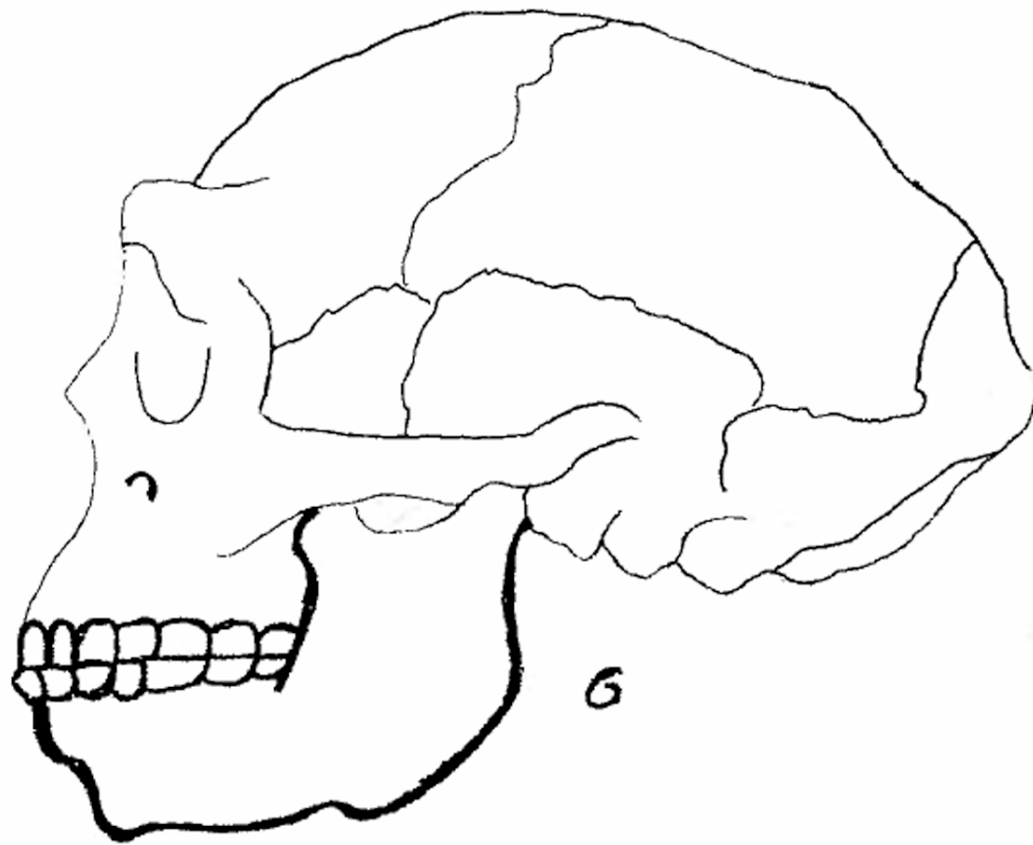


Bone remodeling and drug delivery system

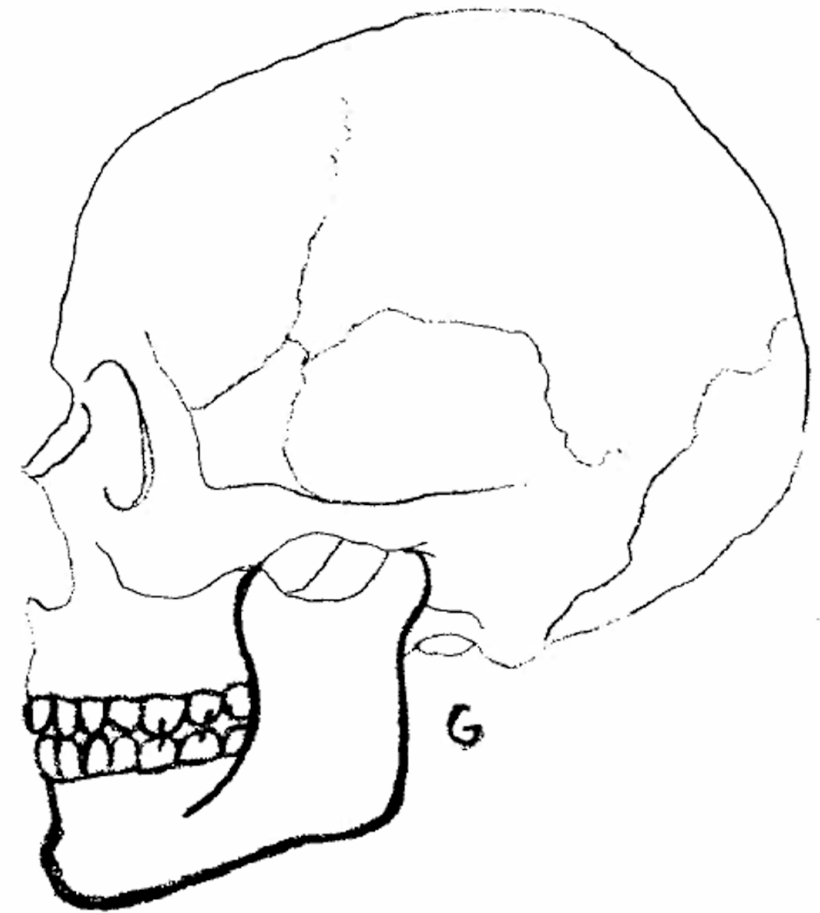
Prof. Dominique Pioletti
Laboratory of Biomechanical Orthopedics
EPFL

The tissues adapt to their mechanical environment: several time scales

Homo sapiens

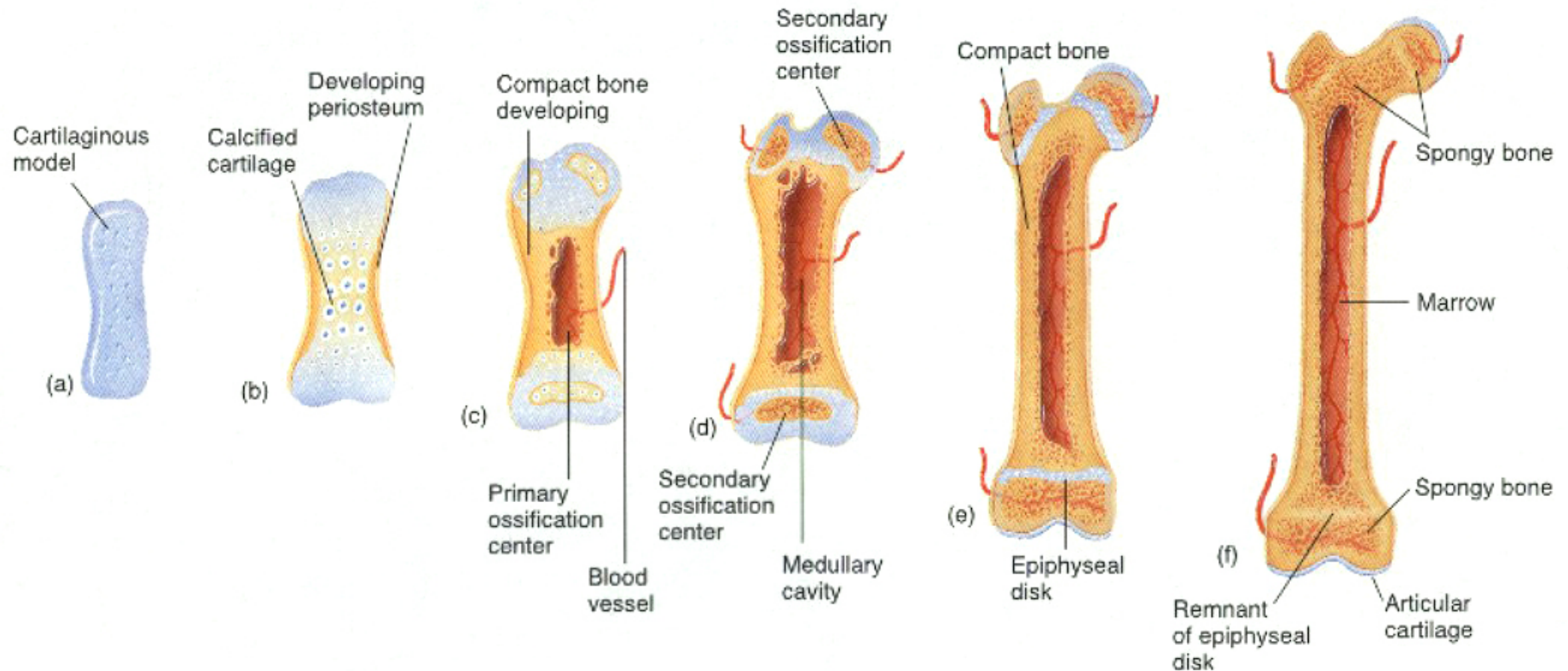


Homo erectus



-> thousands of years

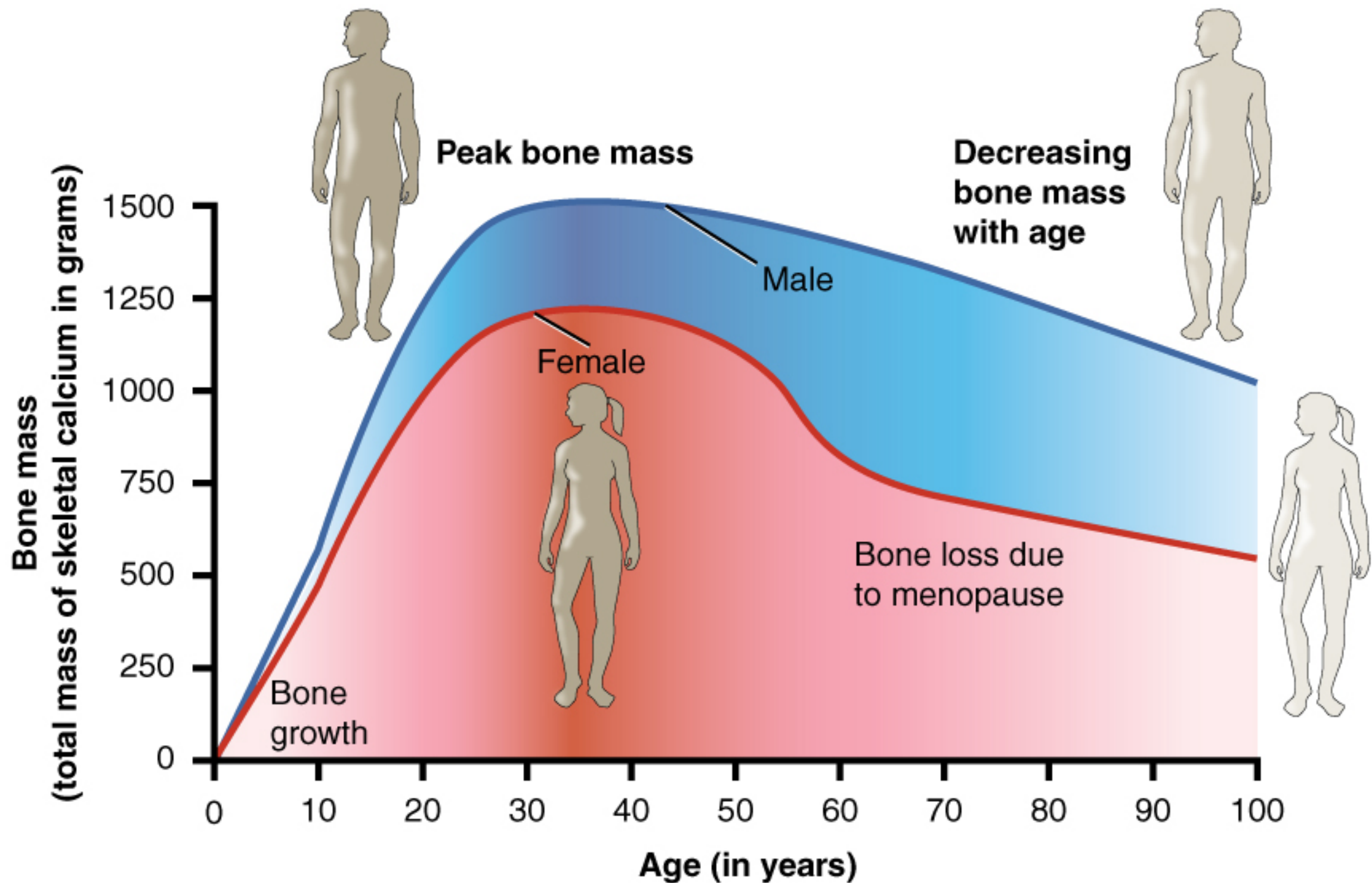
The tissues adapt to their mechanical environment: several time scales



