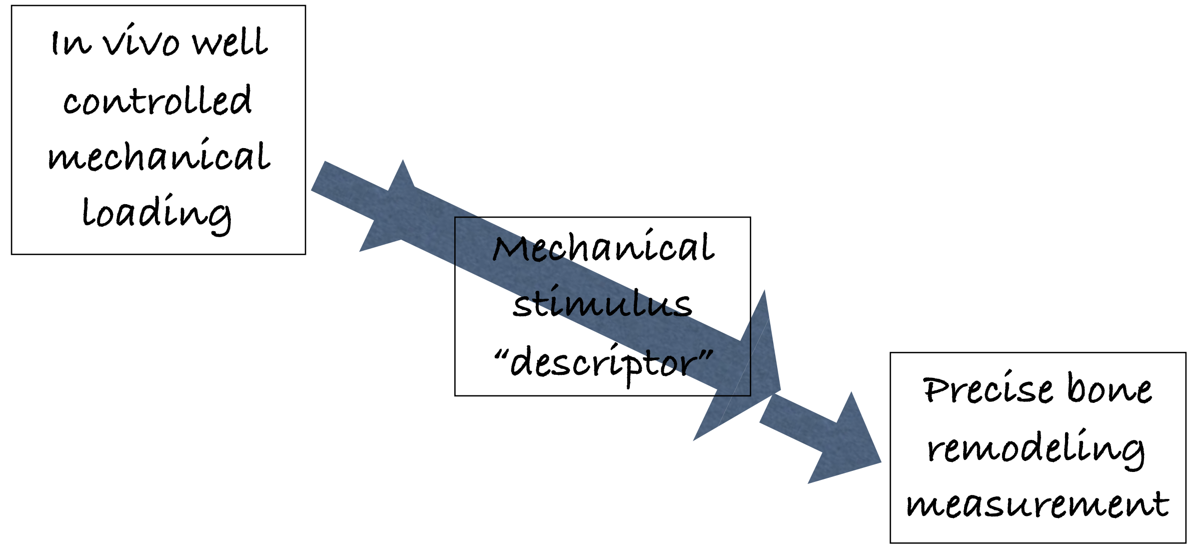
Cyclic constant displacement ?

How the external loading can be correlated to the (internal) “mechanical stimulus”?



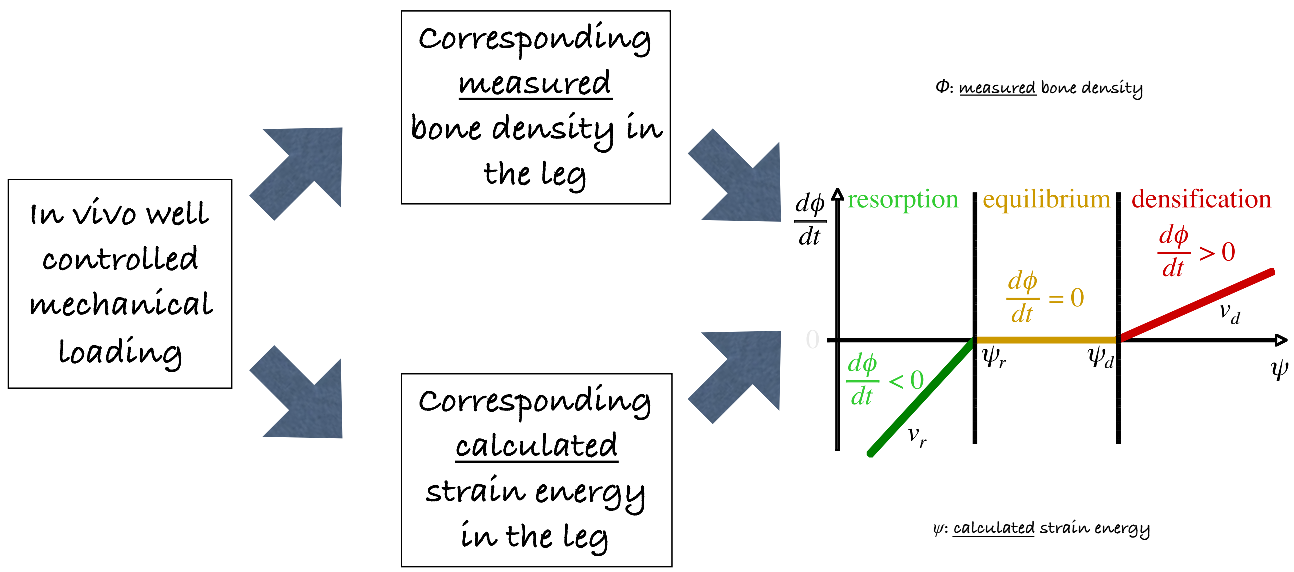
Indeed, the way bone reacts to mechanical stimulation is not so simple (as for example if we consider only the mechanical energy $\psi = \sigma * \varepsilon$). With the mechanical energy as “mechanical stimulus”, one cannot discriminate between the different modes of stimulation such as compression, traction or shear.

Only a confrontation between theory and experiment can justify the choice of a particular mechanical stimulus "descriptor"



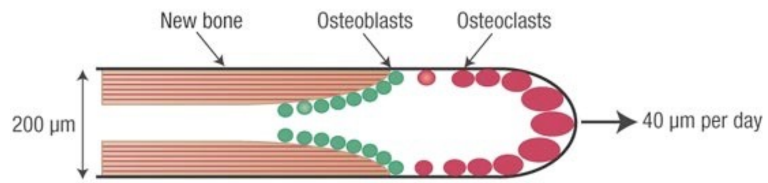
To correlate mechanical loading to bone remodeling, in vivo loading experiment has to be carefully performed and the resulting bone remodeling has to be precisely measured. If we make the hypothesis that the bone remodeling is due essentially to mechanical loading, we have then to find a "transfer function" enabling us to link the input (mechanical loading) to the output (bone remodeling measurement).

