Biomechanics of the musculoskeletal system

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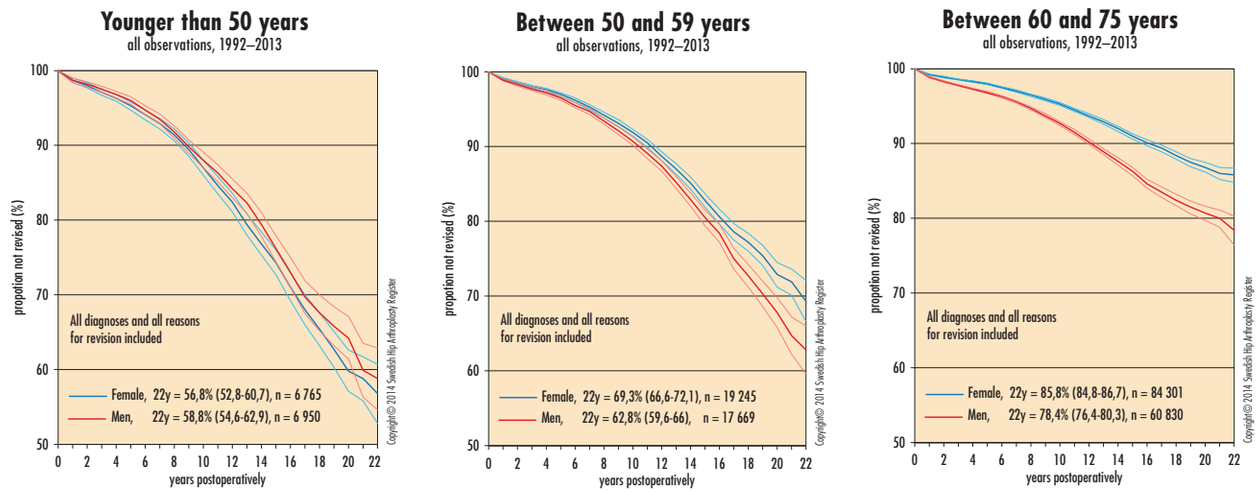
Why do we want to develop a new kind of hip implant?

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

In general the results in total hip arthroplasty are good for the “standard” patients (> 65 year old). However with categories of younger patients, there is still room for improvement.

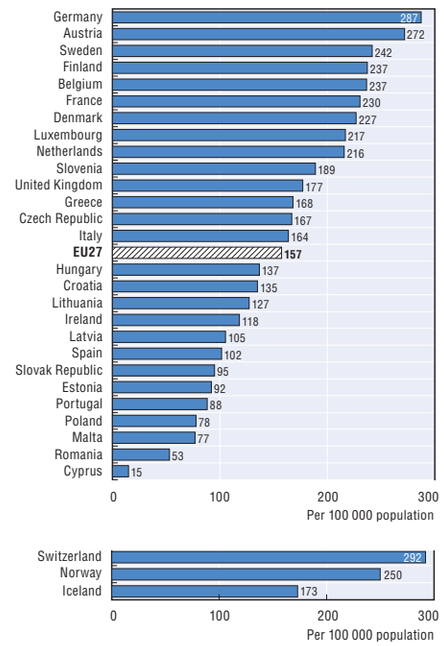
For younger patients, the failure rate of hip implant can reach 30% at10 years



The failure of hip implant (mostly due to aseptic loosening) can be quite important especially for young patients. A secondary surgery is then necessary to replace the first implant. However, the outcome of the second implant is even less good than the first implant and the surgeon can face very challenging situations with failure of the second implant.

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

The clinical and financial implications are important and motivate the need for increasing the performance of orthopedic implant, especially for younger patients. Indeed the total hip replacement procedure represents 10% of the entire orthopedic implant market.

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Since more than 30 years of intense research in different aspects of the implant development, only incremental positive impact has been observed on the clinical outcome.

Strategies proposed to increase the clinical outcome of hip implant

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

www.smithnephew.com

A lot of developments has been done in orthopedic research. Different implant designs have been proposed in order to more evenly distribute the load around the implant. Mechanical properties have also being investigated. Different surface treatments were developed. Surgical techniques can be improved. However, none of the existing implants allow to completely remove the problematic of aseptic implant loosening.

Implants development mainly focused on engineering aspects

Implant design

Straight stem

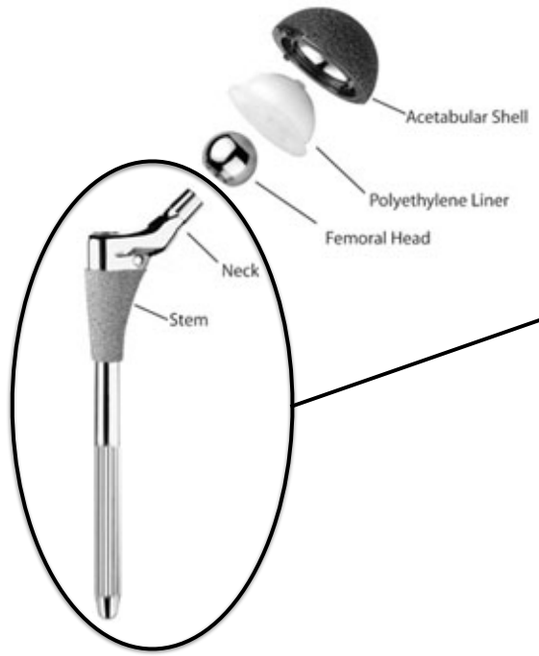
Anatomical stem (collarless)

Anatomical stem (collared)

In order to transfer the load also in the proximal part of the femur, different implant designs have been developed.