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

-> 100 years

The tissues adapt to their mechanical environment: several time scales



The tissues adapt to their mechanical environment: several time scales

Femur of mouse

Normal W/O mech.
 constraint

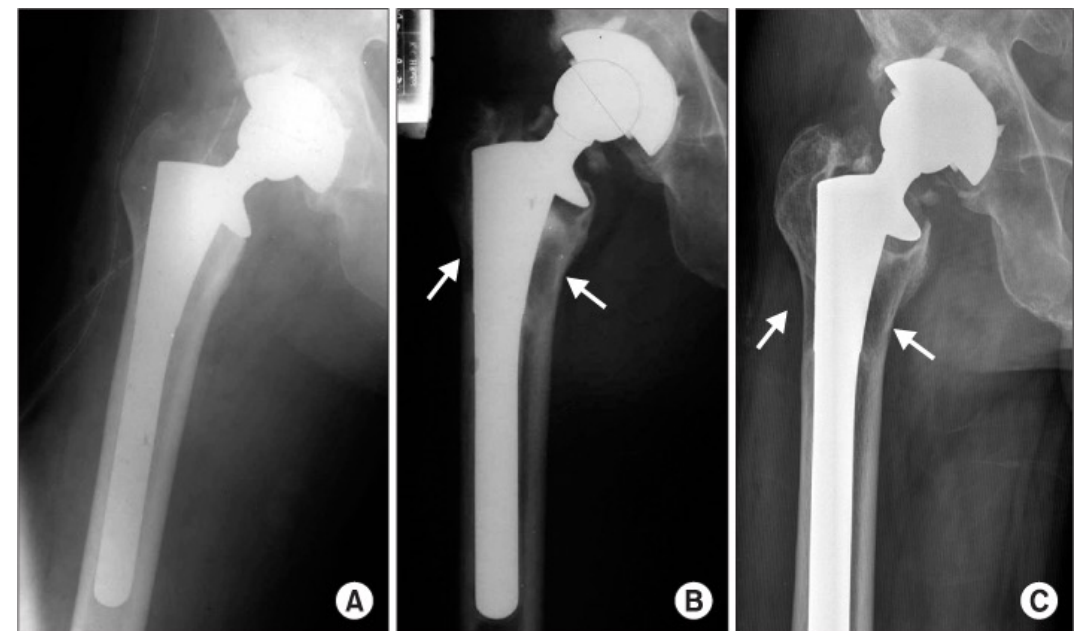


Hip Implant

Post-op

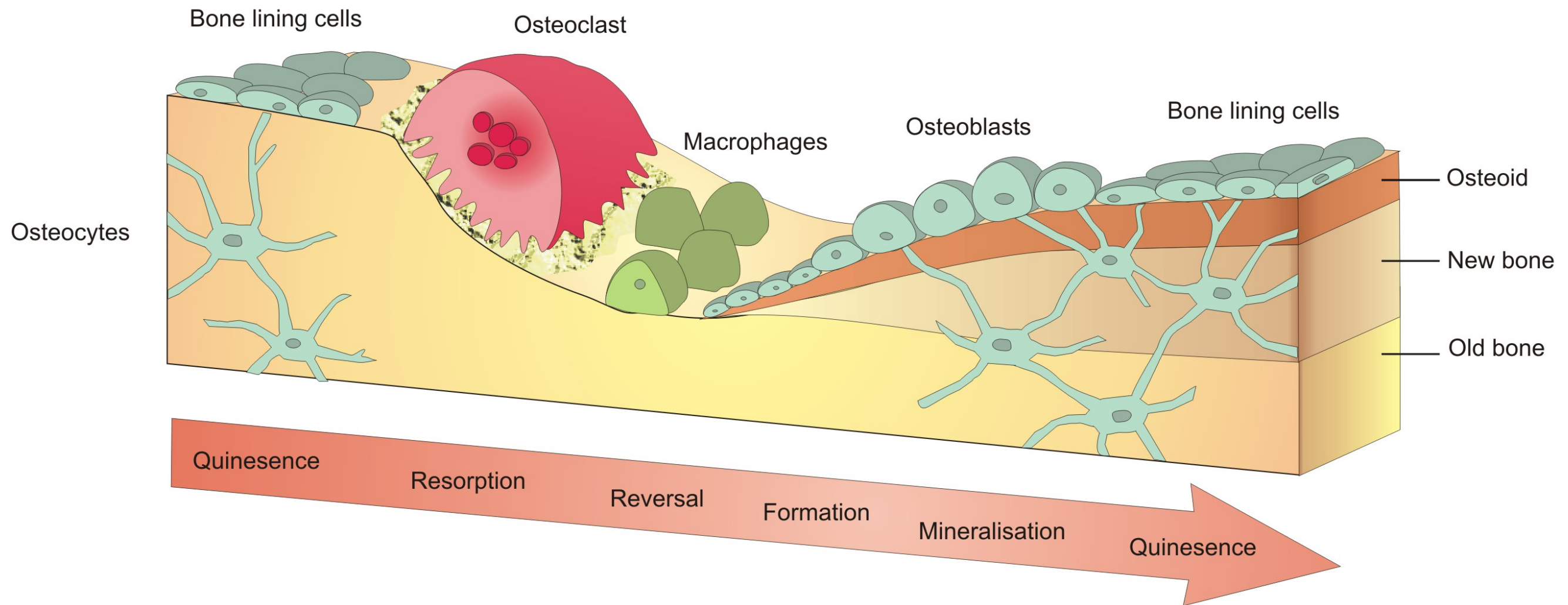
2 years

7 years

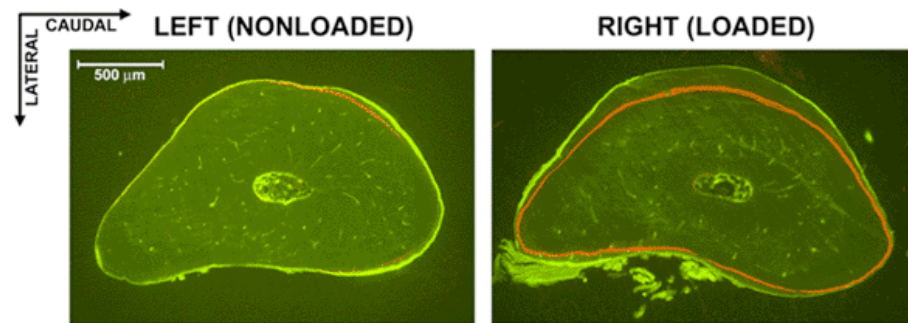
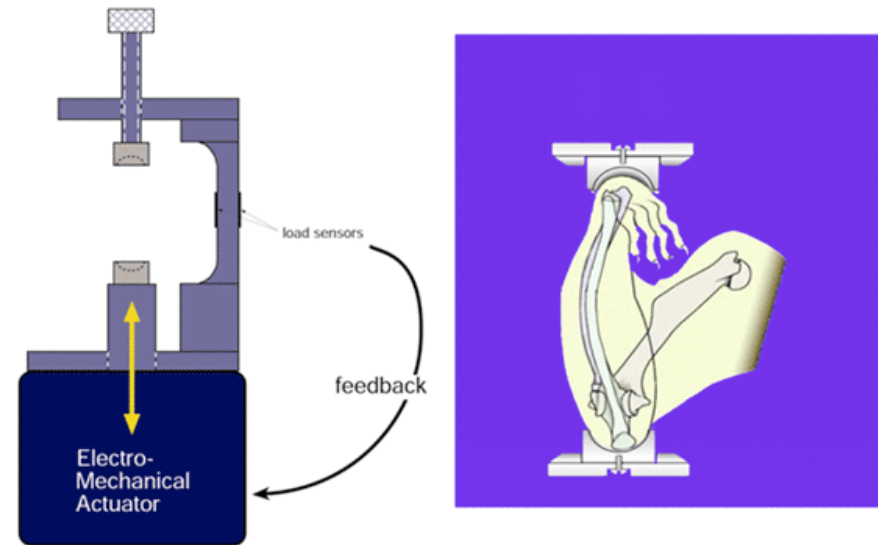


-> months to years

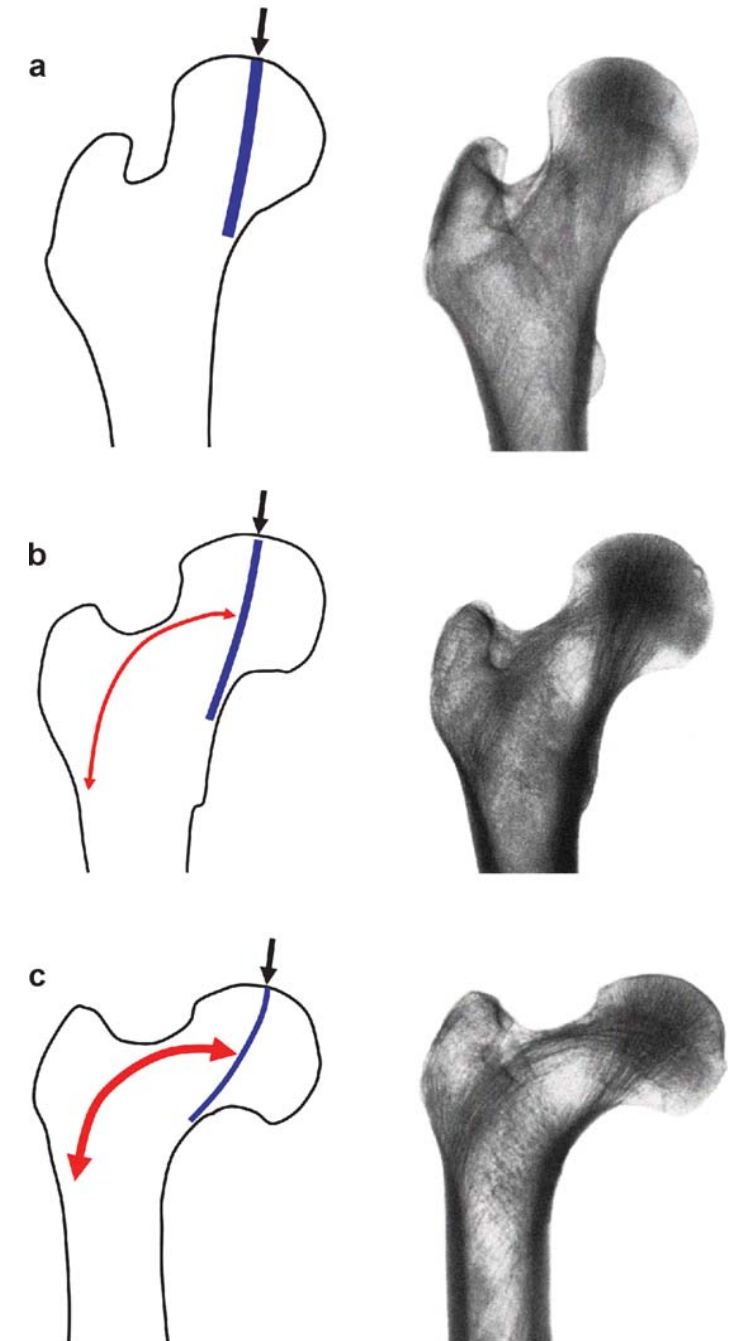
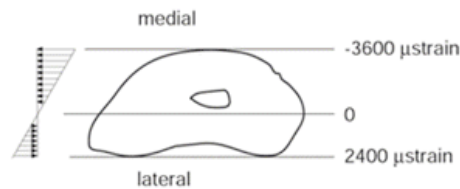
During remodeling, the cells control the structure and composition of the bone



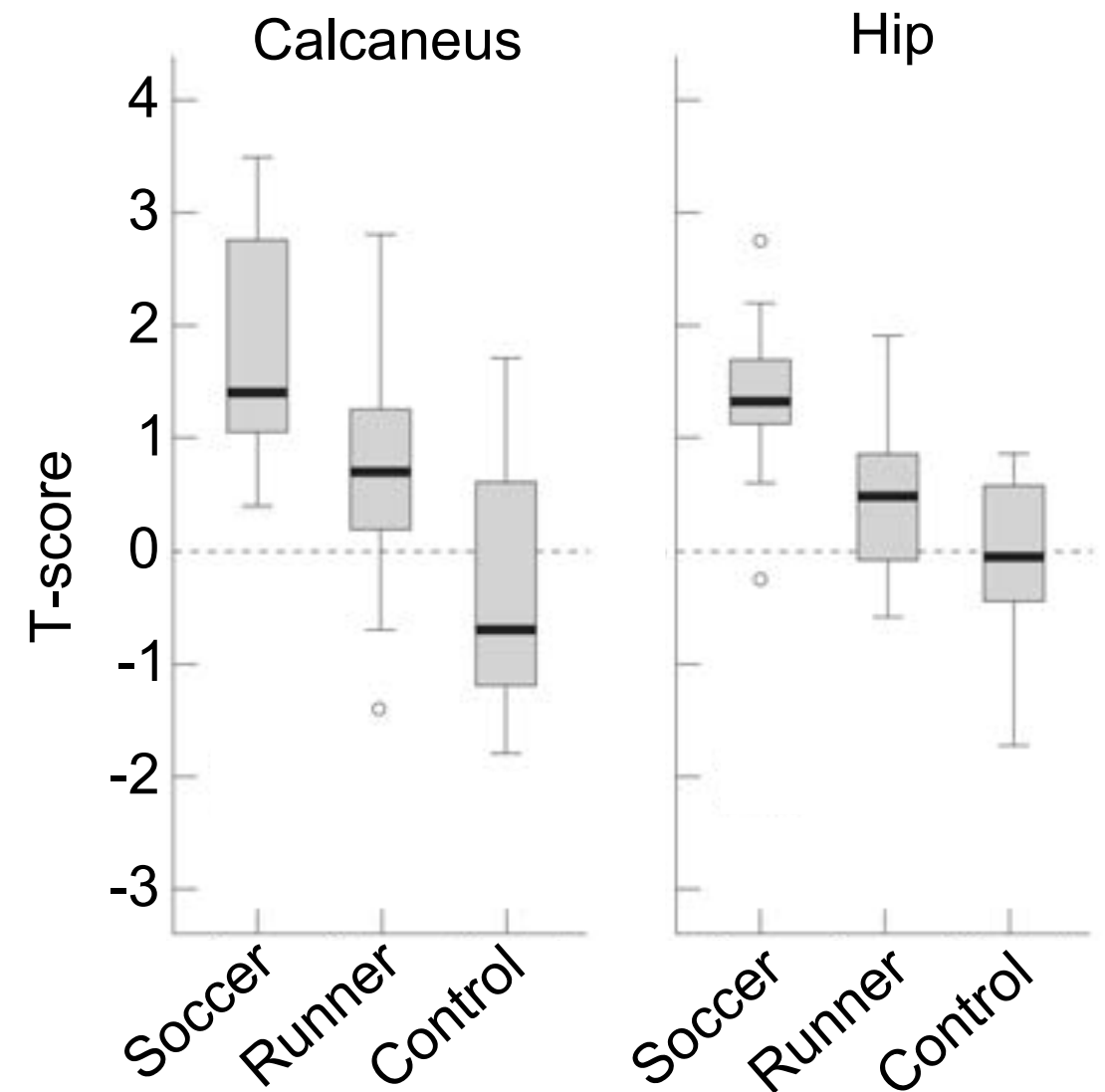
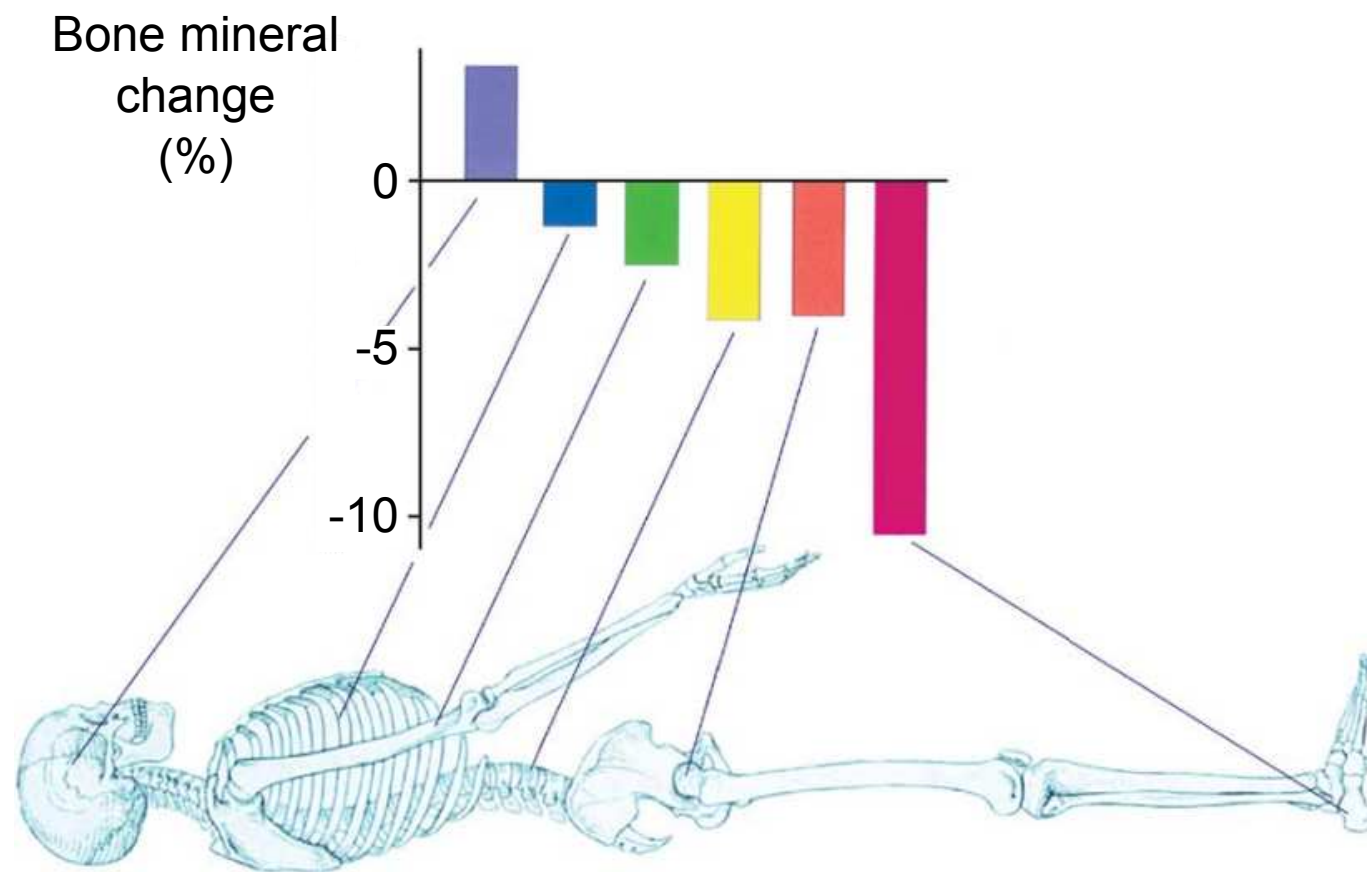
The remodeling affects the shape of the bones (external remodeling), ...