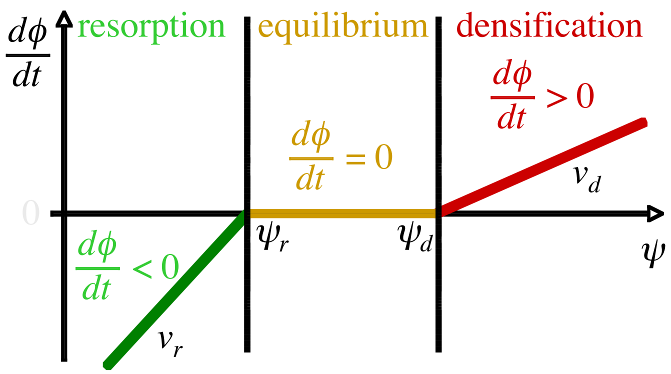
The relationship between bone density rate and mechanical stimulus is dependent on the choice of the "mechanical stimulus" descriptor



The value of the 4 parameters v_r, Ψ_r, v_d, Ψ_d depends then on the choice of the definition of the mechanical stimulus. In this example, the strain energy is chosen as descriptor of the "mechanical stimulus". The strain energy is defined as $\sigma*\varepsilon$. As an alternative "mechanical stimulus", we could have chosen the octahedral shear strain $\varepsilon_{oct} = 2/3[(\varepsilon_{xx} - \varepsilon_{yy})^2 + (\varepsilon_{xx} - \varepsilon_{zz})^2 + (\varepsilon_{yy} - \varepsilon_{zz})^2 + 6(\varepsilon^2_{xy} + \varepsilon^2_{xz} + \varepsilon^2_{yz})]^{1/2}$. The choice of the octahedral shear strain has been suggested by the results of several investigations that highlight the influence of shear on the bone tissue differentiation.

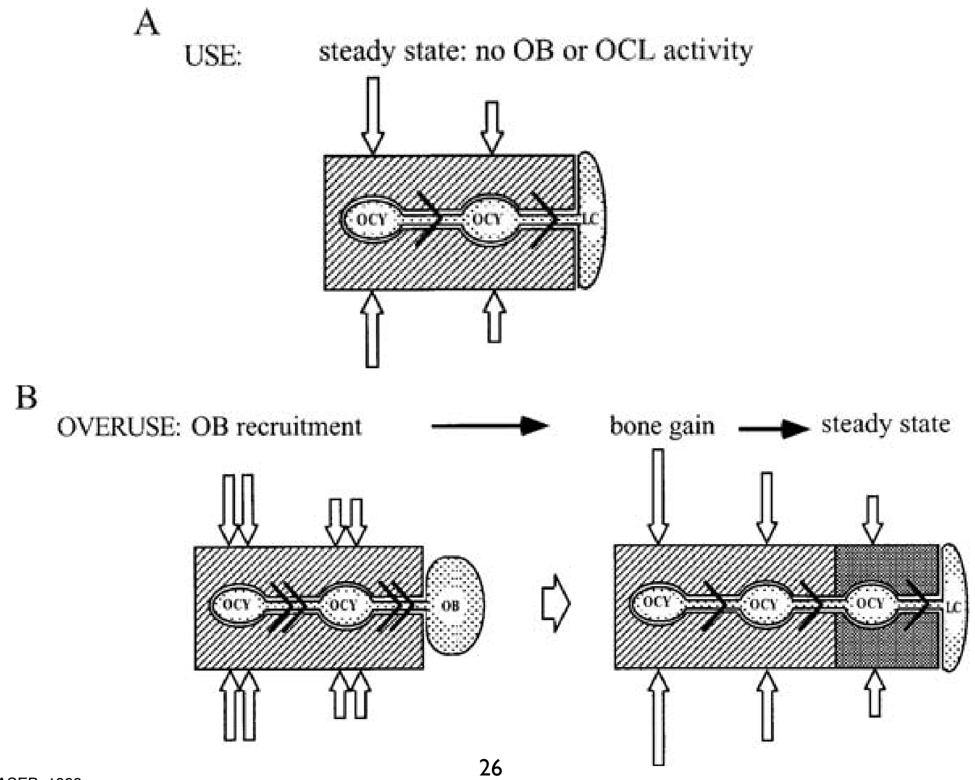
How can we link the biological and biomechanical description of bone remodeling?





On one side, the biologist explains us that there are cells which are responsible for bone remodeling and on the other side biomechanician tries to correlate bone remodeling with mechanical stimulation.

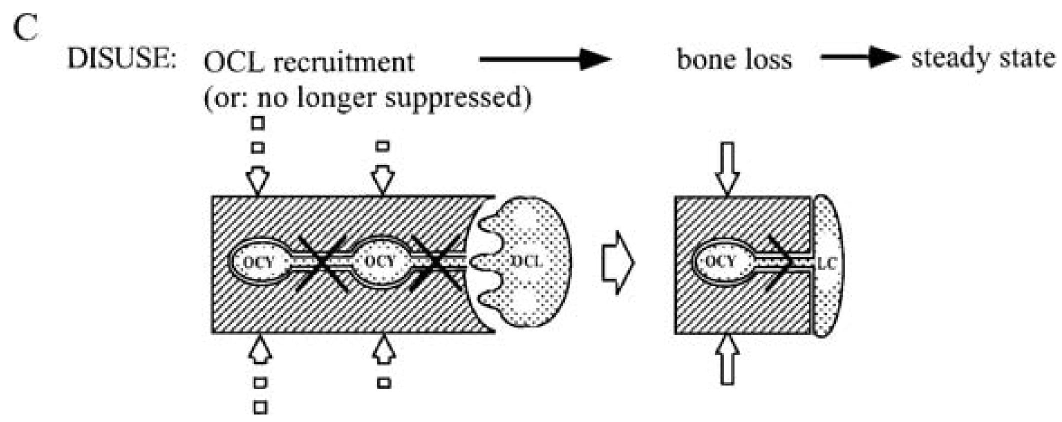
A macroscopical description of mechanical effect in bone brings new insight



source: Burger, FASEB, 1999.