Implants development mainly focused on engineering aspects

Elastic modulus

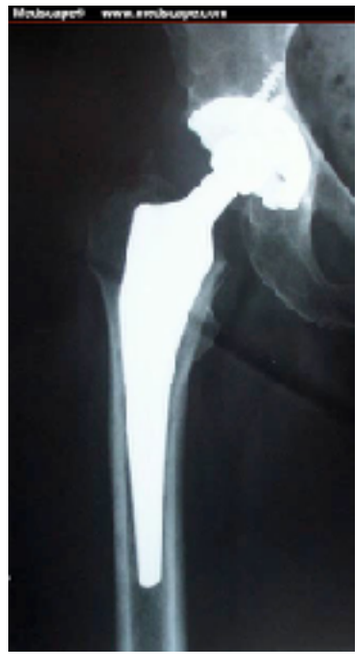


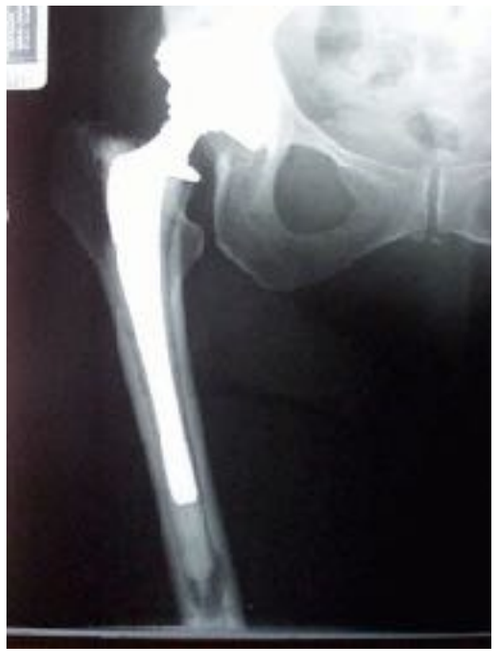
Could be made of polymer

Elastic modulus: 0.5 to 3 GPa

By having an elastic modulus of the implant closer to the bone elastic modulus, it is hoped that the stress-shielding effect can be cancelled.

Uncemented vs cemented

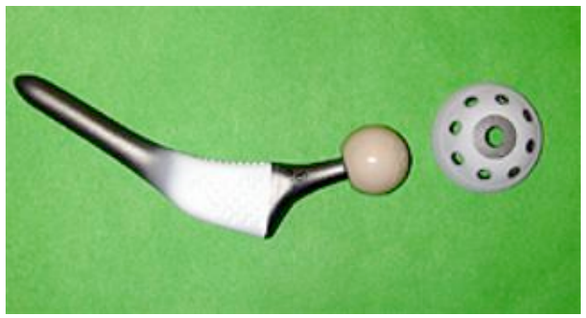


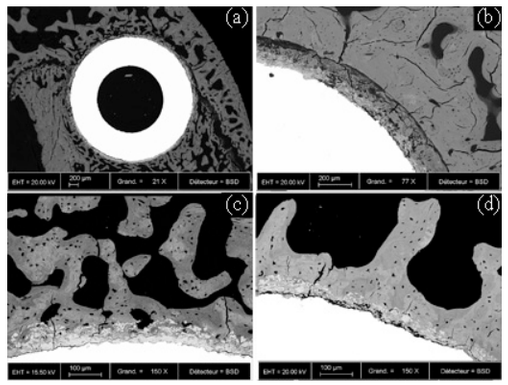


Finally, from a surgical techniques point of view, there are basically two strategies to fix an implant to the bone: uncemented and cemented approaches. For the uncemented approach, the implant geometry fits the intra-medullary canal and the primary stability is insured by a press-fit technique. For the cemented approach, obviously the implant geometry can be less elaborated and the cement will stabilise the implant. Initially, the uncemented approach was designed for younger patients, but it is actually also used for older patients.

For uncemented implant, surface treatment can be developed

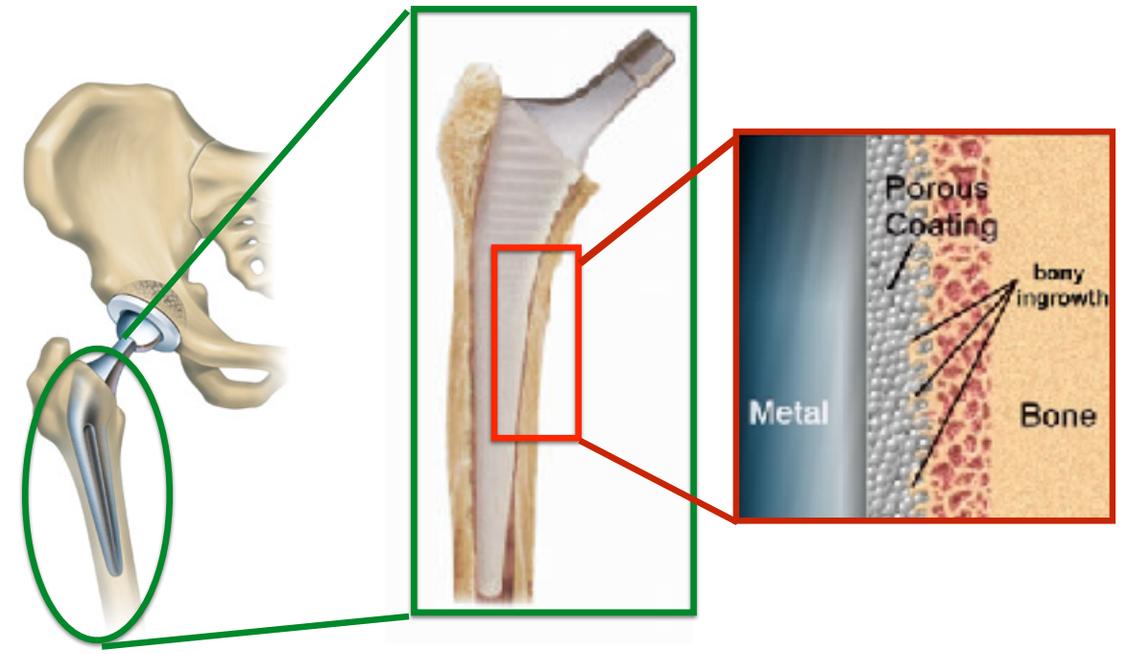
Surface treatment





The surface treatment is used to allow a better osteointegration of the implant with the surrounding bone. Implant can then be coated with an hydroxyapatite layer in order to generate a chemical link between the implant and the bone.

What is then happening in the bone surrounding the implant?



As we know it now, all biological tissues adapt to their mechanical environment. Around the implant, the bone is reacting to the new mechanical situation in a process called bone remodeling.

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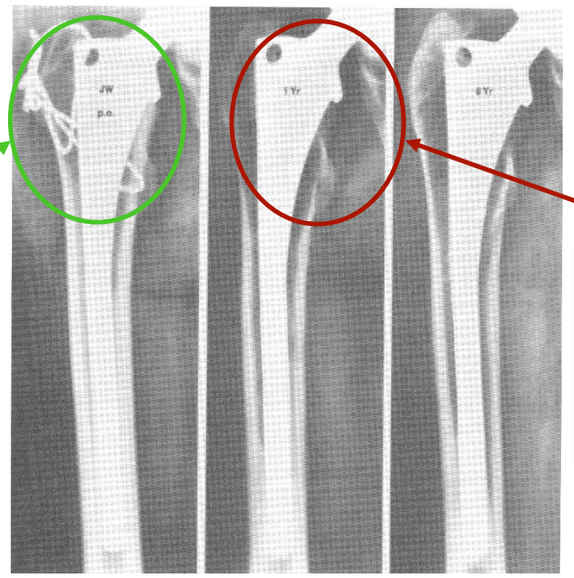
- "Functionalizing" implant to control bone remodeling

Most of what has been proposed from engineering point of view has shown interesting clinical results, however no fully satisfactory solution has been found. A more detailed consideration of biological events related to implant should then be proposed. This could be done to what we call "functionalizing implant".