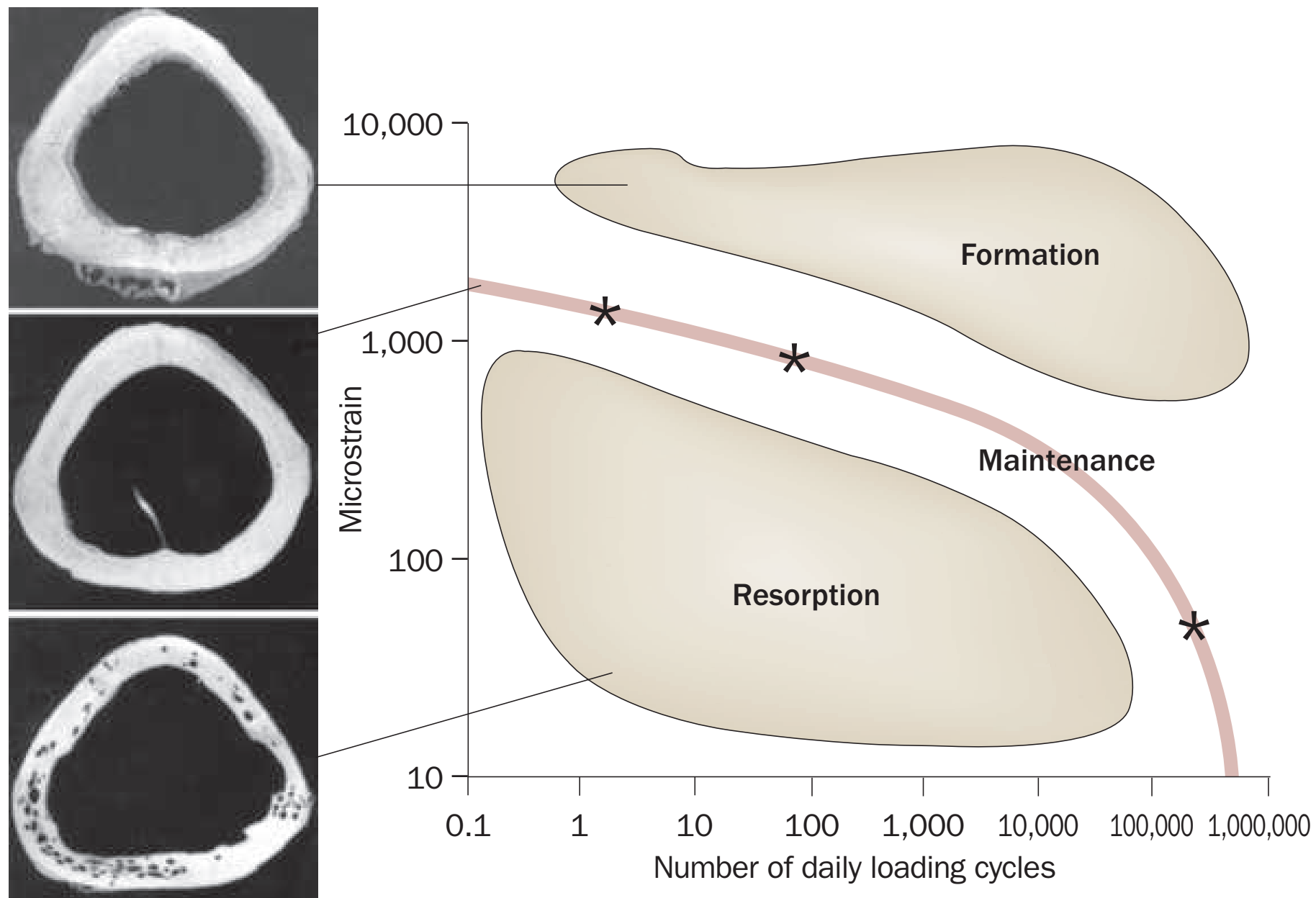
Bone is formed where the biomechanical demands are greatest



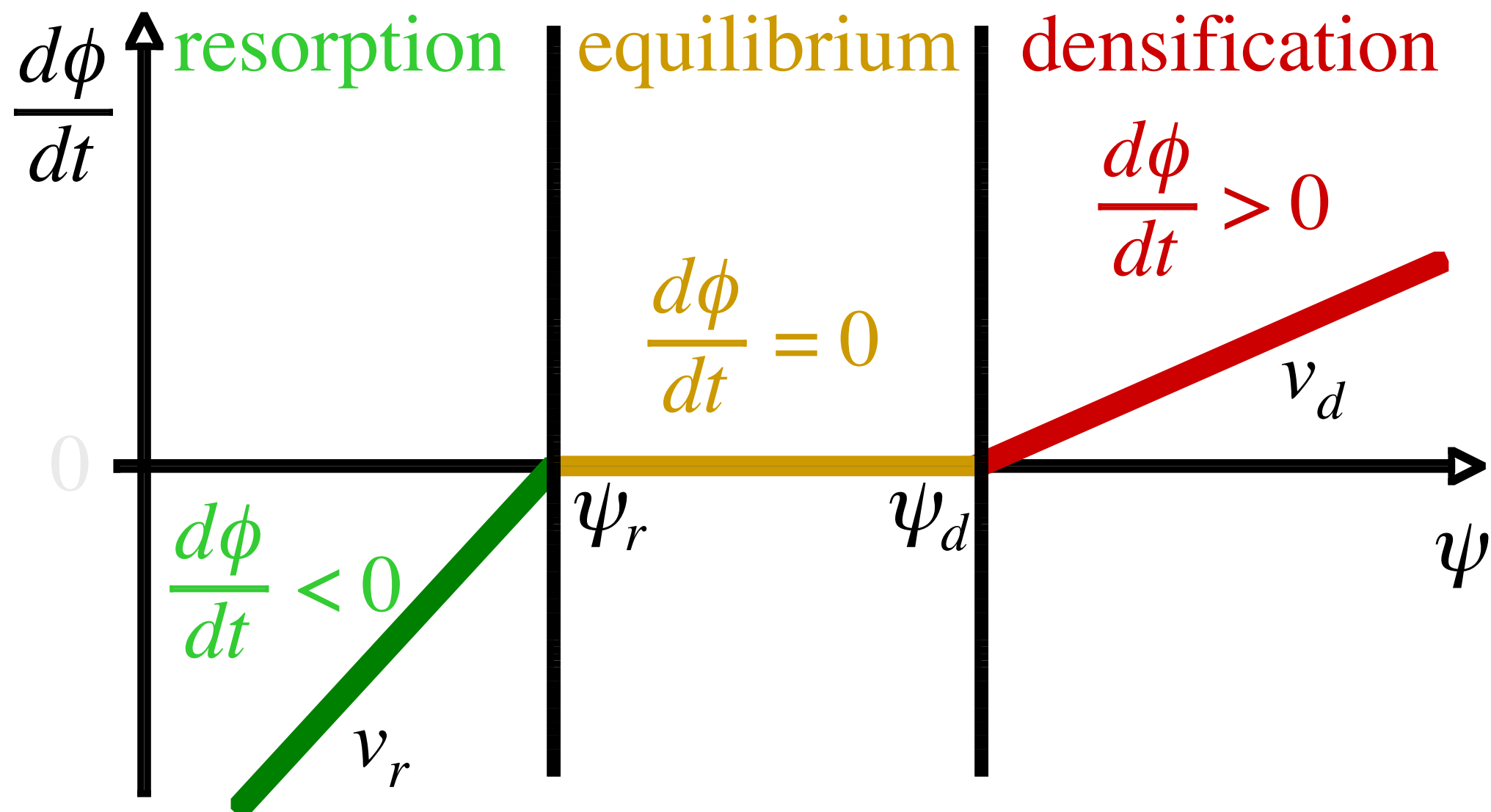
as well as their density (internal remodeling)



Differential effects of mechanical loading on bone remodeling



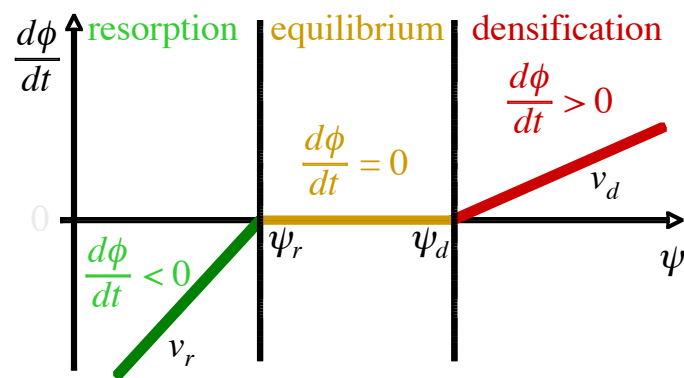
“Mechanical stimulus” has been proposed to drive the bone density evolution



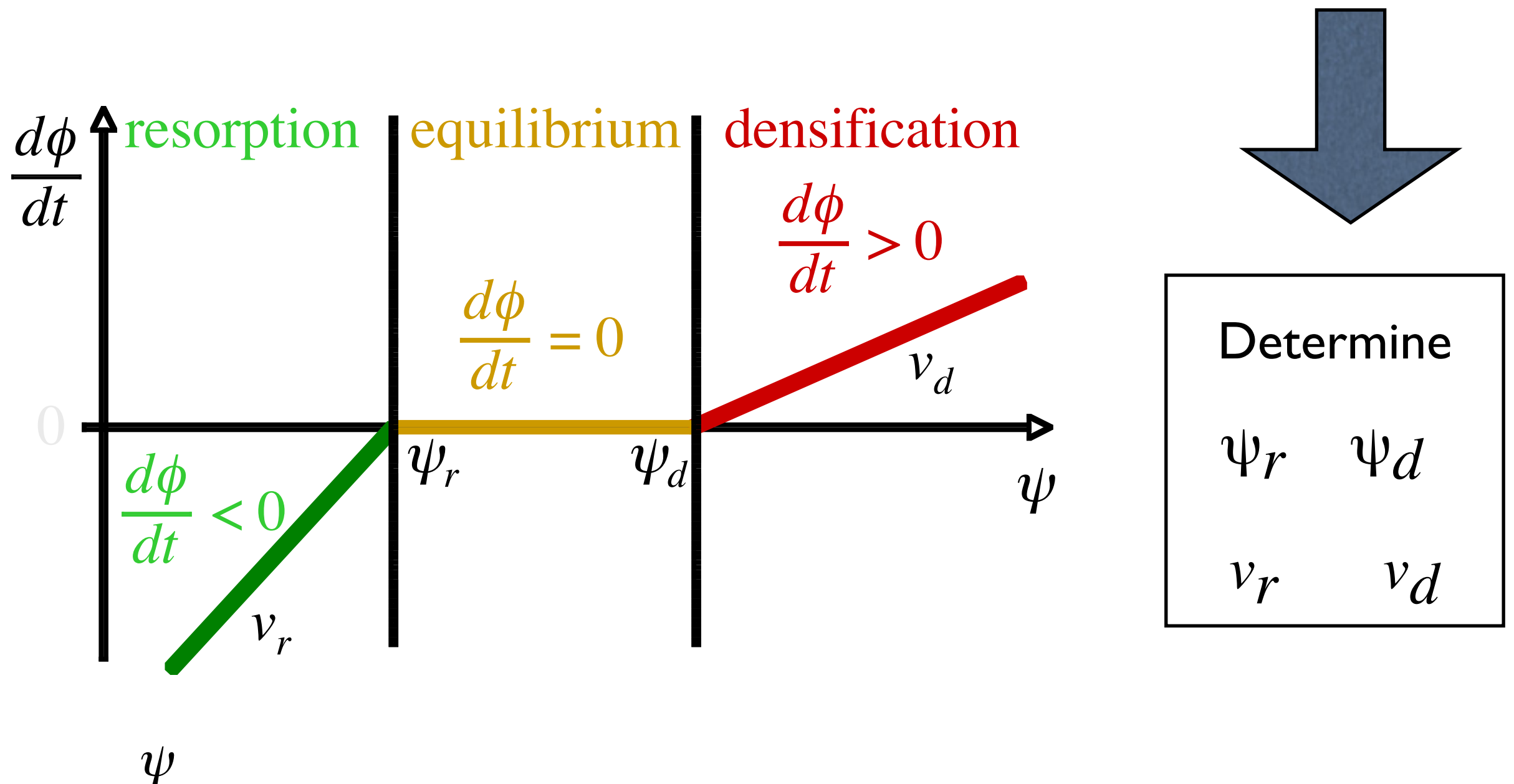
Ψ : mechanical stimulus (scalar invariant)

