BioMaterials

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Biomed

***web.** https://biomed.teiwm.gr*

Biomaterial. A material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body. (ESB Consensus Conference II)

An **implant** is a **medical device*** manufactured to replace a missing biological structure, support a damaged biological structure, or enhance an existing biological structure. Medical implants are man-made devices, in contrast to a transplant, which is a transplanted biological tissue.

Who in this class has an implant/medical device?

The weekend of March 16-17 and on

Pharmaceutical (Nano-) technology & cosmetology
Theory & Hands-on cosmetics/Pharmaceuticals with
Dr. T. Karamanidou (CEO of PLiN Nanotechnology)

*A Medical Device does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but it may be assisted in its function by such means.

Skeletel system	Joint replacement (Hip, knee)	Titanium, Stainless steel, PE
	Bone plate	Stainless steel, Co-Cr alloy
	Bone cement	PMMA
	Artificial tendon and ligament	Hydroxylapatie Teflon, Dacron
	Dental implant	Titanium, alumina, calcium phosphate
Cardiovascalar sysem	Blood vessel prosthesis	Dacron, Teflon, Polyurethane
	Heart valve	Reprocessed tissue, Stainless steel, Carbon
	Catheter	Silicone rubber, teflon, polyurethane
Organs	Artificial heart	Polyurethane
	Skin repair template	Silicone-collage composite
	Artificial kidney	Cellulose, polyacrylonitrile
	Heart-lung machine	Silicone rubber
Senses	Cochlear replacement	Platium electrodes
	Intraocular lens	PMMA, Silicone rubber, hydrogel
	Contact lens	Silicone-acrylate. Hydrogel
	Corneal bandage	Collagen, hydrogel

Categories of Biomaterials

- *Polymeric biomaterials*
- *Bioceramics*
- *Metallic biomaterials*
- *Biocomposite*
- *Biologically based (derived) biomaterials*

Evolution of Biomaterial Science & Technology

- 1st generation (since 1950s)
  Goal: Bioinertness
- 2nd generation (since 1980s)
  Goal: Bioactivity
- 3rd generation (since 2000s)
  Goal: Regenerate functional tissue

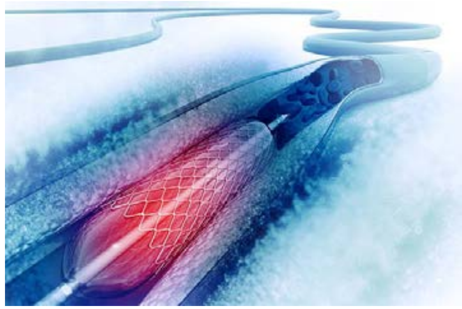
History of Biomaterials

30.000 B.C. — **600 B.C.** — **1940s** — **1950s**

- Sutures (linen, catgut)
- Gold in dentistry
- Tooth implant
- Cell culture
- Intra ocular lenses
- Hip prostheses
- Vascular prostheses
- Artificial heart, kidney

Pros

- Easy to make complicated items
- Tailorable physical properties
- Tailorable mechanical properties
- Surface modification
- Immobilize cell etc.
- Biodegradable



Cons

- Leachable compounds
- Absorb water & proteins etc.
- Surface contamination
- Wear & breakdown
- Biodegradation
- Difficult to sterilize

Commonly used Polymeric Biomaterials

PMMA, PVC, PLA/PGA, PE, PP, PA, PTFE, PET, PUR, Silicones

Pros

- High compression strength
- Wear & corrosion resistance
- Can be highly polished
- Bioactive/inert

Cons

- High modulus (mismatched with bone)
- Low strength in tension
- Low fracture toughness
- Difficult to fabricate

Commonly used Bioceramics

Alumina, Zirconia (partially stabilized), Silicate glass, Calcium phosphate (apatite), Calcium carbonate

Pros

- High strength
- Fatigue resistance
- Wear resistance
- Easy fabrication
- Easy to sterilize
- Shape memory

Cons

- High moduls
- Corrosion
- Metal ion sensitivity and toxicity
- Metallic looking