Schematic representation of how the osteocyte network may regulate bone remodeling. A) In the steady state, normal mechanical use ensures a basal level of fluid flow through the lacuno-canalicular porosity, indicated by an arrowhead through the canaliculi. This basal flow keeps the osteocytes viable and also ensures basal osteocyte activation and signalling, thereby suppressing osteoblastic activity as well as osteoclastic attack. B) During (local) overuse, the osteocytes are over-activated by enhanced fluid flow (indicated by double arrowheads), leading to release of osteoblast-recruiting signals. Subsequent osteoblastic bone formation reduces the overuse until normal mechanical use is re-established, thereby re-establishing the steady state of basal fluid flow. (OCY, osteocyte; LC, lining cell; OB, osteoblast; OCL, osteoclast; hatched area, mineralised bone matrix; dark-grey area, newly formed bone matrix; white arrows represent direction and magnitude of loading).

A macroscopical description of mechanical effect in bone brings new insight



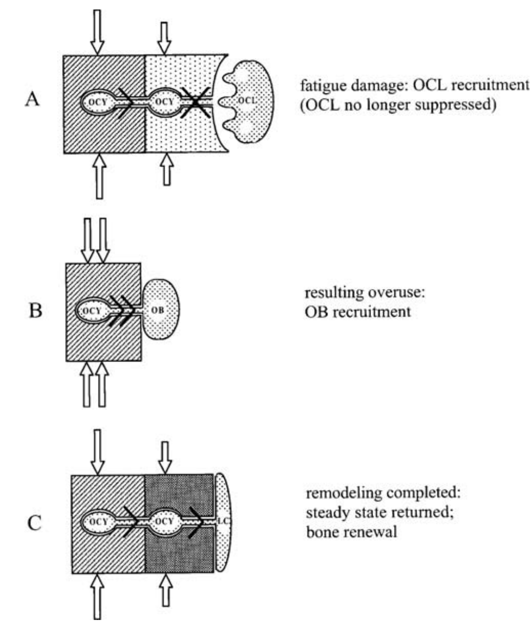
source: Burger, FASEB, 1999.

C) During (local) disuse, the osteocytes are inactivated by lack of fluid flow (indicated by crosses through canaliculi). Inactivation either leads to release of osteoclast-recruiting signals or to lack of osteoclast suppressing signals, or both. Subsequent osteoclastic bone resorption re-establishes normal mechanical use (or loading) and basal fluid flow. (OCY, osteocyte; LC, lining cell; OB, osteoblast; OCL, osteoclast; hatched area, mineralised bone matrix; white arrows represent direction and magnitude of loading).

A correlation between overuse generating micro-damage and bone remodeling can then be proposed

mechanical stimulus

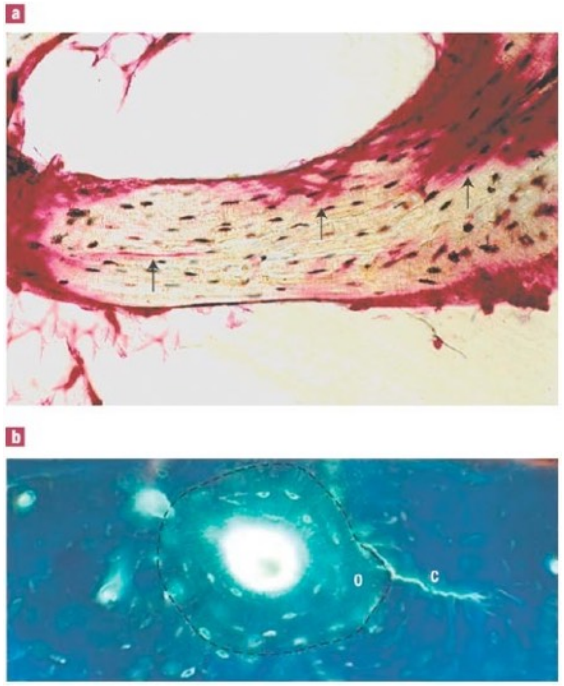
Plastic yield stress



source: Burger, FASEB, 1999.

Schematic representation of how fatigue damage may initiate bone remodeling. A) Accumulation of fatigue micro-damage (stippled matrix) interferes with canalicular fluid flow and osteocyte signalling by disrupting canaliculi and severing osteocyte processes. Fatigue micro-damage results in osteoclast recruitment, suggesting that osteocyte signalling suppresses osteoclast recruitment rather than activating it. Osteoclasts resorb damaged bone until undamaged bone is reached, when they are again suppressed. B) The local loss of bone after osteoclastic resorption leads to (local) overuse of the remaining undamaged bone. The resulting enhanced fluid flow through the lacuno-canalicular network leads to recruitment of osteoblasts. C) Subsequent osteoblastic bone formation reestablishes normal mechanical use and therefore the steady state of basal fluid flow in the renewed bone.
The mechanical stimulus could then be set to a plastic dissipation pseudo-potential characterised by a yield criterion function, which is a way to measure the micro-damage, since plastic deformations are needed to create microcracks.