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

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

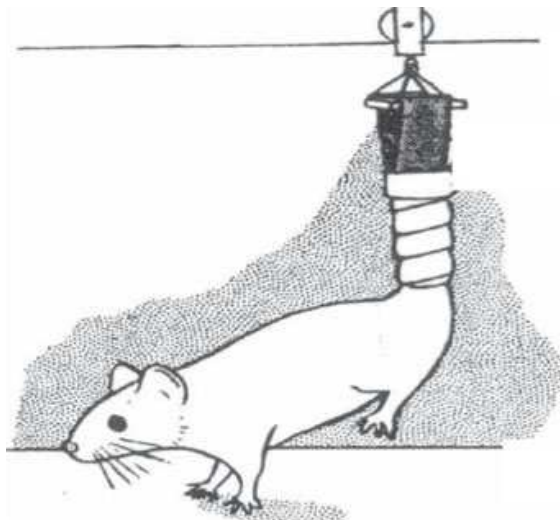


It is necessary to identify the parameters appearing in the evolution law

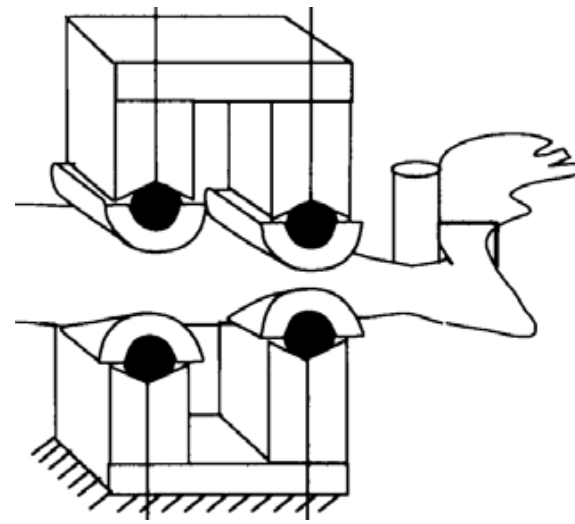


Ψ : mechanical stimulus (scalar invariant)

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



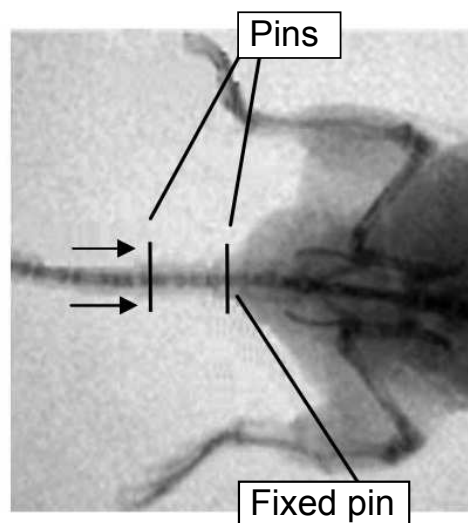
(a)



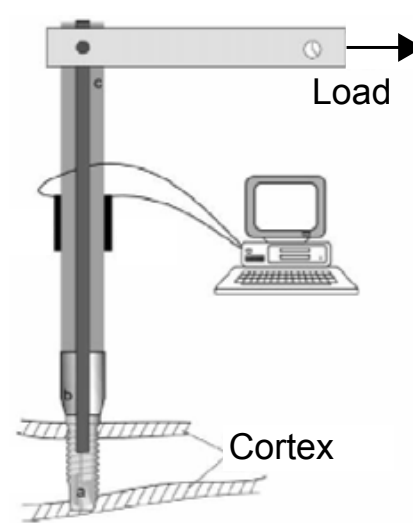
(b)



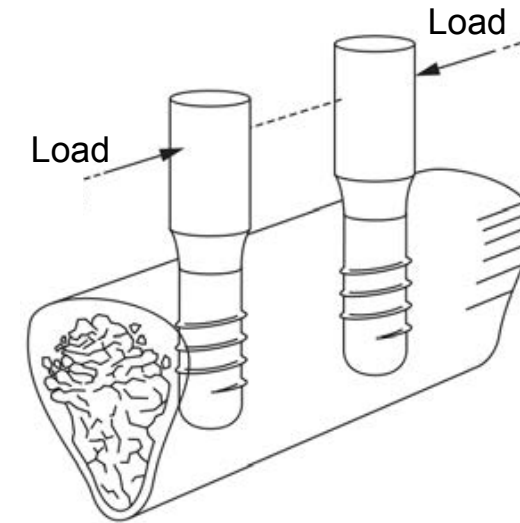
(c)



(d)

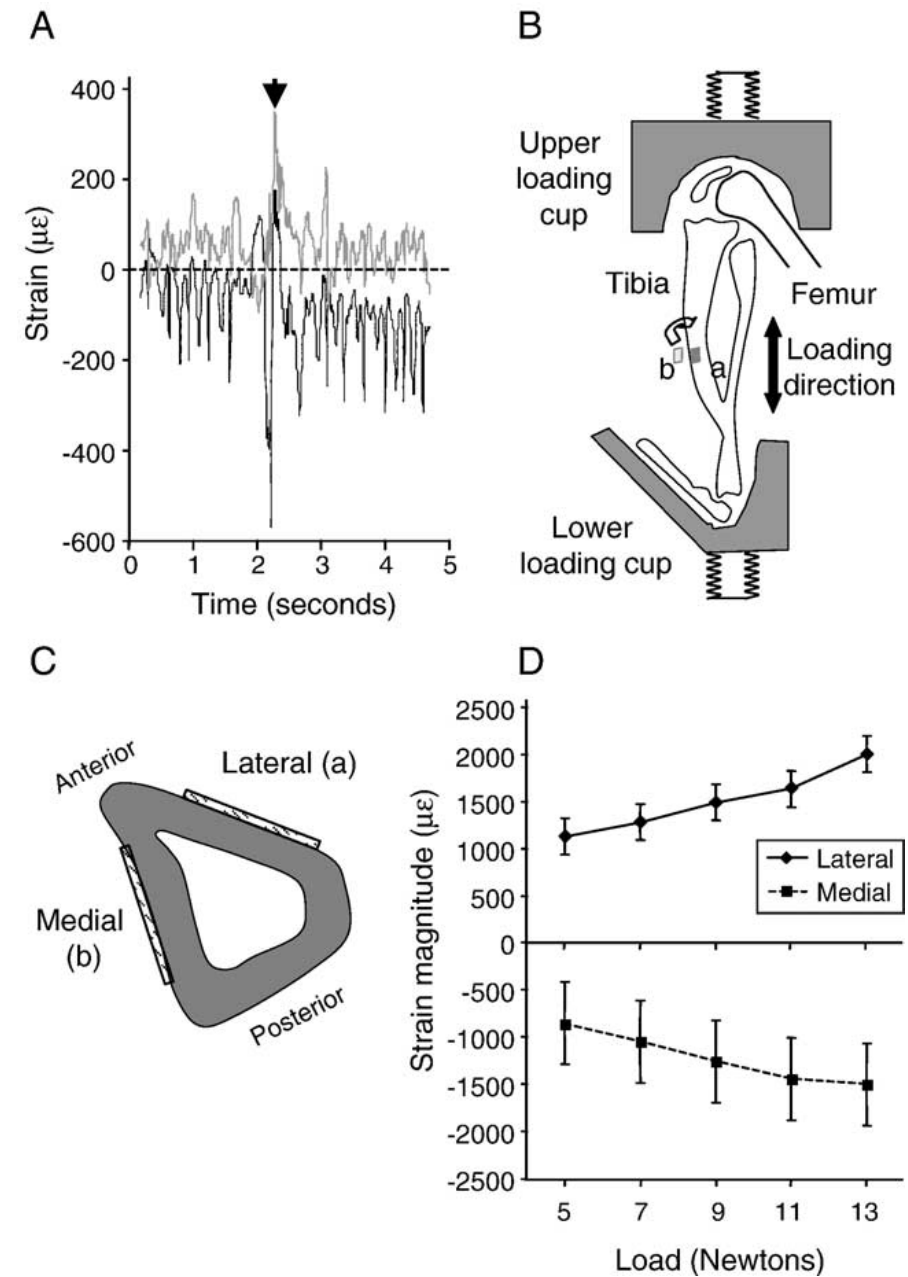
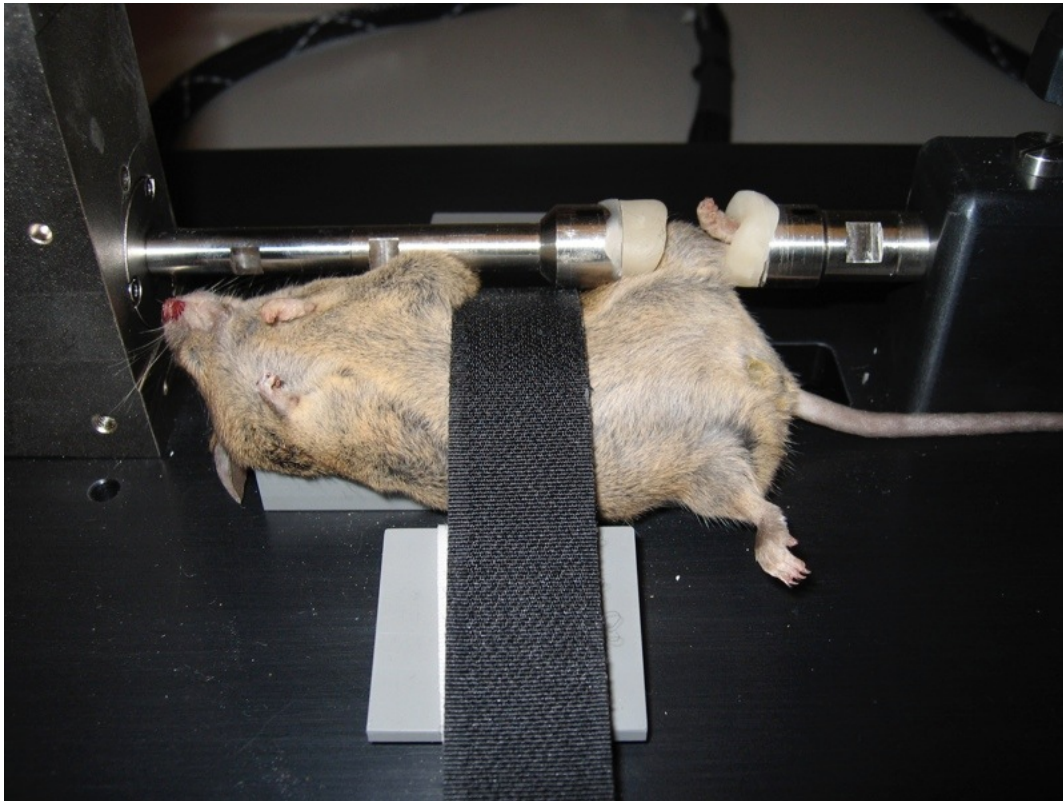


(e)



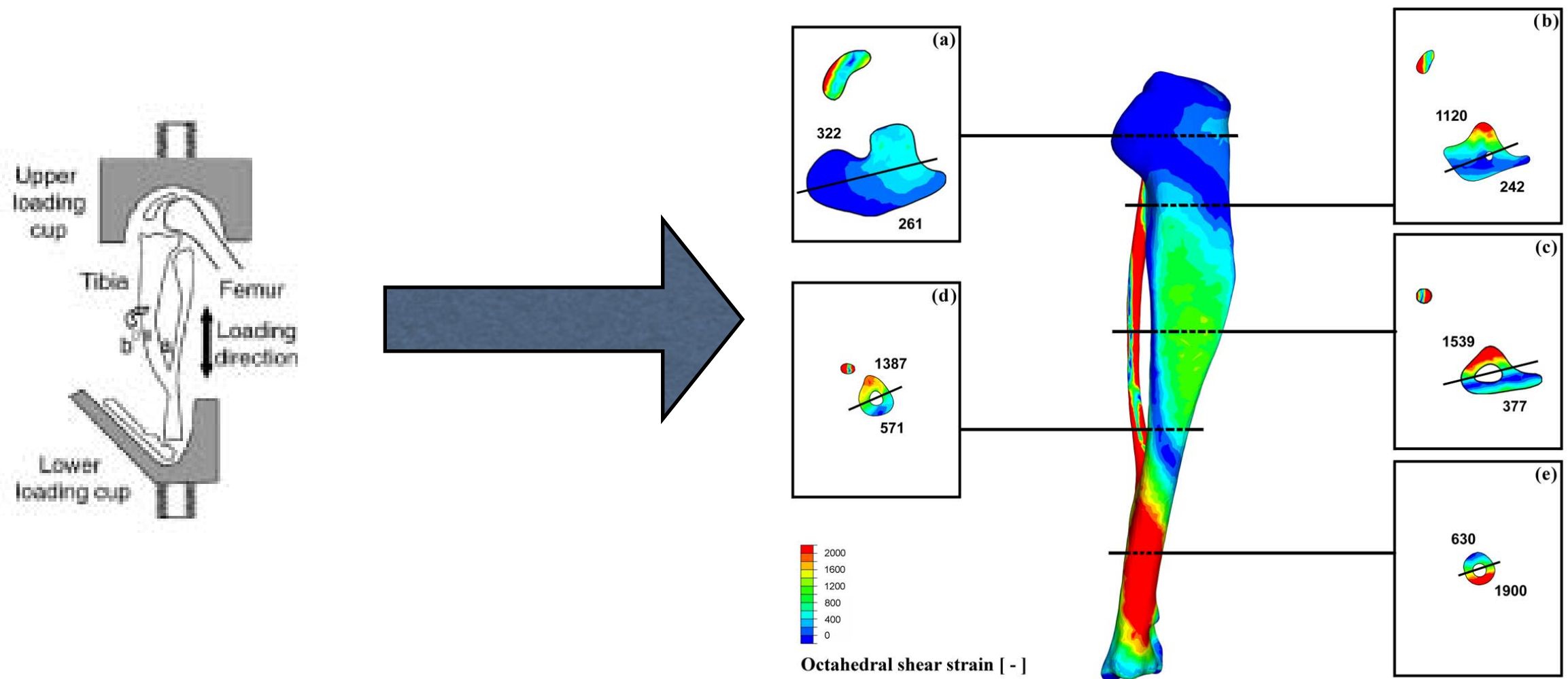
(f)

What is the meaning of “mechanical stimulus”?