A solution could be to control the bone remodeling around the implant



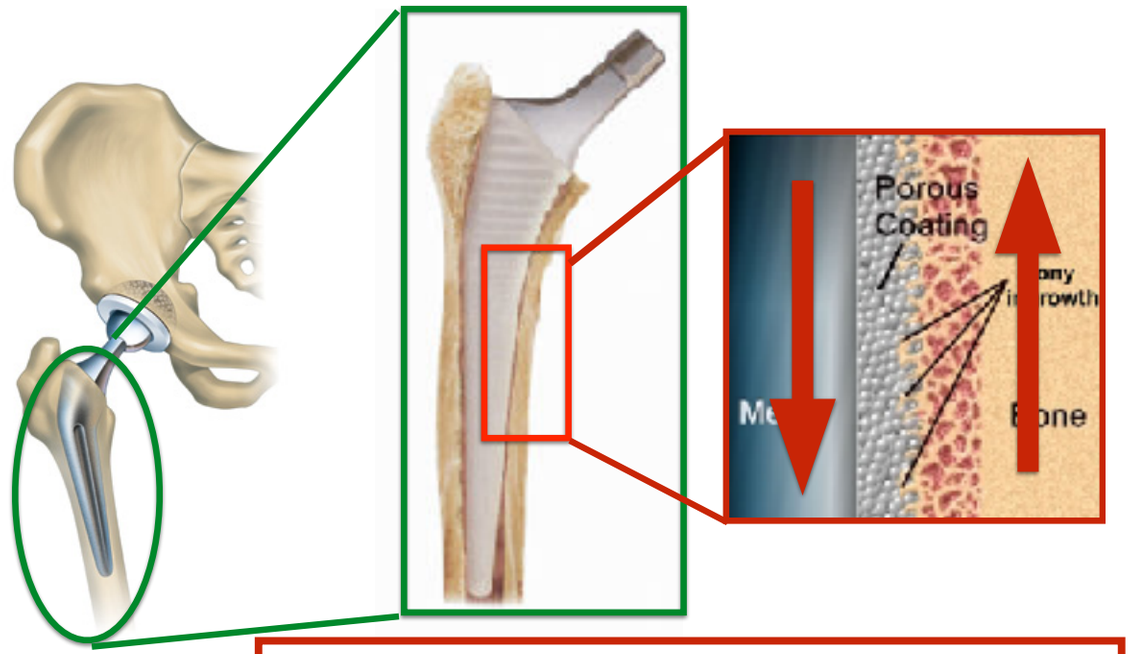
To keep this bone as long as possible

Bone remodeling must be controlled here

Time after surgery: 1 month 2 years 7 years

In order to functionalize the implant surface, we should first understand what is the underlying mechanism leading to the bone loss around the implant.

What is then happening in the bone surrounding the implant?



µmotions between the bone and the implant

Micromotions between the implant and bone are believed to play an essential role in the implant osteointegration. Evaluating the amplitude of micromotions could then provide information on the primary stability of the implant which is a good predictor of secondary stability.

A poor primary stability is characterised by excessive micromotions of the stem

Excessive micromotions at the bone-implant interface has been associated with aseptic loosening

Micromotions at the interface of the implant and bone is inevitable, especially as the two structures present a mechanical mismatch of their properties. When we evaluated the contact force in the articulation, we observed that certain motions induce higher contact force than others (getting out of a car is a typical example of high induced contact force at the hip).

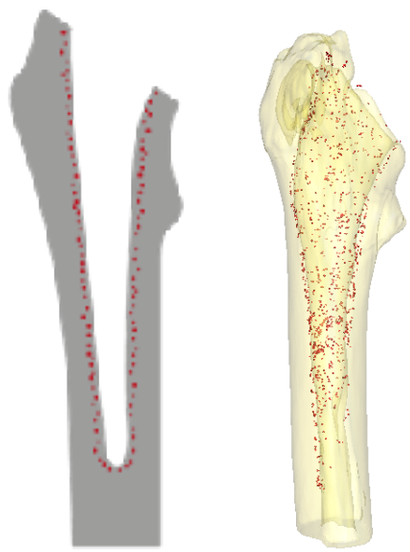
Some physical activities are thought to endanger more stem primary stability

Activities such as stair climbing or rising from a chair induce high torsional loads and micromotions

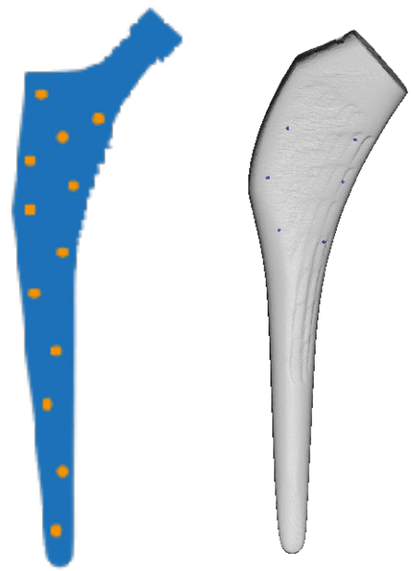
For the evaluation of the micromotions, it is then important to consider the activities inducing the highest possible values, despite obviously some of these activities will be “trained” to be performed in a secure way through physiotherapy.