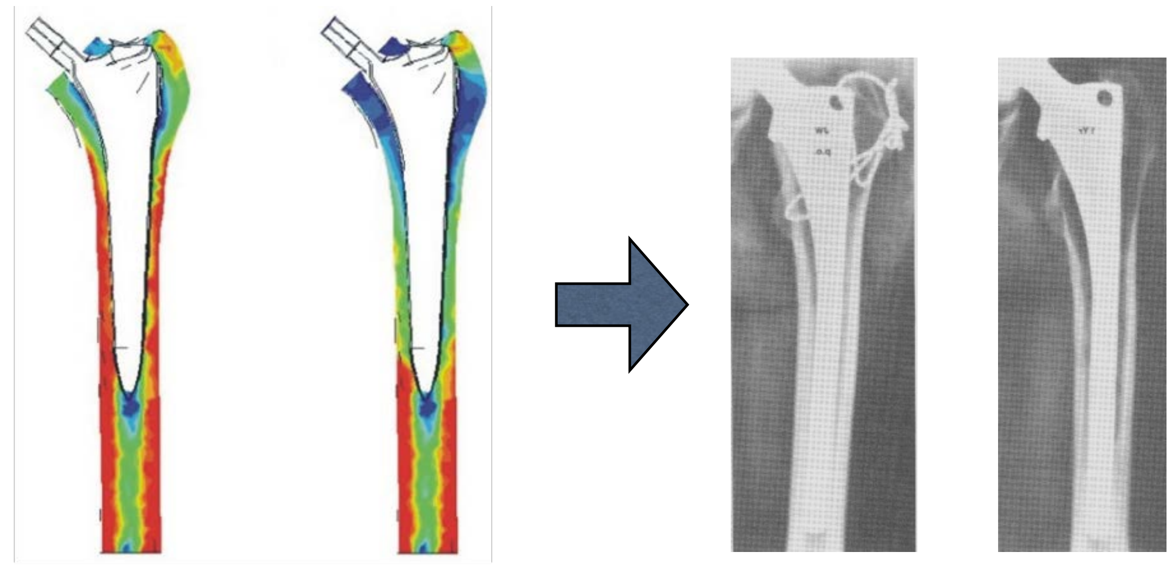
Obviously, micro-damage needs to be experimentally observed to support the theory



source: Taylor, Nature Mat, 2007.

A) Cancellous bone showing examples of micro-damage revealed by staining with basic fuschin (pink).
B) A microcrack 'C' encounters an osteon 'O', and begins to grow around its cement line (dashed line). The microcrack is approximately 100 μm long.

Bone remodeling can then be calculated around implant



source: Leibniz University

The initial bone density is obtained by CT scan and the bone density after two years for example can be obtained. Cold colours indicate low bone density while warm colours indicate high bone density.

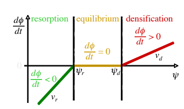
The model of remodeling is coupled with calculations of the constraints

Initial density: ϕ_{init}

External force: F^{ext}

Constitutive law: $\boldsymbol{\sigma} = \boldsymbol{\sigma}(\phi, \boldsymbol{\varepsilon})$

Mechanical stimulus: ψ



Density evolution: ϕ

If the bone remodeling model is coupled with a mechanical description (for example a FE analysis), bone remodeling around a particular implant can be anticipated.

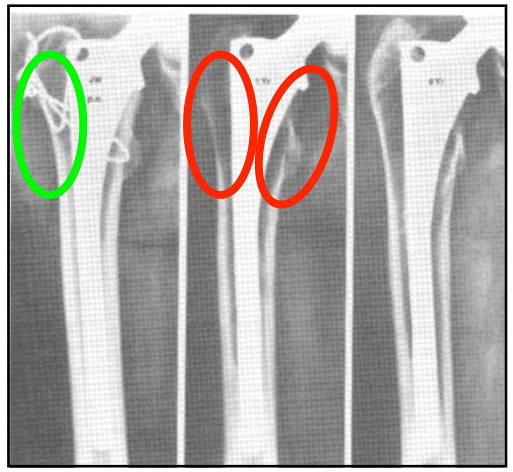
Finite Element Analysis

5 steps are necessary

1. Geometry (obtained by MRI or CT)
2. Constitutive laws (mechanical behaviour)
3. Boundary conditions (force or displacement)
4. Meshing
5. Resolution of conservation laws (numerical solver)

As the geometry, material properties and the boundary conditions of the problems of interest in the musculoskeletal system are usually complex, a numerical approach is needed to solve the conservation of the momenta and to obtain information on stress and strain in the studied tissues or implants. The point 1. is concerned with the domain of the study. The points 2. and 3. described the physics of the problem. The points 4. and 5. deal with numerical considerations of the problem.