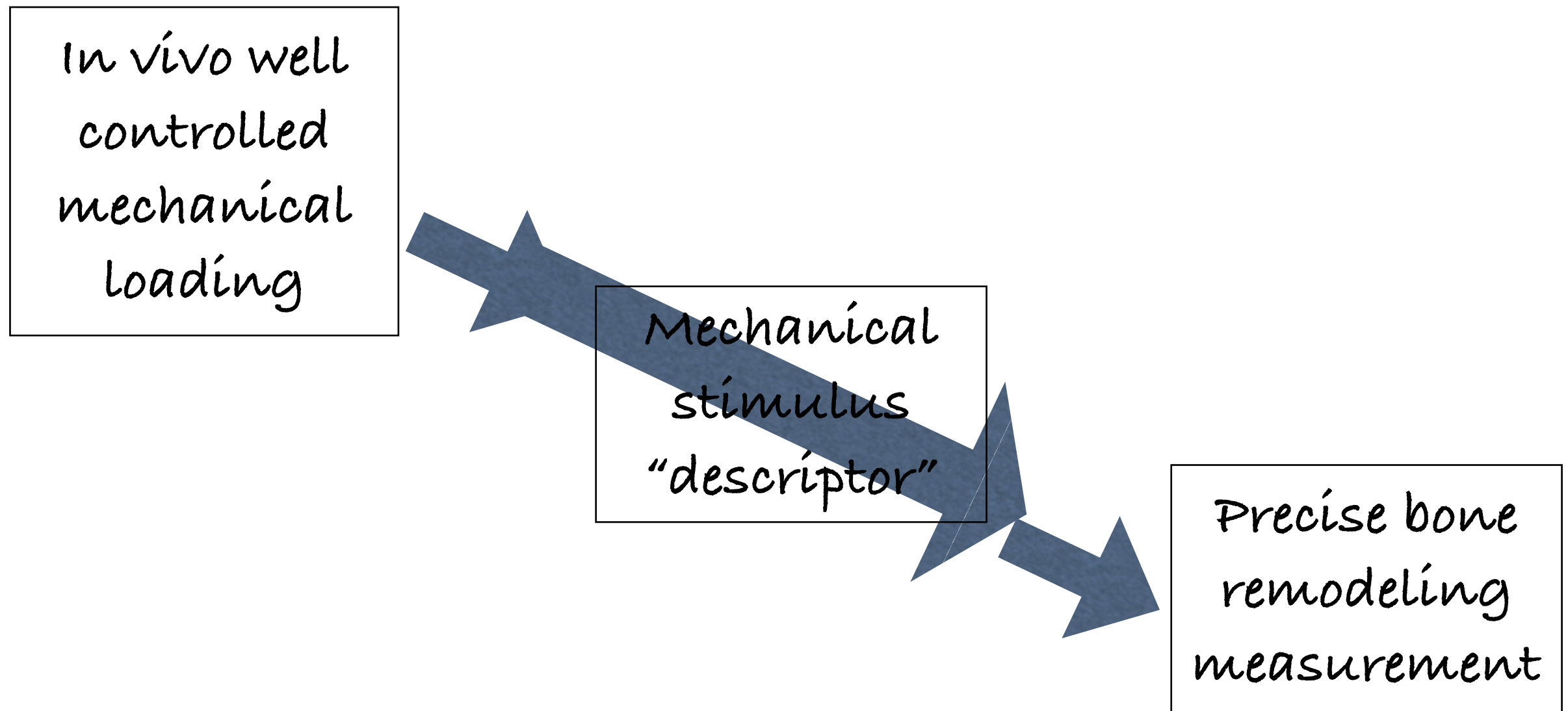


source: De Souza, Bone, 2005.

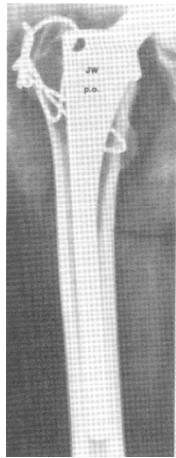
How the external loading can be correlated to the (internal) “mechanical stimulus”?



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



The model of remodeling is coupled with calculations of the constraints



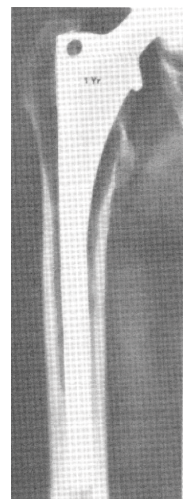
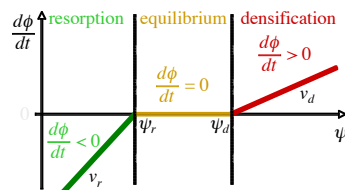
Initial density: ϕ_{init}

External force: F_{ext}

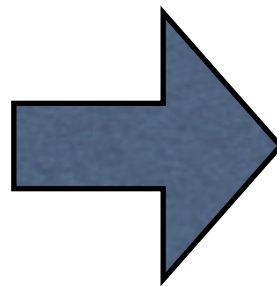
Constitutive law: $\sigma = \sigma(\phi, \epsilon)$

Mechanical stimulus: ψ

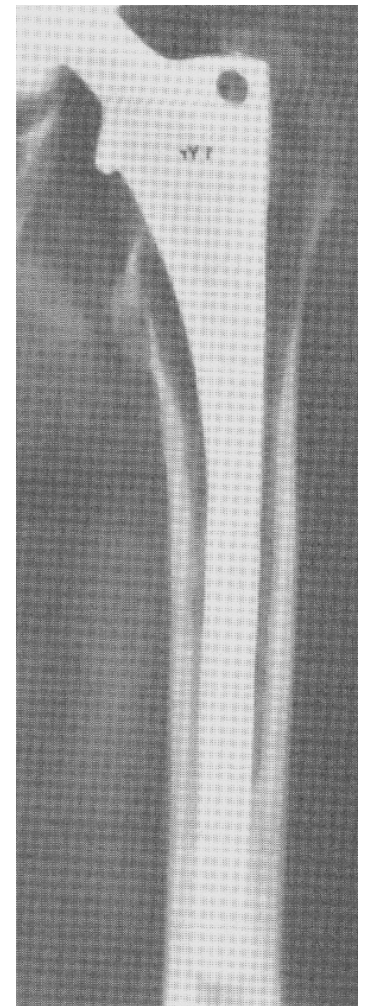
Density evolution: ϕ



Bone remodeling can then be calculated around implant

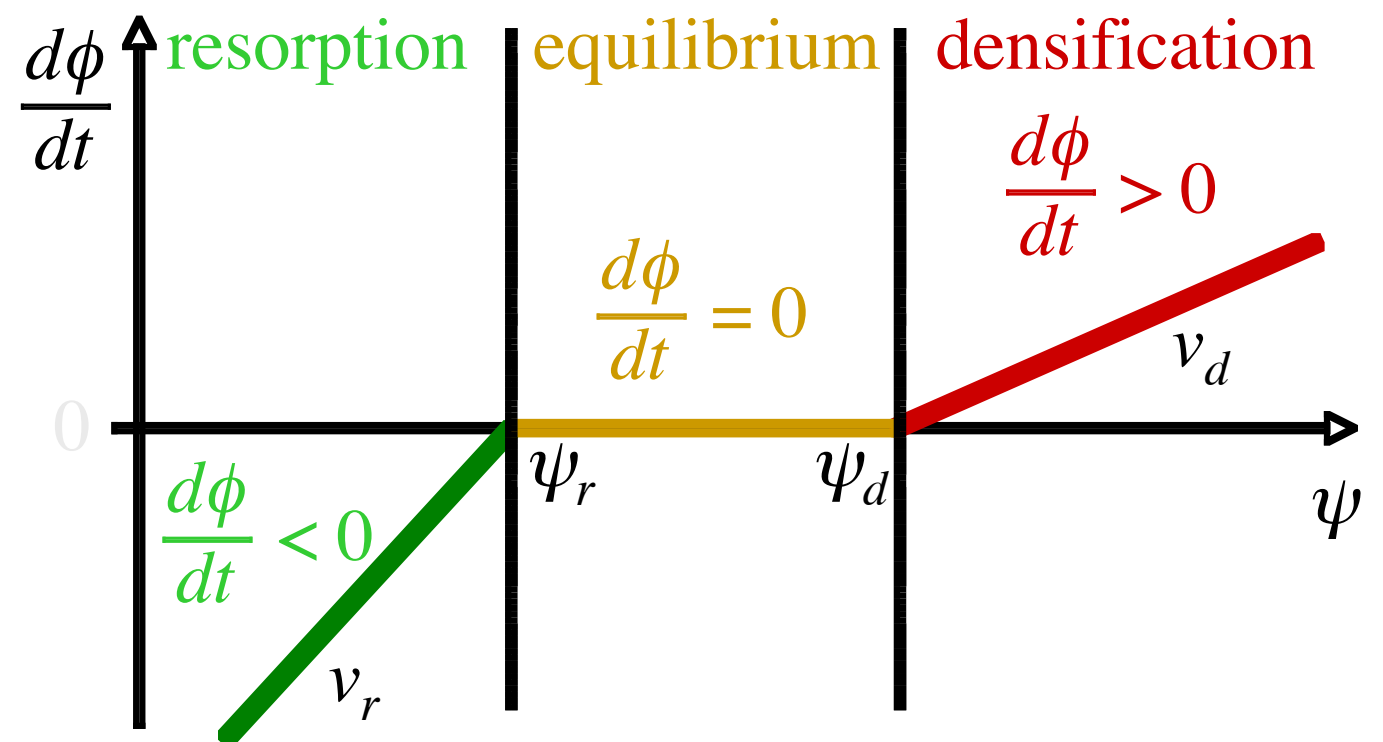
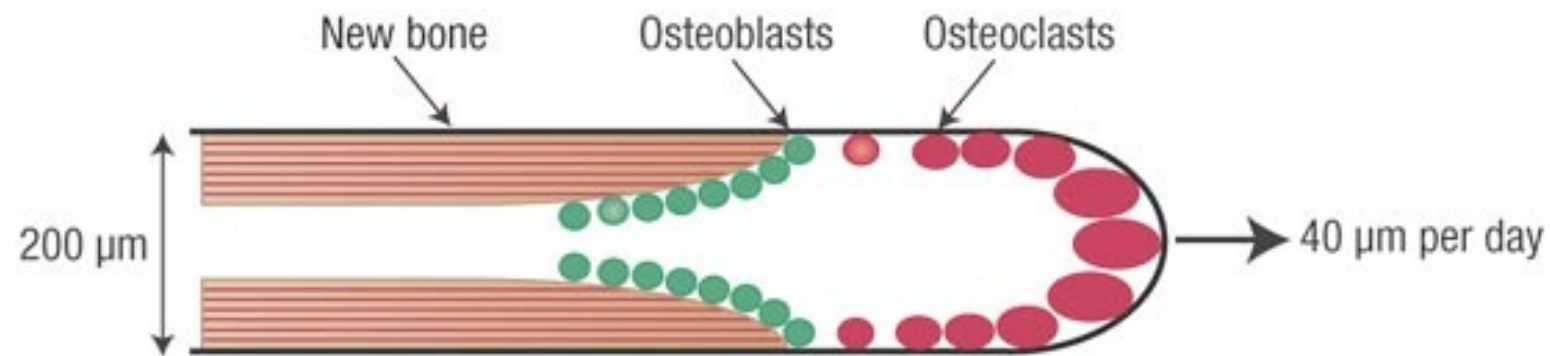