Quantification of micromotions is made by combining an imaging technique to mechanical set-up

Radiopaque markers are fixed to the bone and the stem



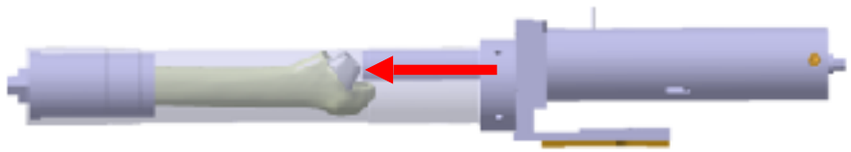
~1000 stainless steel bone markers
(ø 600 µm)



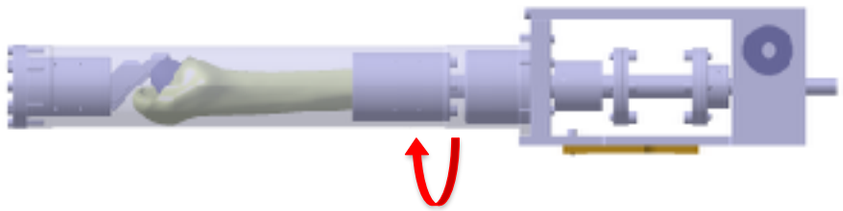
~30 tantalum stem markers
(ø 800 µm)

The experimental evaluation of the micromotions is a difficult task as their values depend on many parameters such as the implant type, the bone shape, the implantation technique, the location around the implant, the physical activities, …
In order to compare the results between different tested situations and to obtain a field for the micromotions values (in opposition to some discrete values obtained at some particular positions around the implant), an in vitro technique combining imaging and mechanical loading has been developed.

The implanted femur is placed in custom-made loading devices



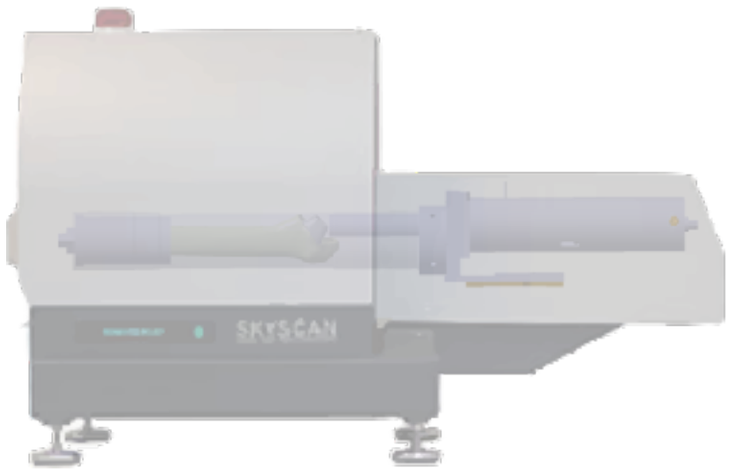
Compressive load: 1800 N



Torsional load: 17 Nm

Several pairs of anatomic femur pieces were used. After implantation of the stem in the femurs by a senior orthopedic surgeon, the implanted bone is placed in a custom made loading device.

The loading devices are designed to fit inside a µ-CT scanner



Skyscan 1076 *in vivo* µ-CT

- *100 kV, 100 µA*
- *35 µm resolution*
- *310 ms exposure time*
- *1.0 mm Al Filter*
- *0.7° Rotation Step*

To get a 3D field of micromotions values at the implant interface, a µ-CT was used to obtain the positions of the different radio-opaque markers with or without loadings.

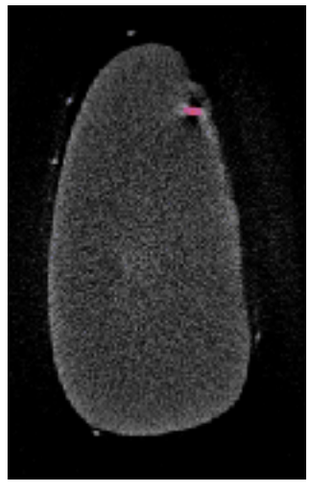
Two successive µ-CT scans are performed

Scan 1:
During loading

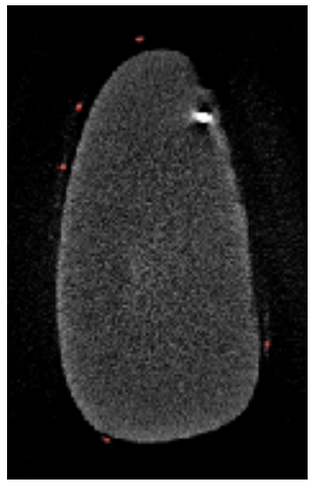
Scan 2:
After loading

Due to the acquisition time of the scanned images, only static measurements can be performed.