Application: hip implant



1 week   2 years   7 years

Clinical background

Peri-implant osteolysis

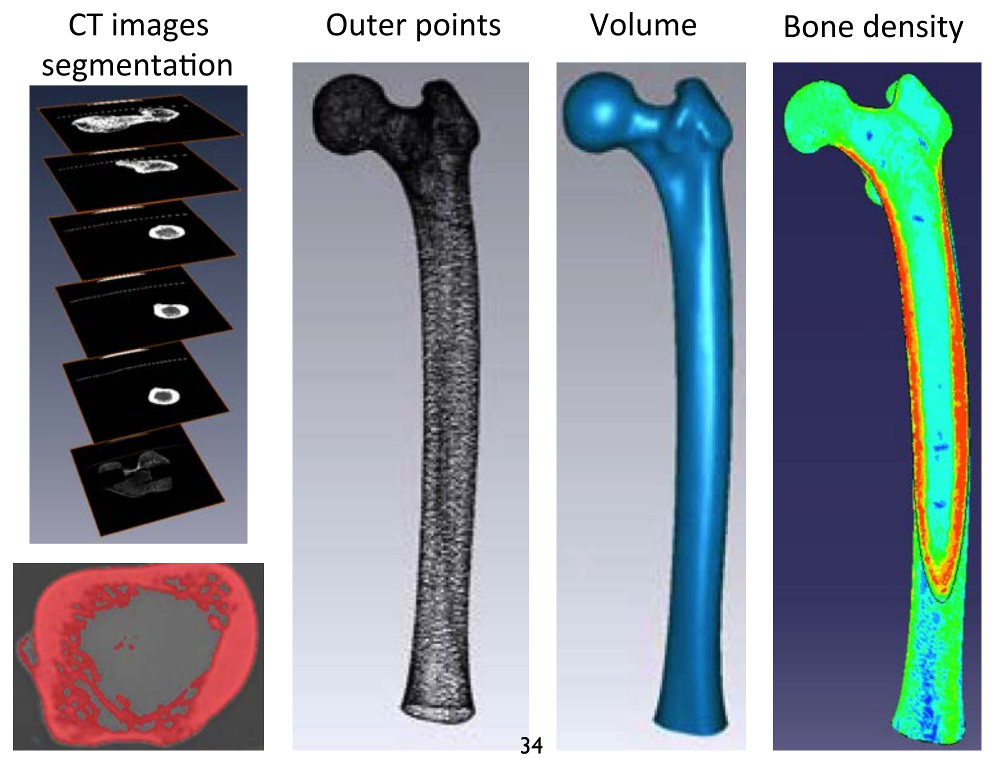
⇩

Quantification of µmotion, stress and remodeling around the hip implant for 2 surgical techniques

As example of the different steps to implement a biomechanical analysis, we will consider the clinical problem of the peri-implant osteolysis. After the implantation of a femoral stem in case of total hip arthroplasty, there is an unfavourable evolution of bone remodeling around the implant. One possible explanation may be an inadequate mechanical loading of the bone surrounding the implant. A mechanical analysis is then proposed to evaluate if this hypothesis is true or not. The analysis followed the five steps presented before.

Application: hip implant

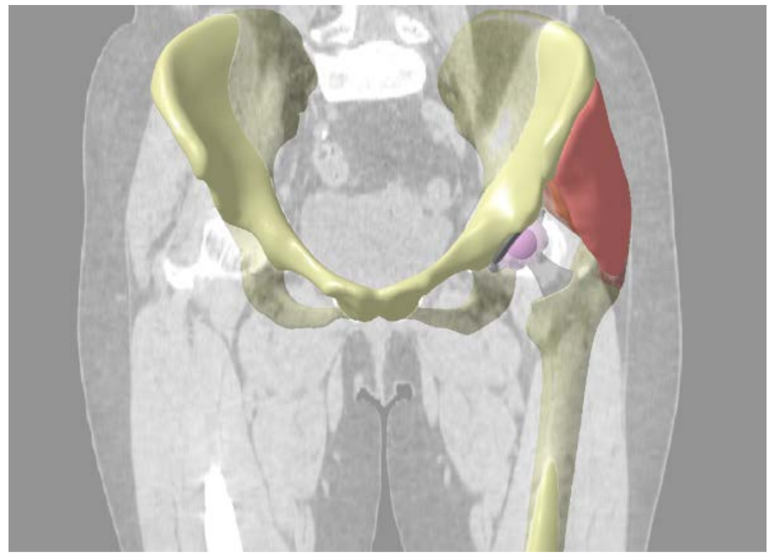
1. Geometry (and density ρ) of the femur

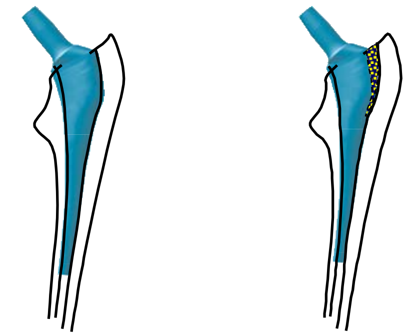


The CT images of a patient are segmented so that a volume of the femur can be obtained. In parallel, the bone density distribution is obtained, as a correlation between density and mechanical properties of the bone can be done. With this approach a precise map of the femur mechanical properties can be obtained.

Application: hip implant

1. Geometry (and positioning) of the implant





Cortical leaning

Trabecular leaning

The stem needs to be virtually placed in the femoral medullary cavity. This is done following a surgical planning under the guidance of a surgeon. In this particular picture, a fusion of CT (used to visualise hard tissues such as bone) and MRI (used to visualise soft tissues such as bone) images are obtained. The effect of two surgical techniques on micromotions and bone remodeling are evaluated: cortical vs trabecular leaning of the implant.