post-surg

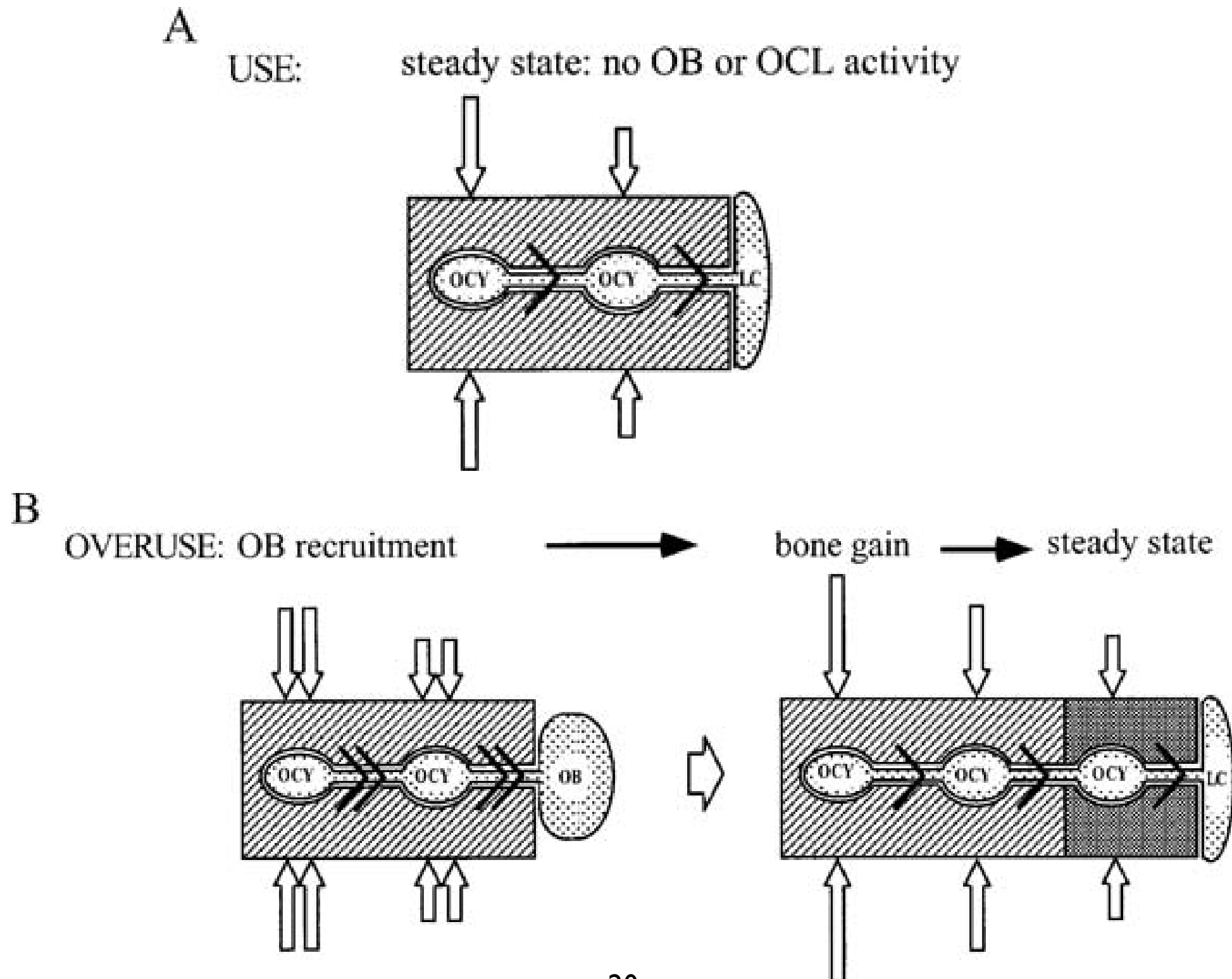


2 years

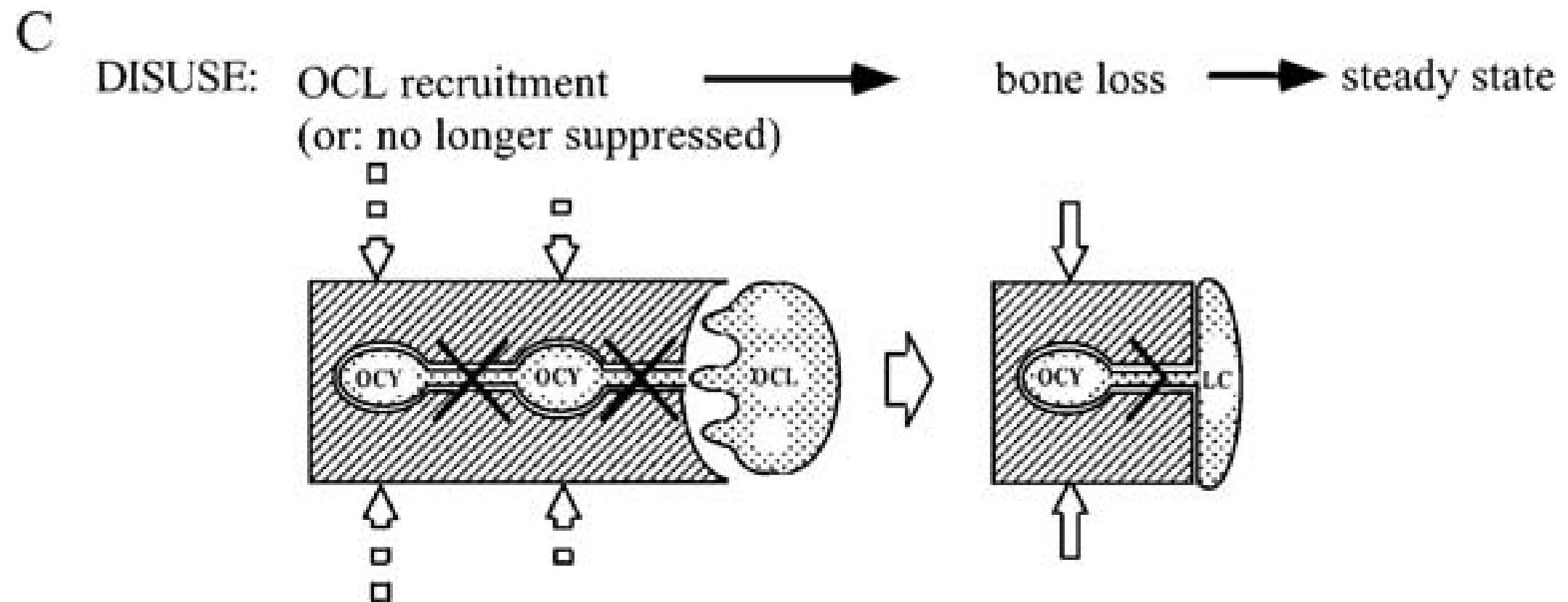
How can we link the biological and biomechanical description of bone remodeling?



A macroscopical description of mechanical effect in bone brings new insight



A macroscopical description of mechanical effect in bone brings new insight

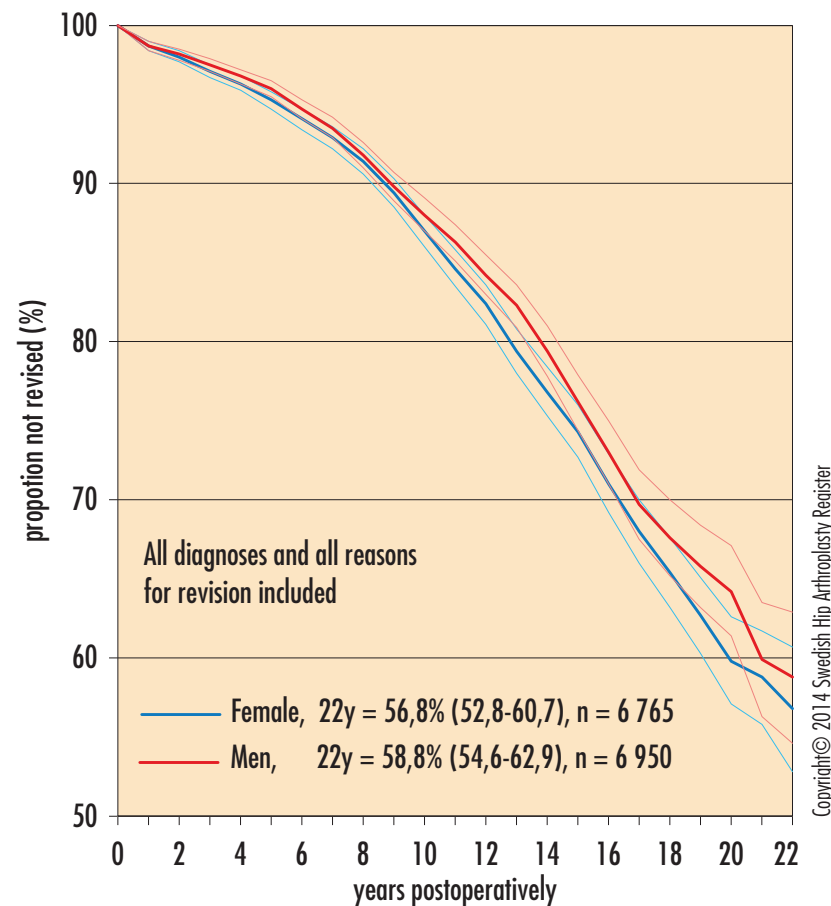


Why do we want to develop a new kind of hip implant?

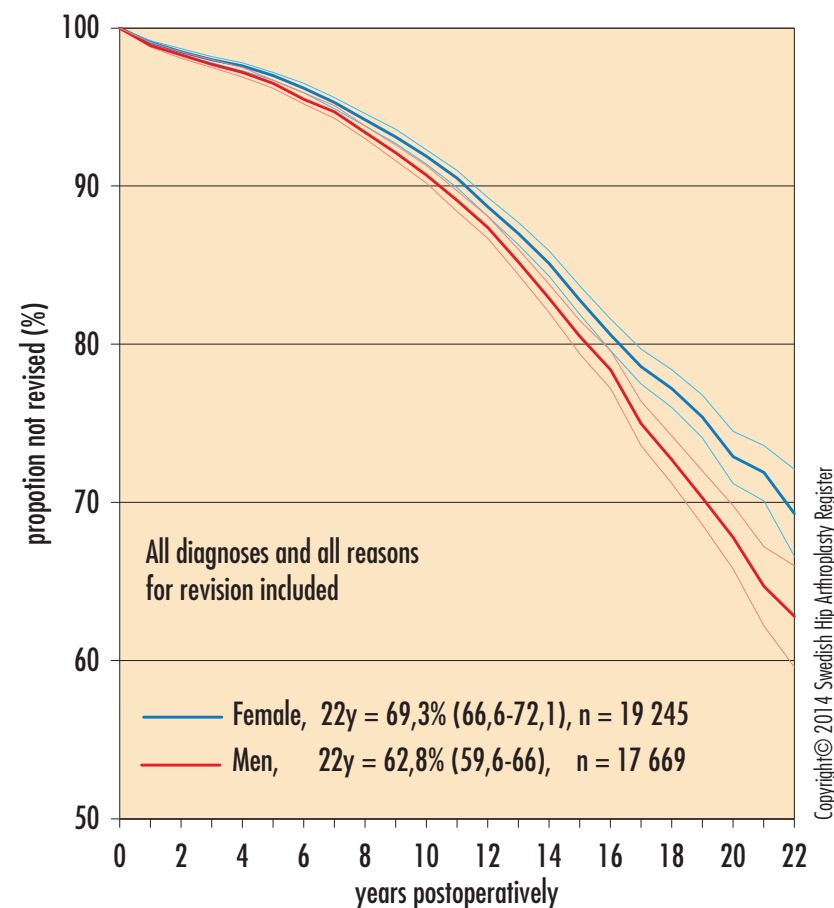
- Success rate is limited in some clinical situations
- All “classical” approaches have been tested
- “Functionalizing” implant to control bone remodeling

For younger patients, the failure rate of hip implant can reach 30% at 10 years

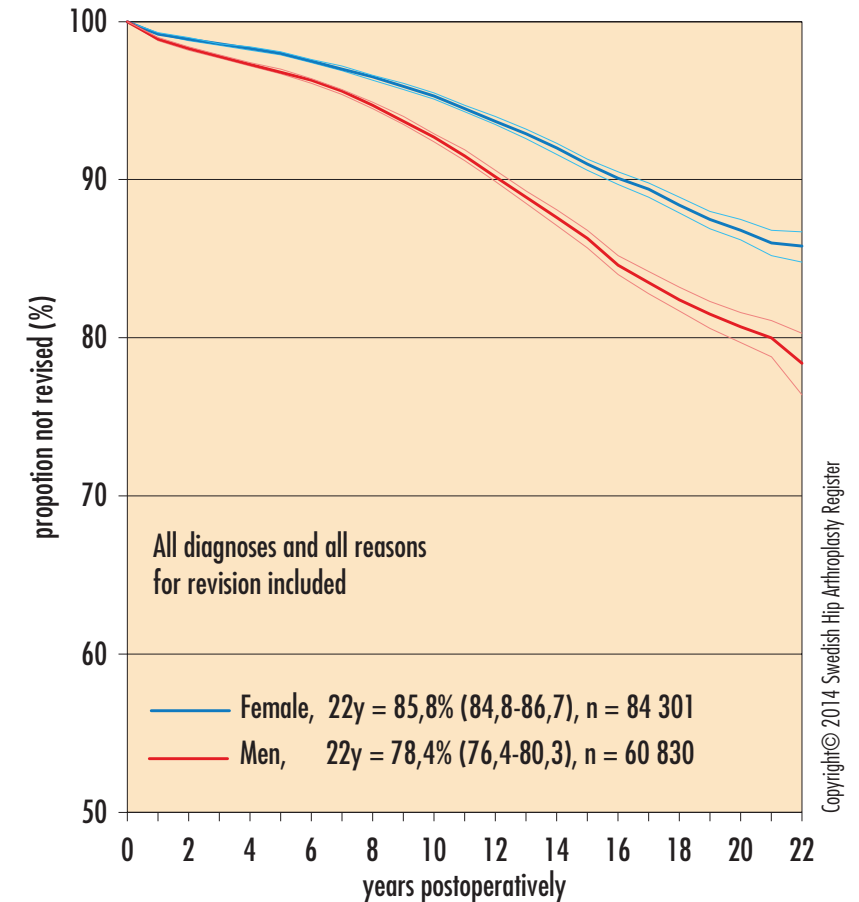
Younger than 50 years
all observations, 1992–2013