Images are processed and the position of all markers are computed

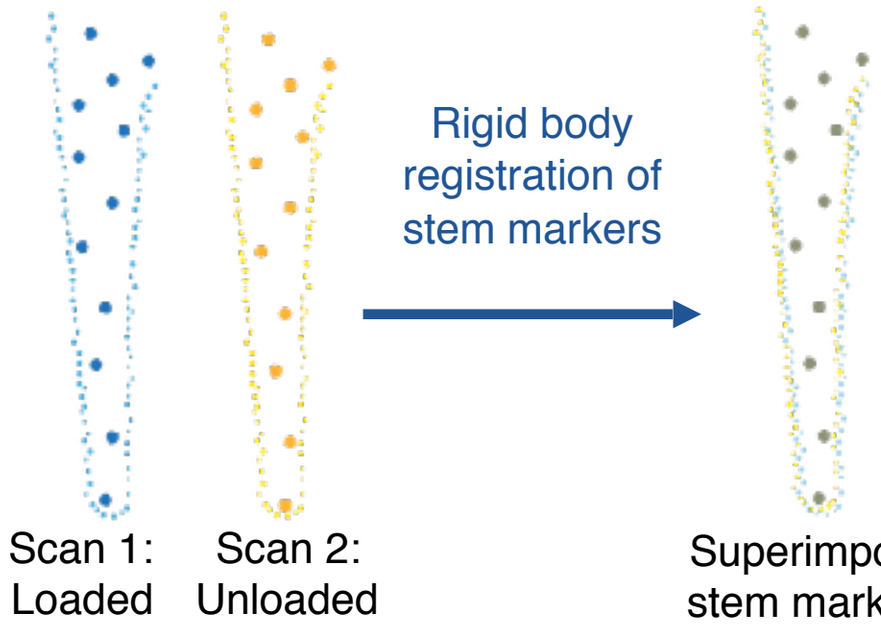


Implant markers



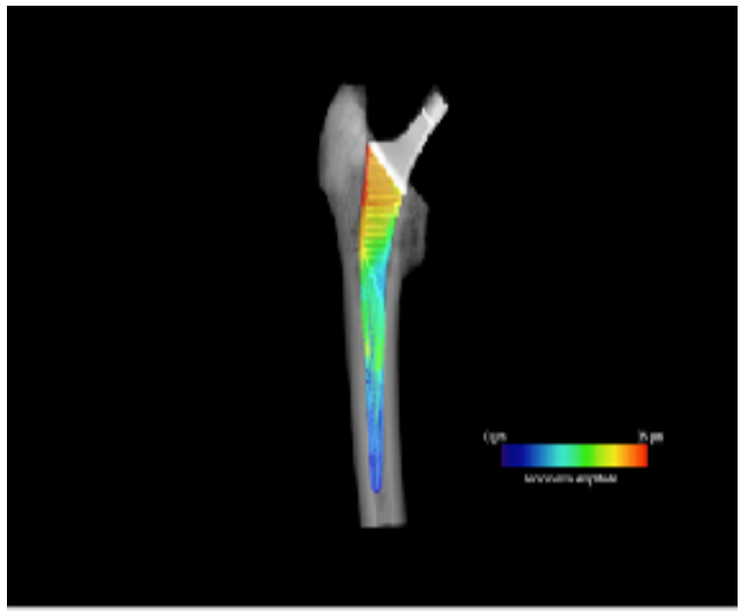
Bone markers

Micromotions are defined as the 3D displacements of bone markers during loading



The implant markers on both scans are superimposed (rigidly = translation+ rotation only). The correspondence between the bone markers is then found. The distance between markers from one scan to the other represents the 3D micromotions.

Micromotions in compression

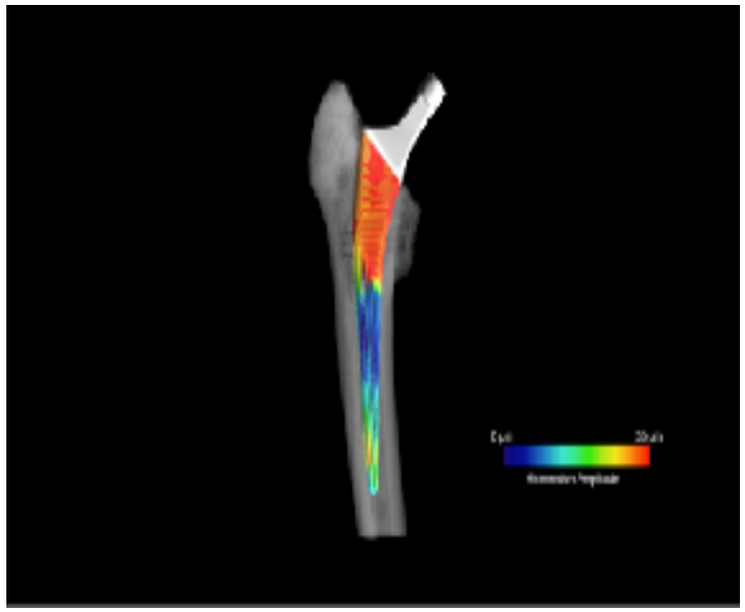


Valérie Malfroy Camine - CMBBE 2015, Montreal, Canada

- 400 measurement points
- Error: 18 μm
- Range: 2 μm to 34 μm
- Median: 15 μm

The field of micromotions values around the implant can then be obtained for the particular tested mechanical loading. The highest values of the micromotions are found in the proximal part of the femur. This part of the bone corresponds to the location where bone osteointegration is usually not satisfactory.

Micromotions in torsion



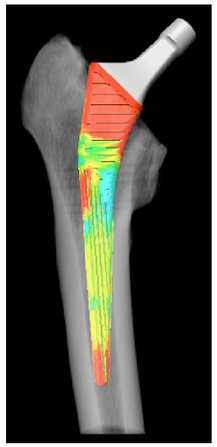
- 289 measurement points
- Error: 11 μm
- Range: 1 μm to 38 μm
- Median: 15 μm

Valérie Malfroy Camine - CMBBE 2015, Montreal, Canada

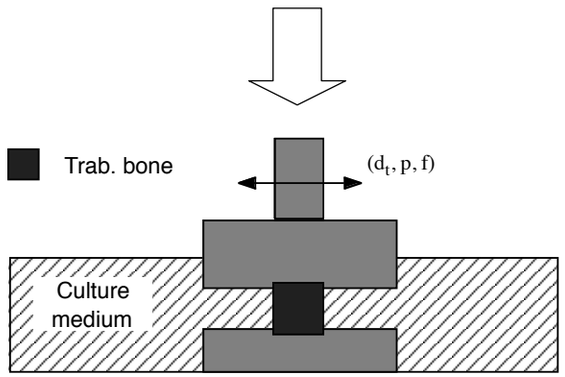
Under torsion, the effect on micromotions is even more pronounced.

What is the biological effect of micromotions and pressure on bone remodeling?

***µ*motions** (exp) and **pressure** (FEM) at bone-implant interface



Controlled *µ*motion between
2 surfaces (**100 *µ*m**)
at constante pressure (**0.1 MPa**)

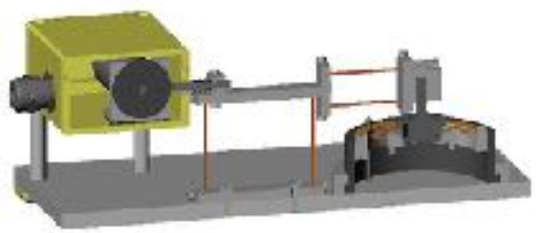


From the in vitro measurement, it has been observed that micromotions are present at the interface, from a FEM numerical study, it was also observed that a pressure is present at this interface. In order to evaluate the effect of this mechanical situation on bone remodeling, an ex vivo study is developed.

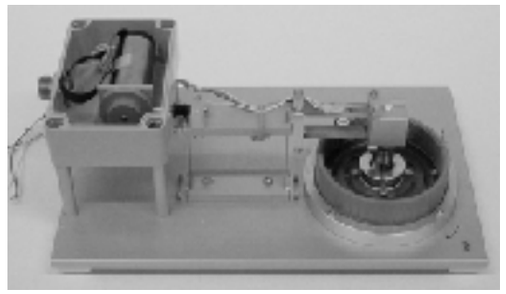
An ex vivo experiment is then developed

1) Controlled μmotion between 2 surfaces (**100 μm**) at constant pressure (**0.1 MPa**)
2) Device must work in an incubator (37°C, 100% humidity) several days
3) Automatic alignement between the 2 surfaces
4) Motion transmission without play
5) Pressure control between the 2 surfaces