Application: hip implant

2. <u>Constitutive laws</u> (linear elastic isotropic for bone and implant)

$$\boldsymbol{\sigma} = \lambda(\mathrm{tr}\,\boldsymbol{\varepsilon})\mathbf{I} + 2\mu\boldsymbol{\varepsilon}$$

For bone:

$\lambda = \lambda(\rho)$

$\mu = \mu(\rho)$

For implant (Ti6Al4V):

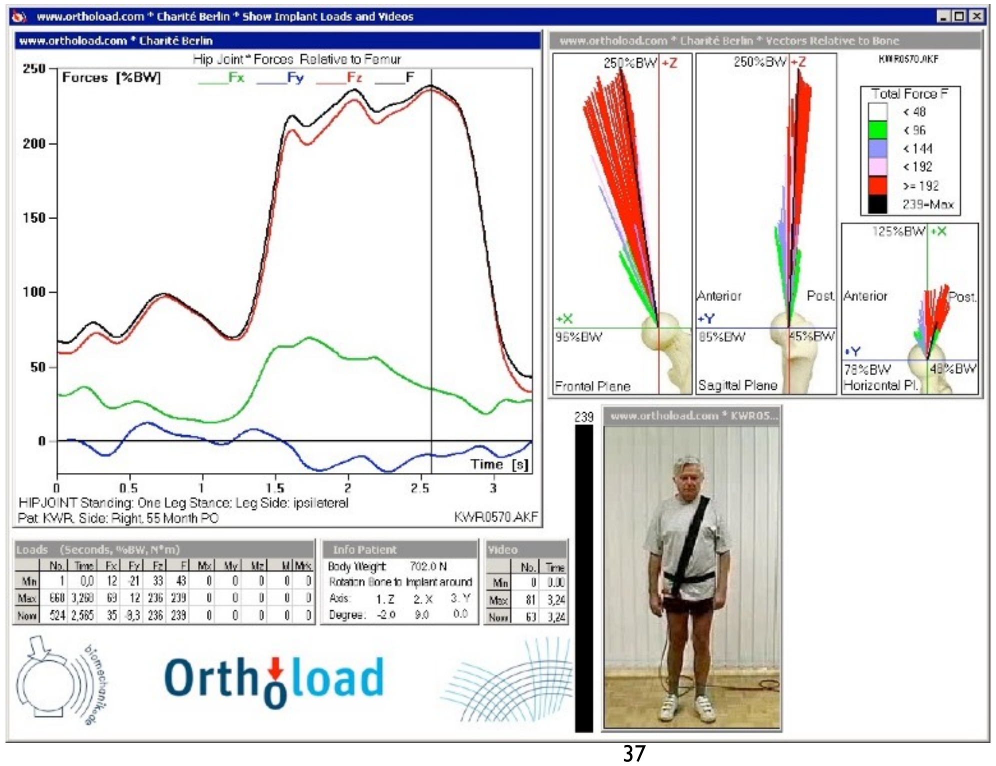
$\lambda = 89$ GPa

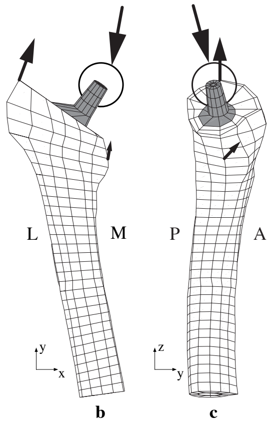
$\mu = 42$ GPa

As we are interested to evaluate the behaviour of the bone in its physiological mechanical range, we consider its behaviour as linear elastic isotropic. The values of the Lamé parameters depend on bone density and is then directly obtained with the CT images. The distribution of the bone density will represent the initial condition. For the metallic implant made of an Ti_6Al_4V alloy, as most of metallic material, linear elastic isotropic behaviour is a very good approximation of its mechanical behaviour. Its Young's modulus and Poisson ratio are transformed into the corresponding Lamé parameters.

Application: hip implant

3. Boundary conditions

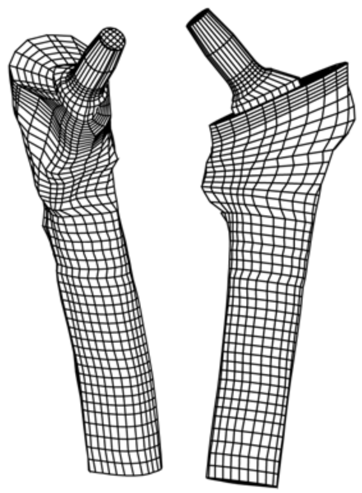




The loading of the implant can be obtained from the hip contact force calculated during the class or obtained from published scientific work or from the orthoload.com database. This kind of information is then transformed into boundary conditions (force applied on the implant in the example) which will be applied in the numerical model of the bone/implant.

Application: hip implant

4. Meshing

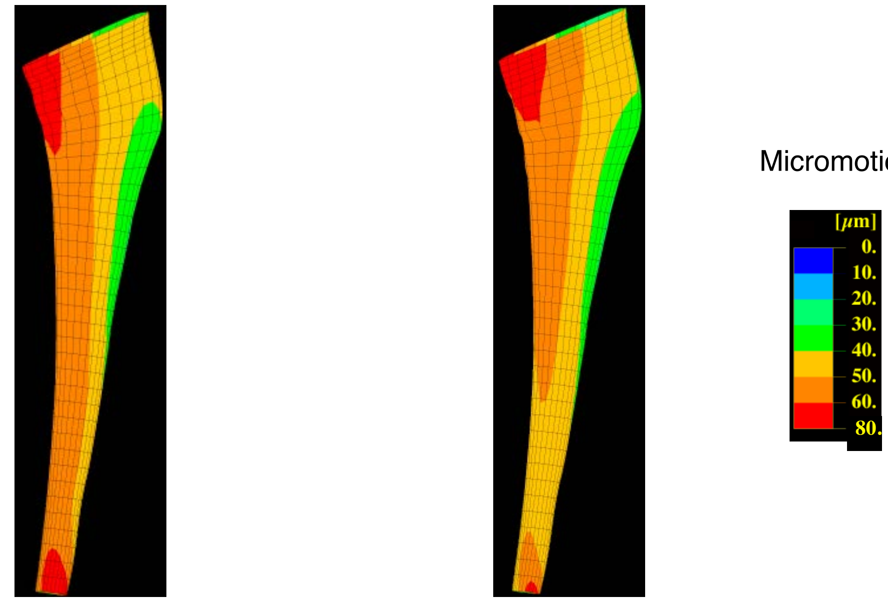


source: Terrier, PhD thesis, EPFL, 1999

The bone and the implant are meshed prior to the numerical resolution. This procedure is performed semi-automatically by specific softwares.