Between 50 and 59 years
all observations, 1992–2013

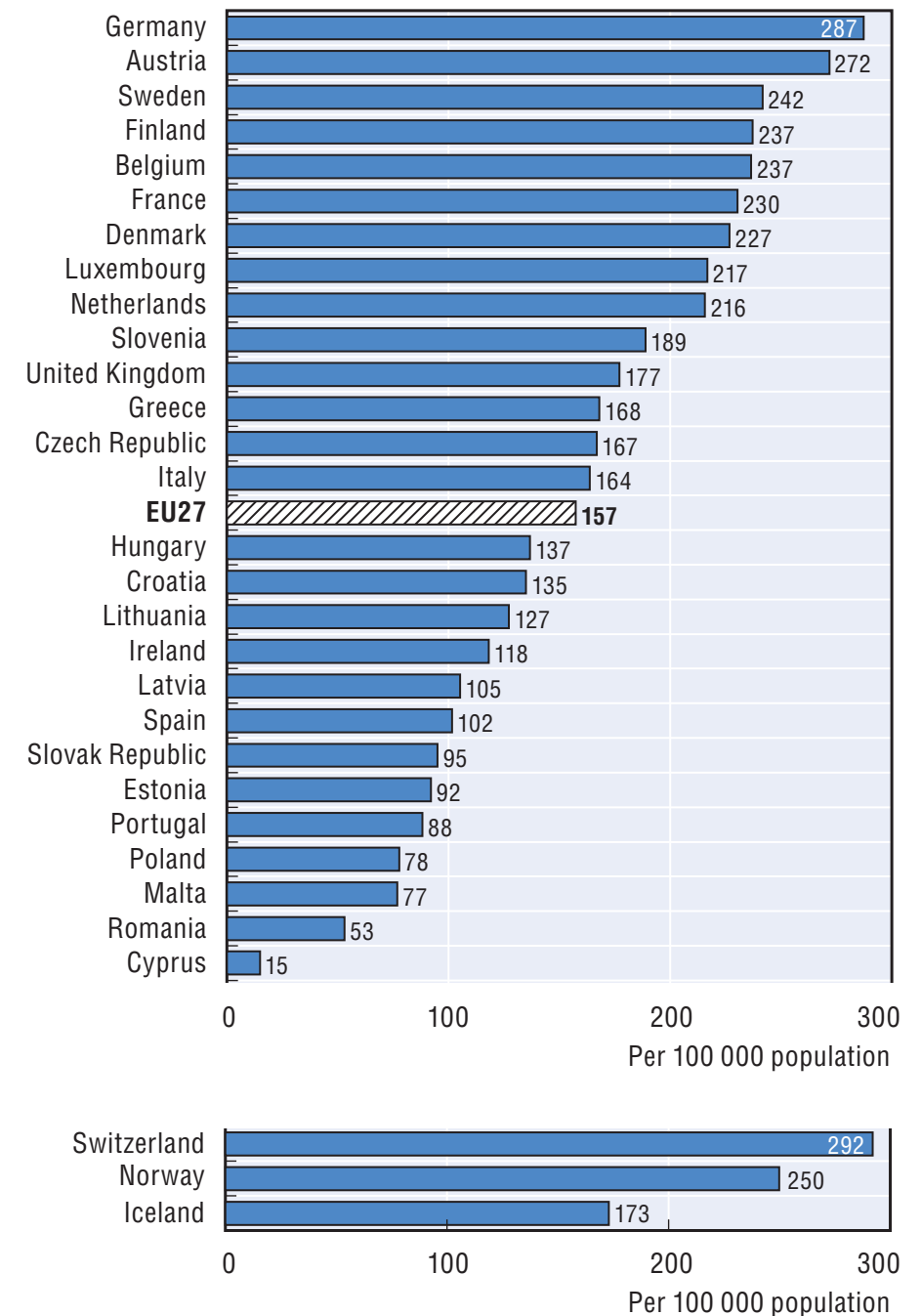


Between 60 and 75 years
all observations, 1992–2013



The clinical and financial implications are important

- > 1.5 million hip implants/year world wide
- Market of > 5 billions \$/year world wide
- Cost for revisions 25% higher than for primary surgery



Source: OECD Health Statistics 2014

Why do we want to develop a new kind of hip implant?

- Success rate is limited in some clinical situations
- All “classical” approaches have been tested
- “Functionalizing” implant to control bone remodeling

Strategies proposed to increase the clinical outcome of hip implant

- Implant design
- Elastic modulus of implant
- Surgical technique
- Surface treatment
- Drug

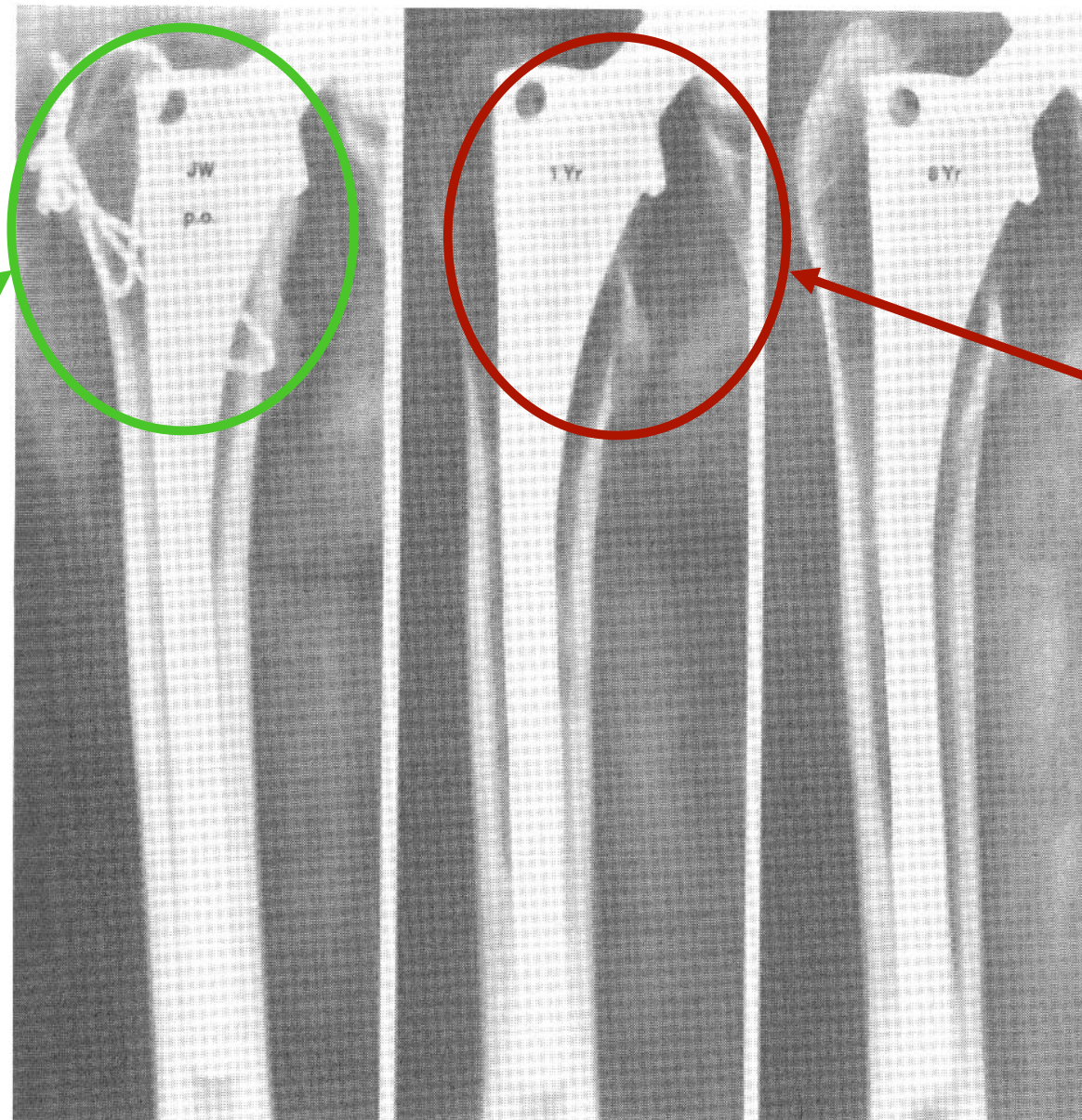


www.smithnephew.com

Why do we want to develop a new kind of hip implant?

- Success rate is limited in some clinical situations
- All “classical” approaches have been tested
- “Functionalizing” implant to control bone remodeling

A solution could be to control the bone **resorption** around the implant

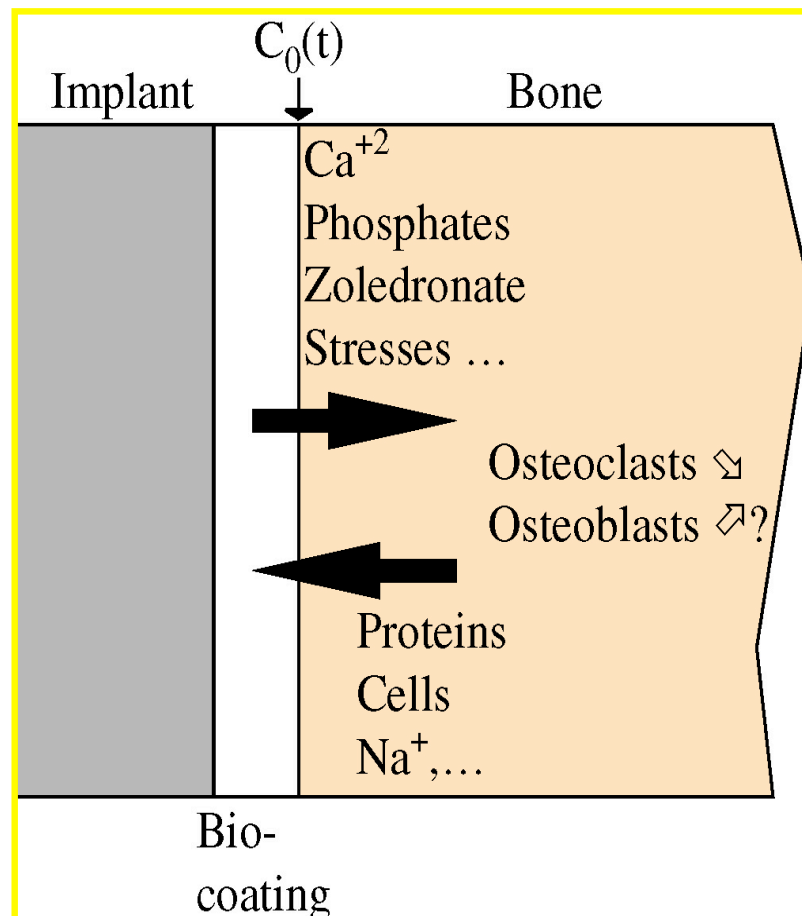


To keep this bone as long as possible

Bone resorption must be controlled here

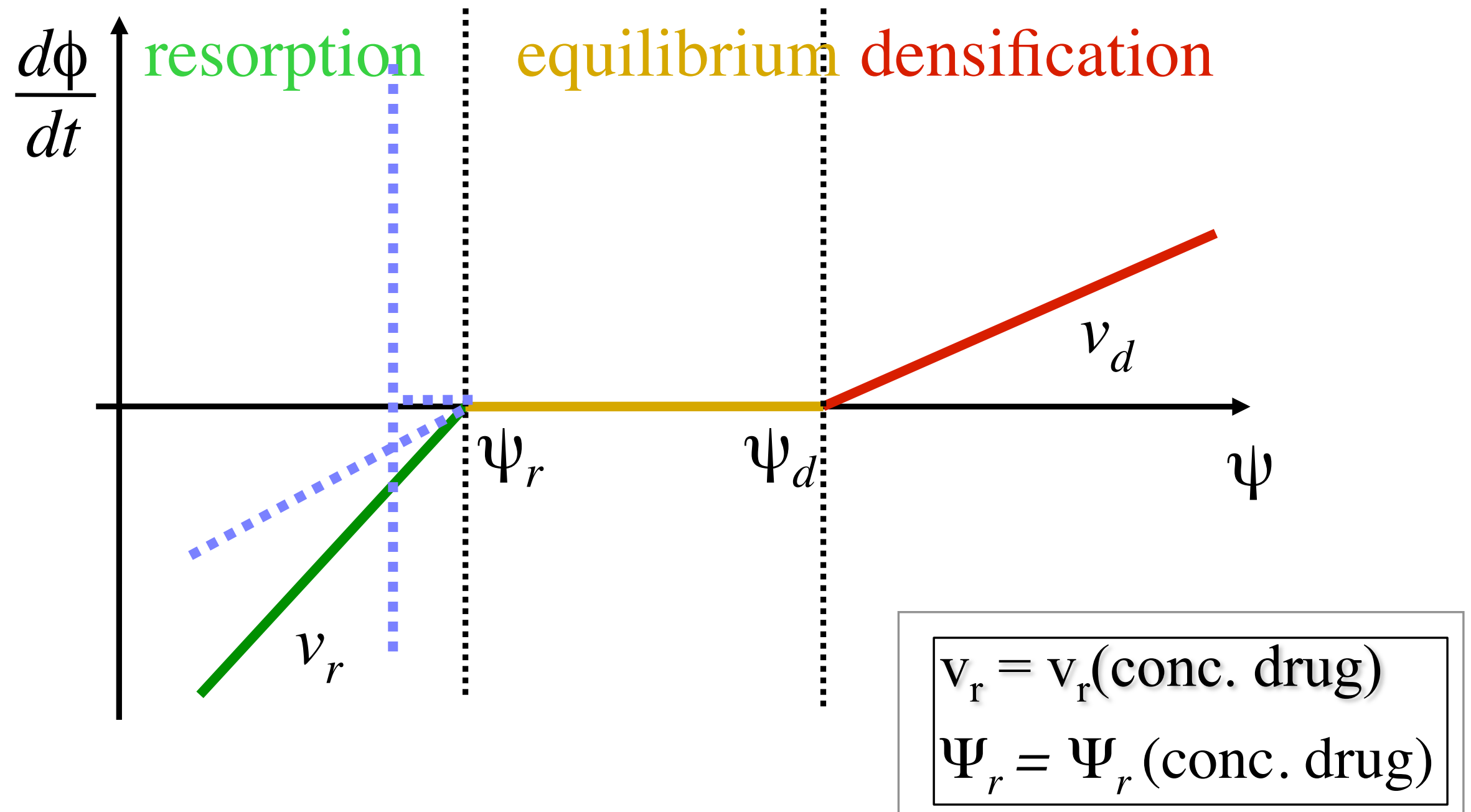
Time after surgery: 1 month 2 years 7 years

The basic idea is to use the implant as drug delivery system

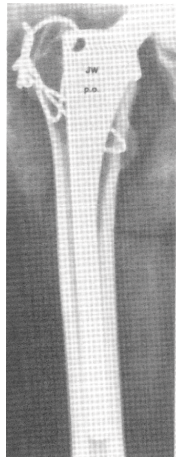


- Biocoating: hydroxyapatite + drug
- Local action
- Low dose
- Decrease of side-effects

How could we describe the BP effect on peri-implant bone remodeling?