CAD prototype

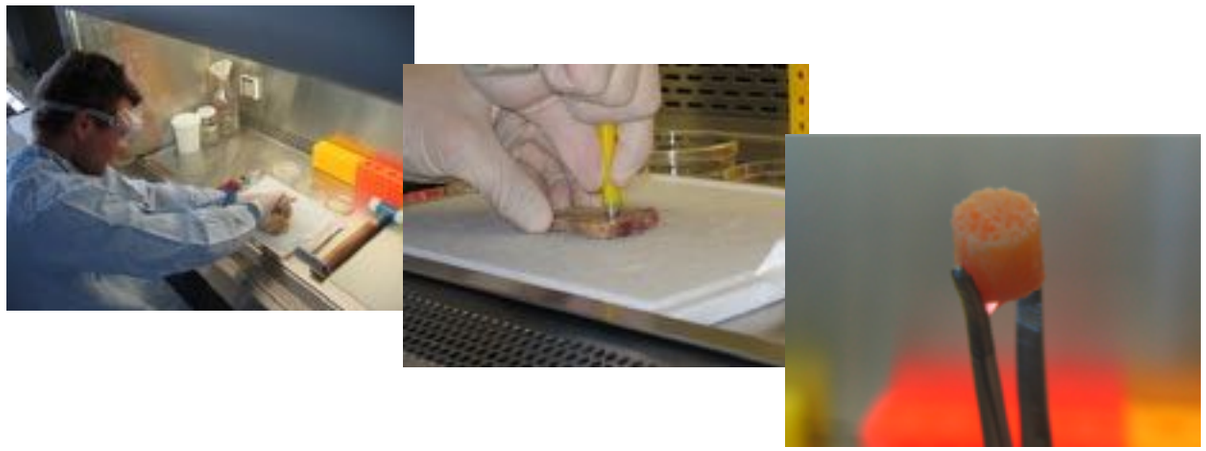


Realised device



To reproduce the mechanical stimulation at the interface of the bone and implant, a custom-made loading device is developed.

The bone samples are obtained from total hip replacement surgery procedures



3 cylinders (diam 3 mm, height 6 mm) were punched per bone sample (n = 3, female, age = 60 ± 10 years)

A close collaboration with surgeons allowed us to collect pieces of “live bone” so that they can be tested on the developed mechanical device.

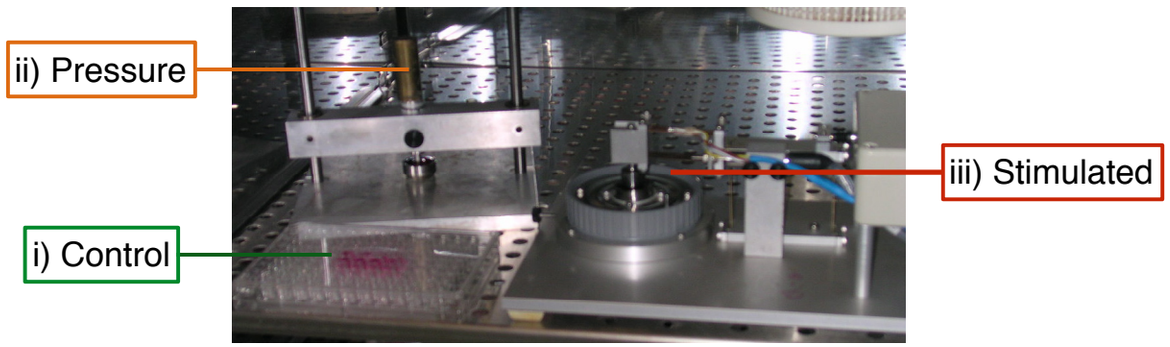
The bone samples were mechanically stimulated

Three conditions were tested during one hour:

i) in 96 well plate (control).

ii) pressure (0.1 MPa);

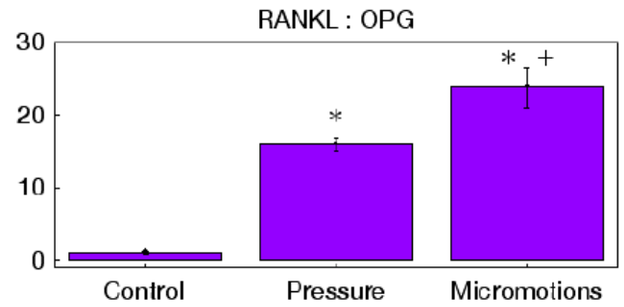
iii) micromotions (100 µm, 1 Hz) and pressure (0.1 MPa);



From the same piece of bone, 3 samples can be punched and tested under the 3 different mechanical conditions. A comparison of the sample biological reaction can then be quantified in a relative way, diminishing then the inherent biological variations present in this kind of experiment. The tests are performed inside an incubator (37°C, 5% CO_2).

RANKL/OPG signalling is up regulated by micromotions after only one hour

Real-time qPCR (gene expression)

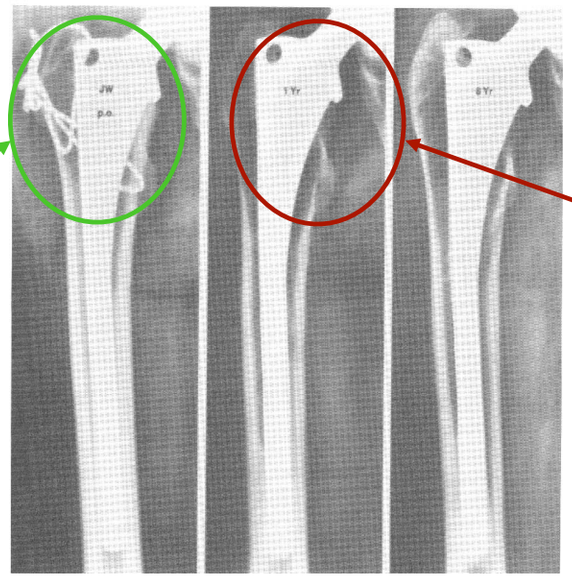


➡ Micromotions activate significantly osteoclasts differentiation and activation already after 1h !

Stadelmann et al, Bone, 2008

After the stimulation, the samples are collected, the mRNA of the bone cells are isolated and a quantification of gene expression for specific bone remodeling markers is performed with a technique called “real-time qPCR. In particular for this experiment, we evaluated the ratio of the expression of 2 genes produced by the osteoblasts: RANKL which is necessary to activate the osteoclast function and OPG which is inhibiting the action of RANKL. Hence if the ratio of RANKL/OPG is high, it means that in the particular condition tested, the osteoclast differentiation and activation is favoured, bone resorption will then be favoured.