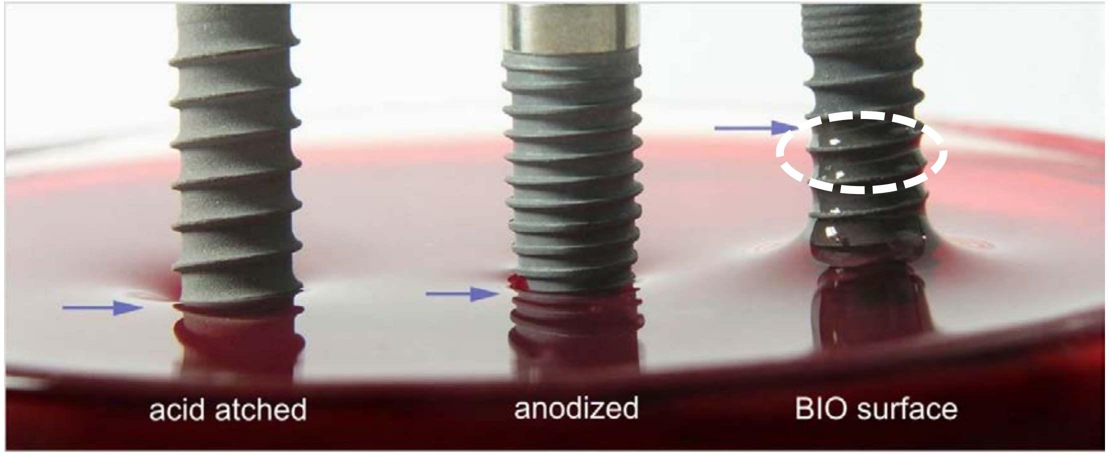
Commonly used Polymeric Biomaterials

Stainless steel (316L), Co-Cr alloys, Ti6Al4V, Au-Ag-Cu-Pd alloys, Amalgam (AgSnCuZnHg), Ni-Ti, Titanium

- Mechanical and chemicals properties
- No undersirable biological effects carcinogenic, toxic, allergenic or immunogenic
- Possible to process, fabricate and sterilize with a good reproducibility
- Acceptable cost/benefit ratio

<u>Surface Properties of Materials</u>

- Contact angle (Hydrophilic & Hydrophobic)
- ESCA & SIMS (surface chemical analysis)
- SEM (Surface morphology)



It is a transition metal, meaning will change crystal state (HCP to BCC) at 882°C.

- High Young's Modulus (107GPa) when compared to Aluminum (70GPa) or Magnesium (42 Gpa). **Which is more elastic?**
- Excellent anti-corrosion properties due to a TiO_2 layer forming ontop of its free surfaces.
- Excellent mechanical properties (e.g. strength).
- High strength to weight ratio (3,9 g/cm^3)

BUT… there is always a but!

- Difficult to machine, thus complex geometries (airplane turbines) pose a challenge
- It is expensive and bio-compatible fabrication… a nightmare!

Ti-6Al-4V (Grade 5) is the most popular implantable Bio-maeterial, but why?

Comparing a Ti plate with an Al and a Mg one… which is lighter?

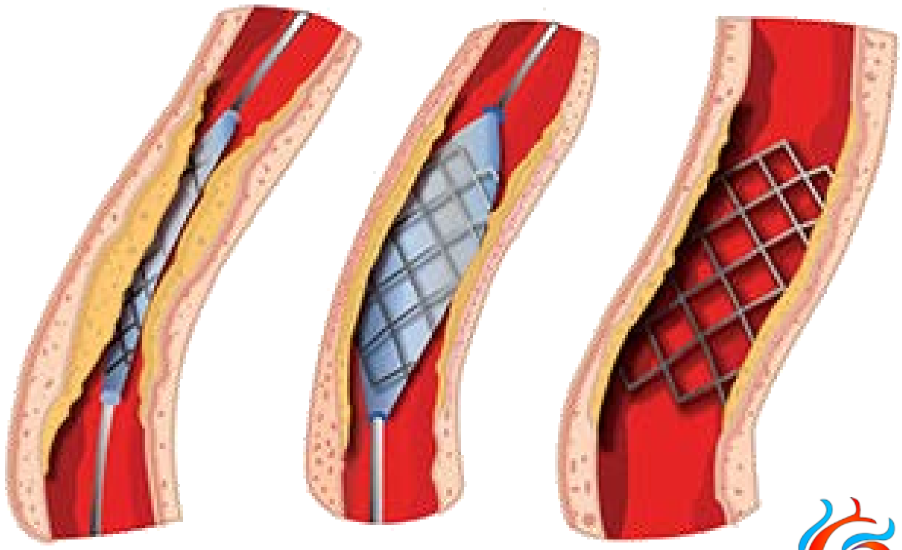
Would Al or Mg implants make sense?

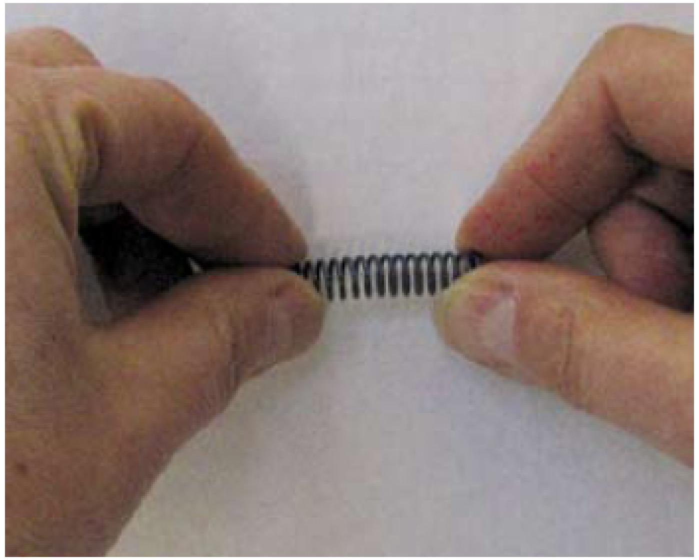
Nitinol, also called Shape Memory Alloys (SMAs)