The model of remodeling is coupled with calculations of the constraints



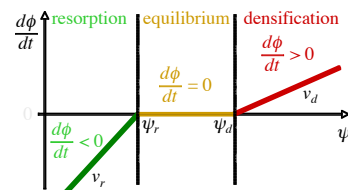
Initial density: ϕ_{init}

External force: F_{ext}

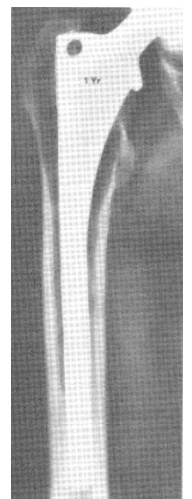
Constitutive law: $\sigma = \sigma(\phi, \epsilon)$

Mechanical stimulus: ψ

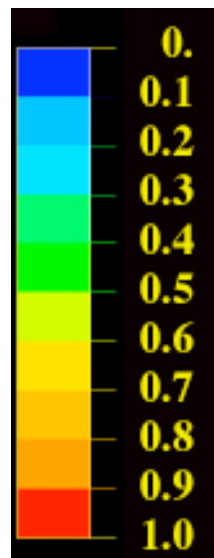
Density evolution: ϕ



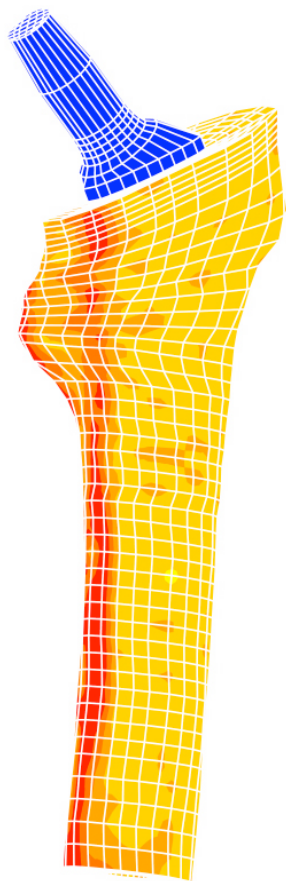
and drug concentration



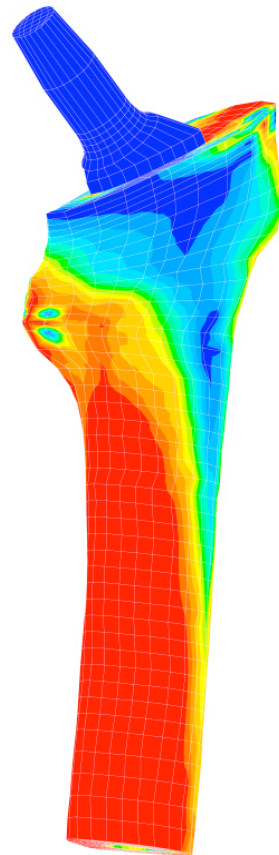
A numerical evaluation of the implant used as drug delivery can then be performed



Bone density



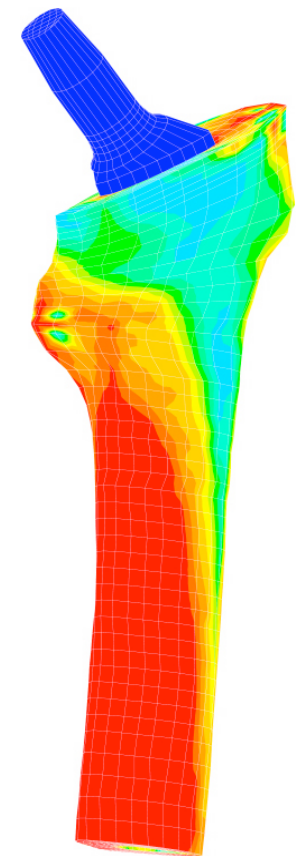
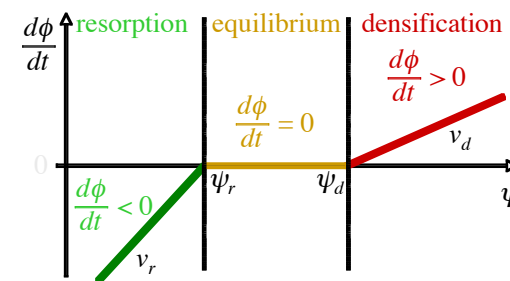
Post-op



Without drug (2 y.)

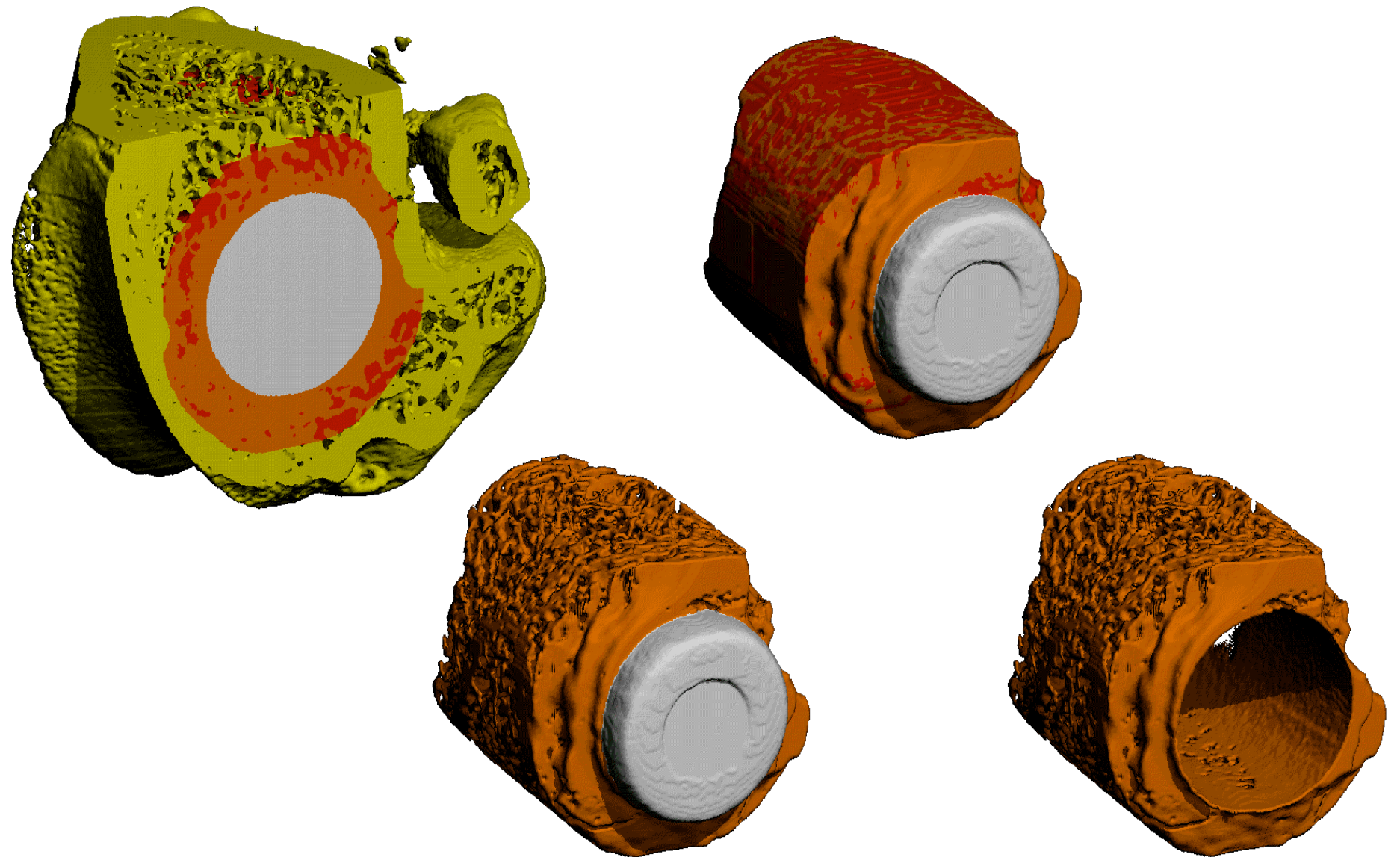
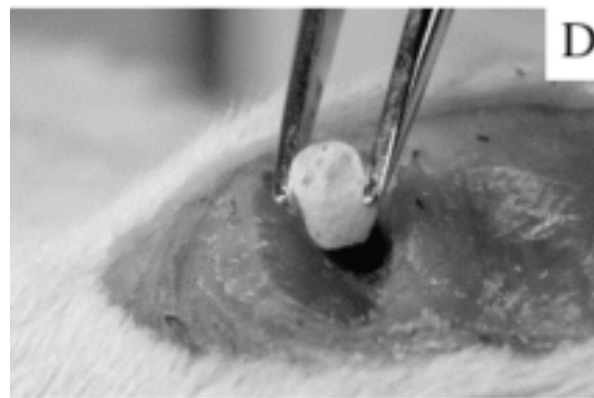
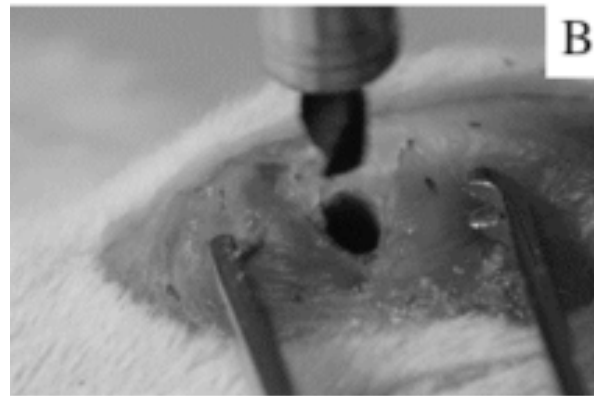
$$v_r = v_r(\text{conc. drug})$$

$$\Psi_r = \Psi_r(\text{conc. drug})$$



With drug (2 y.)

The idea of using implant as drug delivery system is tested in vivo



The implant containing the drug decreases the peri-implant osteolysis

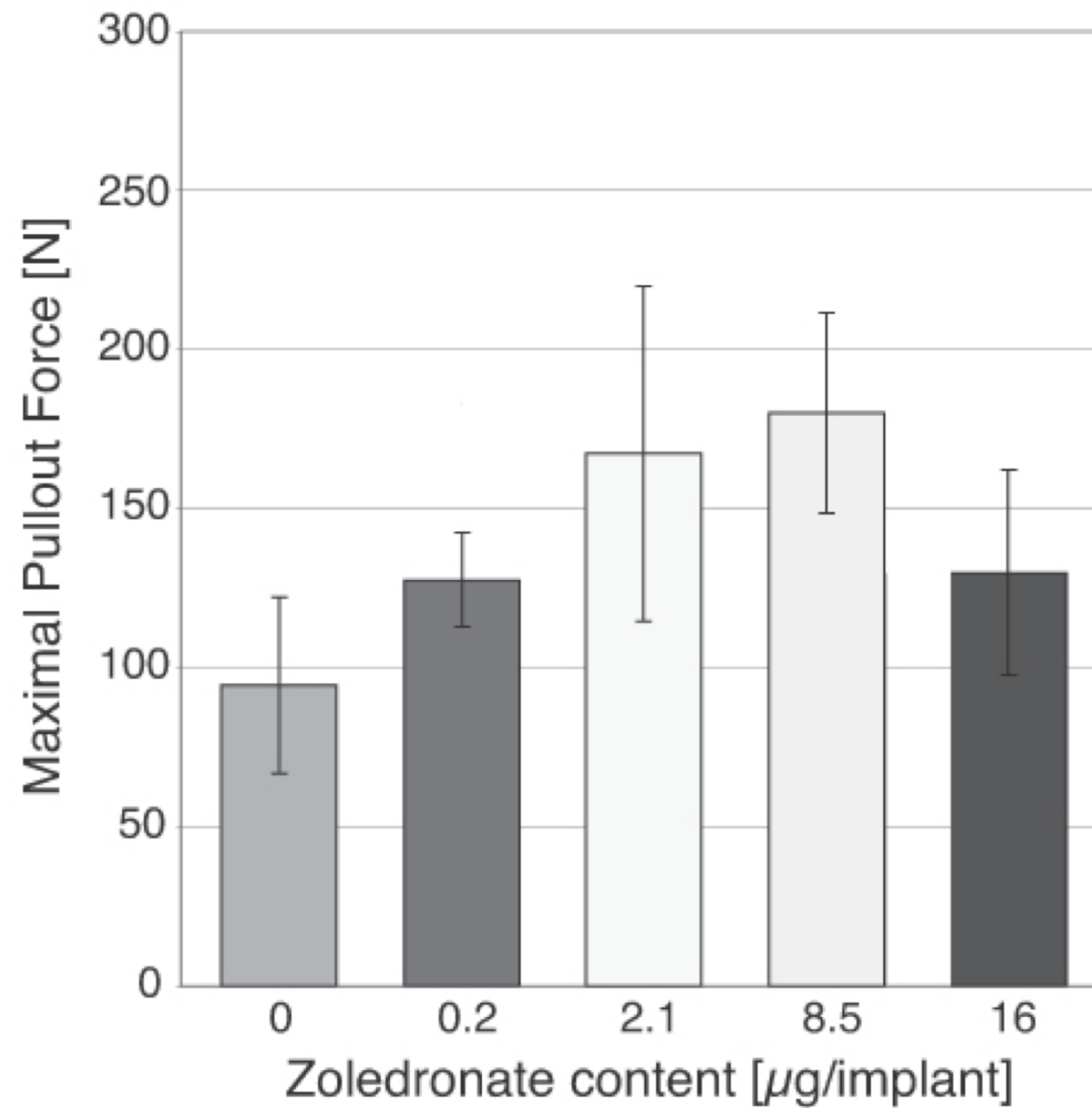


Without drug



With drug

The implant containing the drug increases the mechanical stability (proof of concept)



Why do we want to develop a new kind of hip implant?

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