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



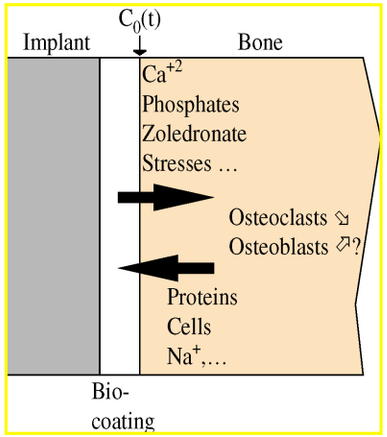
To keep this bone as long as possible

Bone **resorption** must be controlled here

Time after surgery: 1 month 2 years 7 years

Based on the in vitro and ex vivo studies, we can propose that the peri-implant bone loss around the proximal part of the implant is probably due to an increased resorption activity (as a reminder, as bone density is the result of two concurrent phenomena, bone resorption and bone formation, a decreased bone formation would also have resulted in a decreased bone density).
As only a small amount of bone needs to be “under” control, a drug affecting bone resorption could be delivered locally.

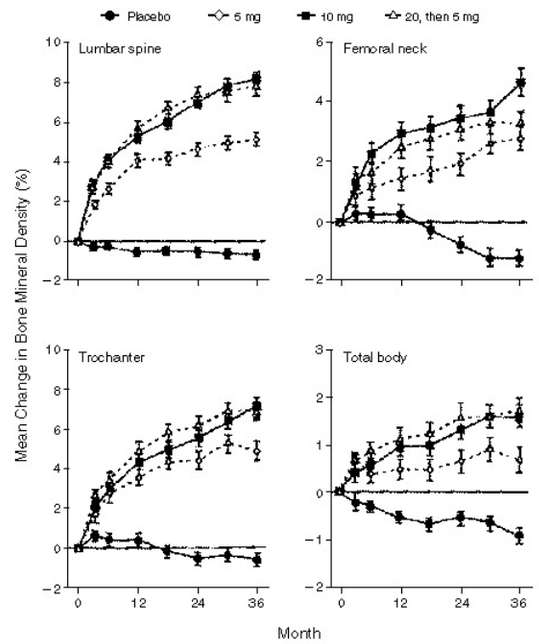
The basic idea is to use the implant as drug delivery system



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

Indeed, as we have an access to the bone to be treated and this access is the implant, so why not using the implant itself as the drug carrier? In this approach, the implant will not only be used for its structural aspects (mechanical support of the articulation), but also for its active aspect by directly affecting the bone remodeling around the implant. In this approach, we will then combine an implant and a drug, the classification for this treatment by the regulatory agencies will be: “combination product”. From a practical point of view, the question is then: what kind of drug?

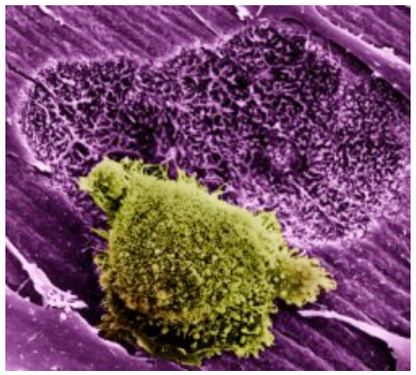
The chosen drug (bisphosphonate) affects bone resorption



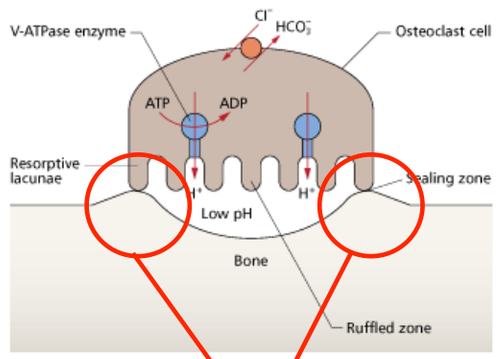
Liberman UA et al. N Engl J Med 1995;333:-1444. 1437

Changes in bone mineral density from base-line values in women with postmenopausal osteoporosis receiving Alendronate (bisphosphonate from Merck) or placebo for three years.

The chosen drug (bisphosphonate) affects bone resorption



source: www.abdn.ac.uk/ims/bone/research/pharmacology/

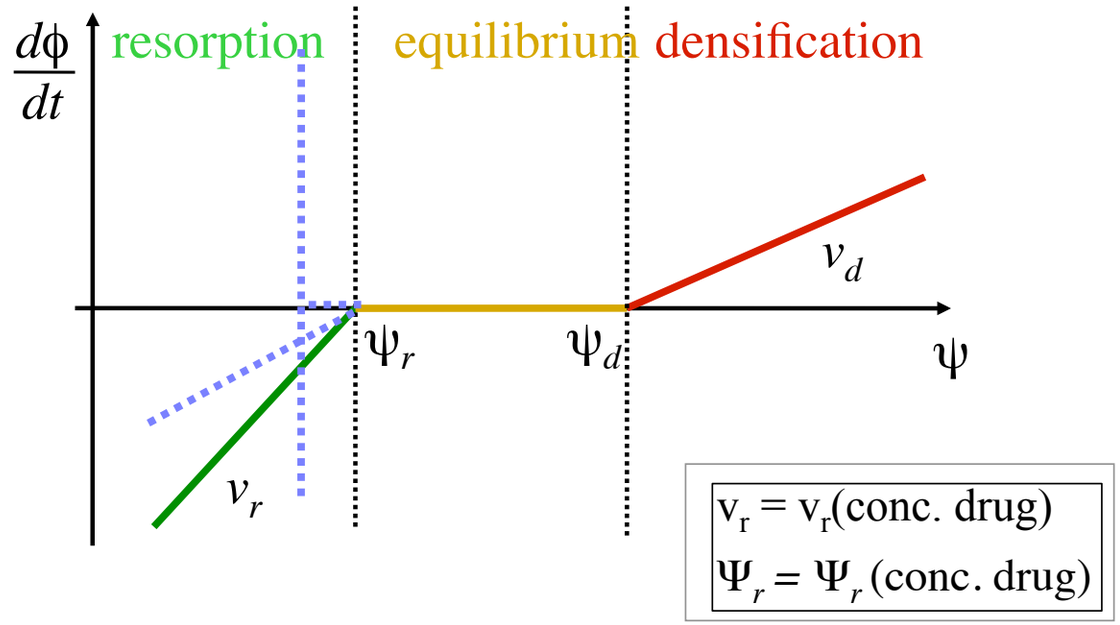


source: www.chemsoc.org/chembytes/ezine/2001/kee_oct01.htm

BP breaks the sealing zone

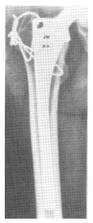
The action of the bisphosphonate (BP) is on osteoclasts rendering them ineffective to resorb bone.