Application: hip implant

5. <u>Resolution</u> (micromotions post-surgery)



Cortical leaning

Trabecular leaning

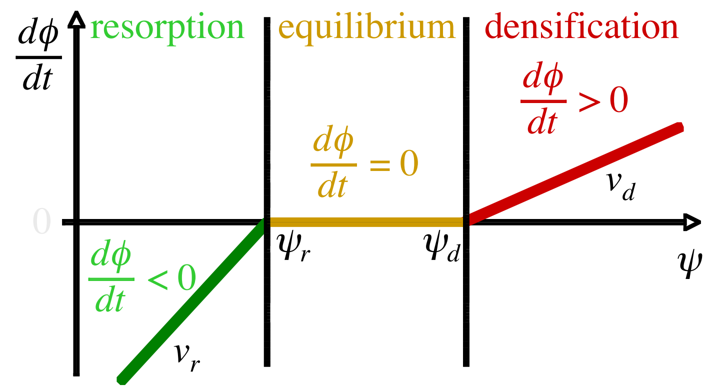
The numerical resolution is performed with usually open source or commercially available softwares. A list can be found at: http://en.wikipedia.org/wiki/List_of_finite_element_software_packages.

The distribution of the micromotions amplitude between the implant and the surrounding bone is calculated in the situation corresponding to 1 week post-surgery (initial condition). It can be observed for the two surgical techniques (cortical or trabecular leaning) that micromotions amplitude can be higher than 70 μm. From the literature, micromotions around 30 μm seems to favour bone tissue formation, while micromotions above 100 μm would favour fibrous tissue formation. No clear difference can then be observed between the two techniques immediately after the surgery. However, the situation immediately after surgery (referred to primary stability) is only one part of the problem. The long term outcome of the implant (referred to secondary stability) should also be evaluated. A bone remodeling model is then used to evaluate the situation after 2 years.

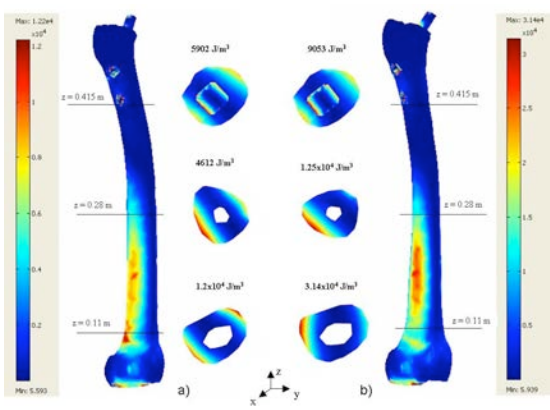
Application: hip implant

5. Resolution (strain energy density)

Bone remodeling model



Strain energy density [J/m³]



walking

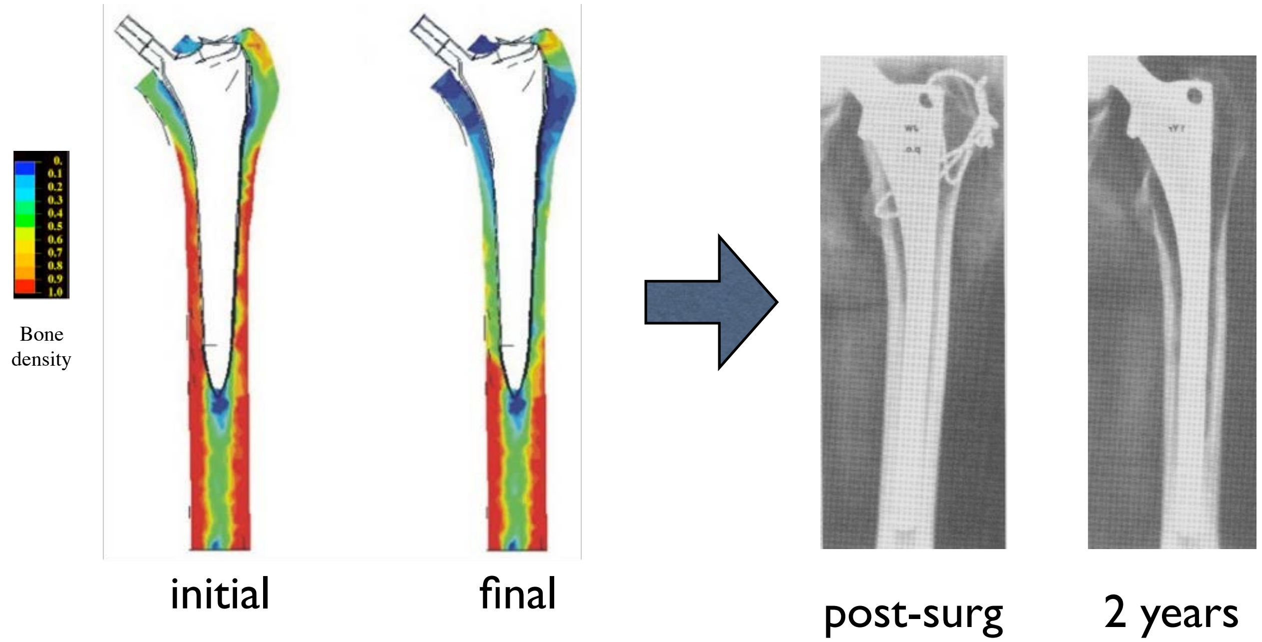
stair climbing

source: Andreaus U. et al. Biophys. and Bioengin. Letters (2008)

From the calculation of the stress and strain in the bone induced by the loading of the implant, a map of strain energy density (roughly σ multiplied by ε) around the implant can be obtained. This strain energy density can be used as a measured of the mechanical stimulus Ψ sustained by the bone and correlated to a bone remodeling model. If the mechanical stimulus Ψ is lower than a threshold value Ψ_r, a bone resorption will be induced (decrease of the bone density), while if it is above a threshold value Ψ_d, a bone formation will be induced (increase of the bone density).

Application: hip implant

5. Resolution (bone remodeling)

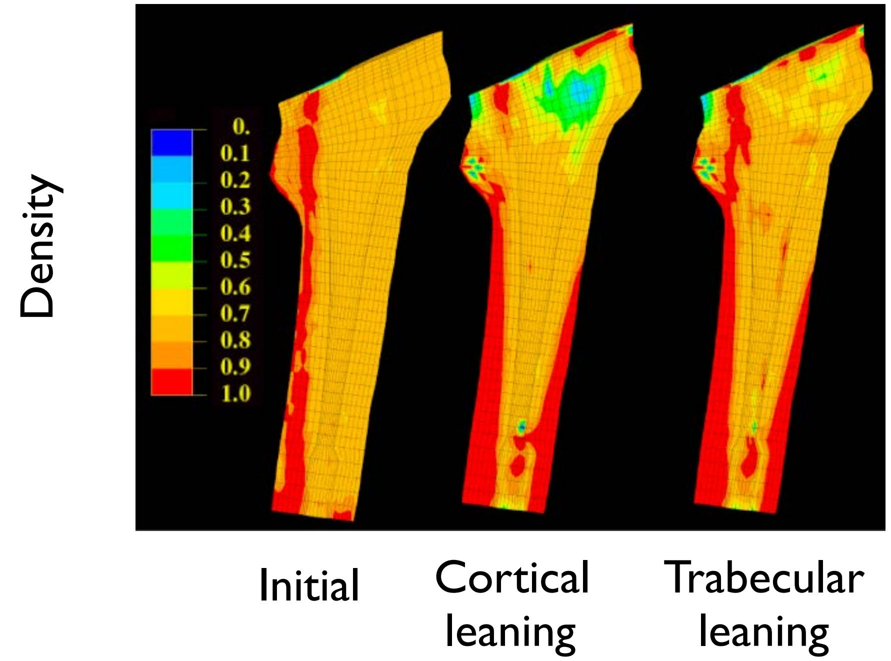


source: Leibniz University

As a validation, the results of the numerical simulation for the density evolution is compared to the clinical situation. It can be observed that the distribution of the bone density for the simulation is qualitatively similar to the clinical situation after 2 years. The bone remodeling model can then be used to compare the results for the cortical and trabecular leaning.

Application: hip implant

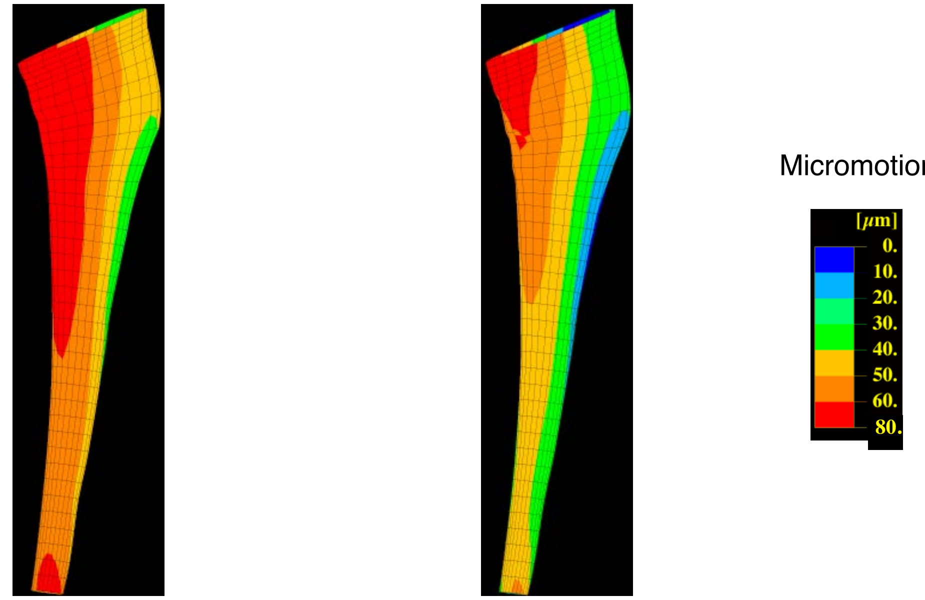
5. Resolution (Evolution of density distribution (2 years))



The cortical leaning seems then to induce a higher bone resorption in the proximal femur.

Application: hip implant

5. Resolution (micromotions 2 years)



Cortical leaning

Trabecular leaning

The calculation of the micromotions is repeated with the bone density corresponding to 2 years of evolution (obtained from the previous slide). It is then clear that the secondary stability is better for the technique using the trabecular leaning than the cortical leaning. This kind of results would be difficult to obtain with clinical data as comparison between techniques are always biased by the fact that different surgeons, patients, rehabilitation conditions, ... so that the parameters would never be the same.

Bone remodeling

i) Mechanical aspect

ii) Hormonal aspect