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



We propose to keep the biomechanical description of bone remodeling and incorporate the drug effect in it.

The model of remodeling is coupled with calculations of the constraints



Initial density: ϕ_{init}

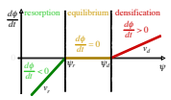
External force: F^{ext}

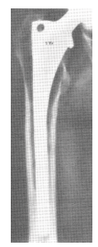
Constitutive law: $\boldsymbol{\sigma} = \boldsymbol{\sigma}(\phi, \boldsymbol{\varepsilon})$

Mechanical stimulus: ψ

Density evolution: ϕ

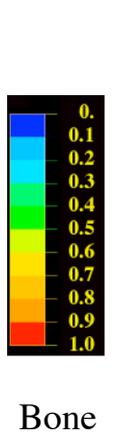
and drug concentration



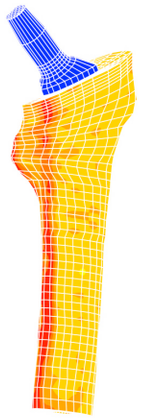


If the bone remodeling model is coupled with a mechanical description (for example a FE analysis) and the remodeling parameters are dependent on the drug, bone remodeling around a particular implant used as drug delivery system can be anticipated.

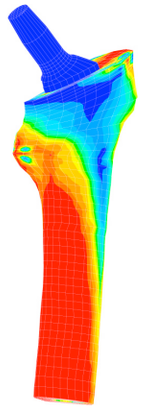
A numerical evaluation of the implant used as drug delivery can then be performed



Bone density



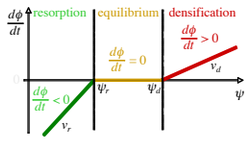
Post-op

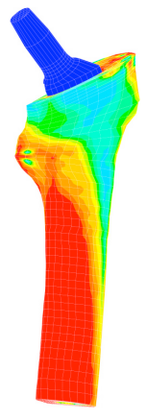


Without drug (2 y.)

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

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



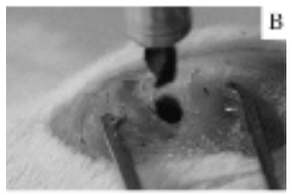


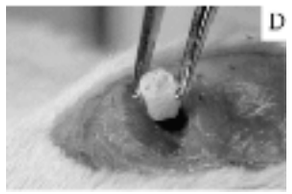
With drug (2 y.)

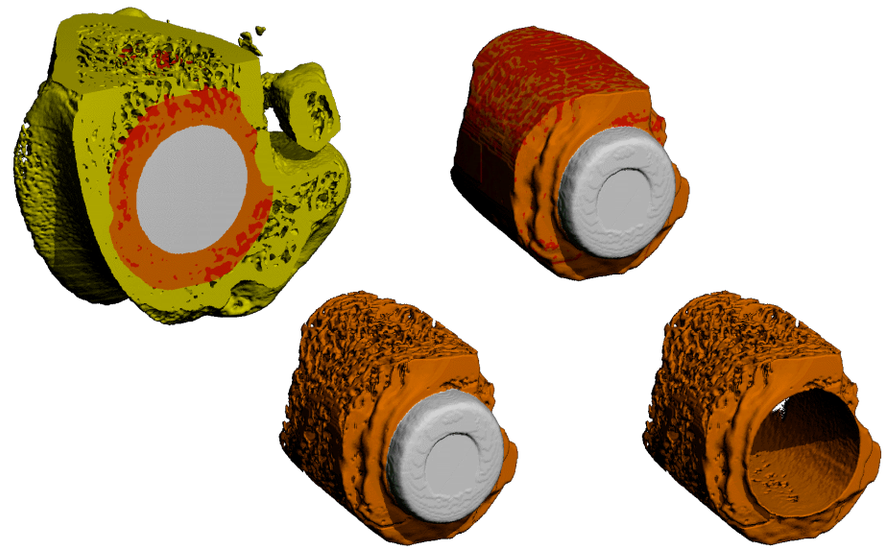
CMBBE, 2004

The effect of the drug can then be quantified.

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



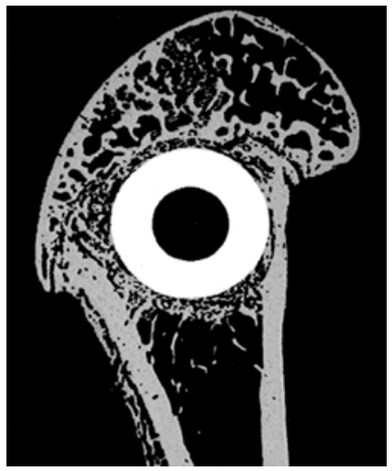




Osteoporotic rats are operated under general anaesthesia and the implant covered or not with bisphosphonate are inserted in the condyle for 3 weeks. Bone remodeling around implant is evaluated.

The implant containing the drug decreases the peri-implant osteolysis

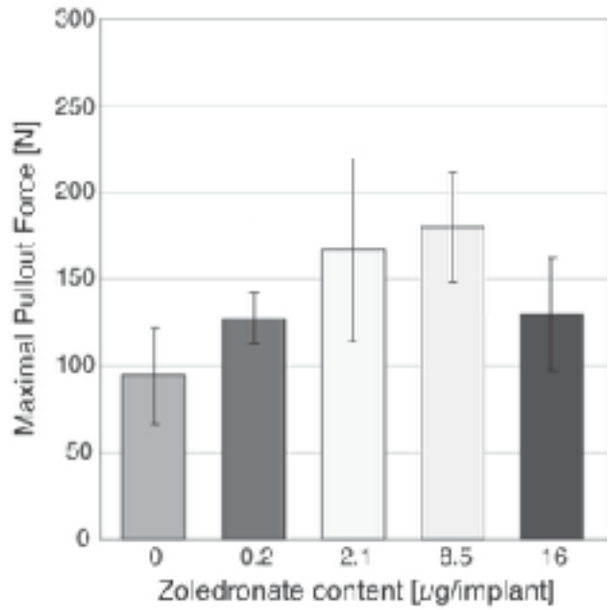
Without drug



With drug

Spectacular results are obtained.

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



There is a drug concentration effect on the implant stability. Above 8.5 µg/implant, the drug has a decreased efficacy.

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

Despite the positive results obtained by combining a drug and an implant, there is almost no such device on the orthopedic market. Why?