- Iso-atomic Ni-Ti alloys, where even the slightest compositional changes may affect transition temperature or stress by order of magnitude.
- They transit back and forth among martensite and austenite, which affects their shape in a retentional way!
- This phase transition provides a pseudo-elasticity of up to 7-8% (metals are usually around 0.2%)

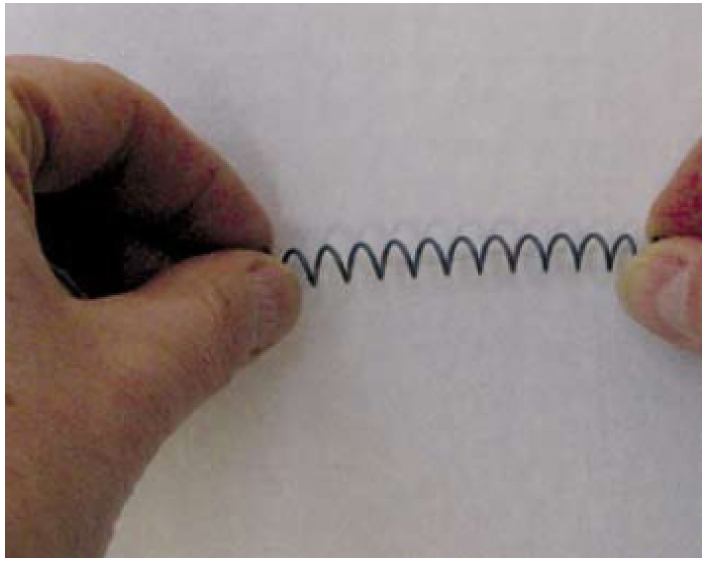
Bio-medical applications of SMAs

- Mainly tools, as their poor fatigue properties restrict their use in chronic implantation.
- Ni-leaching is also a significant problem.
- Shape Memory Polymers however have multiple applications in Medicine, with stents being the most prominent one!

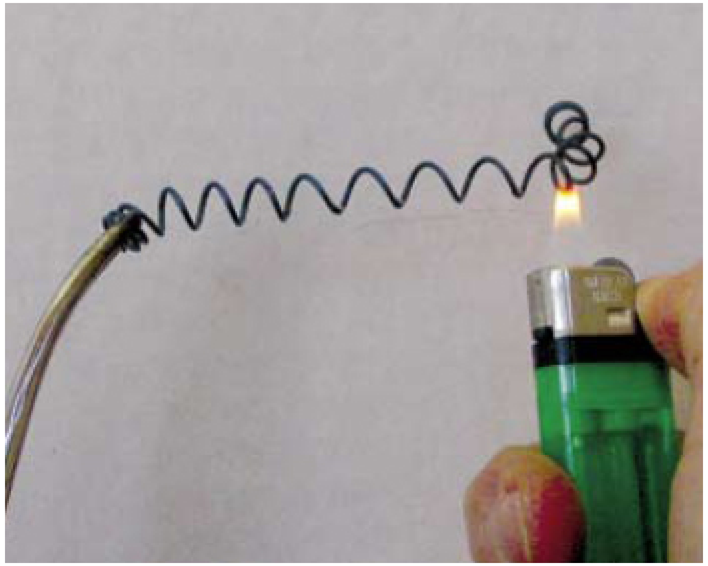




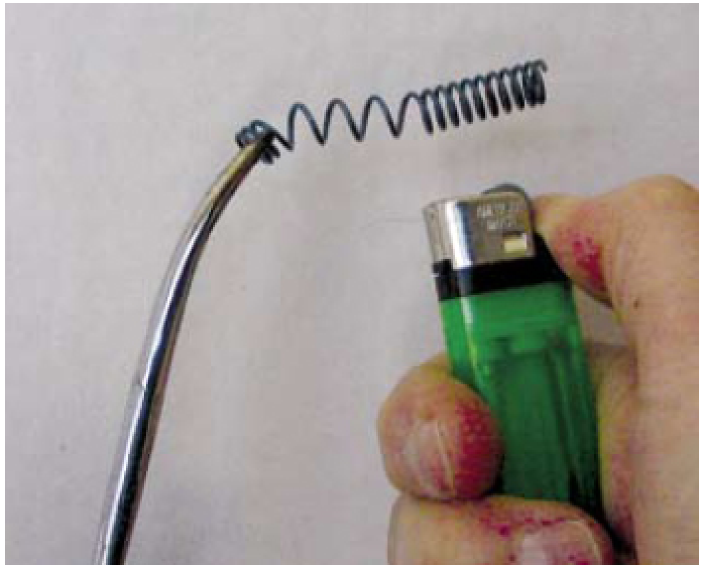
Εφαρμογή τάσης

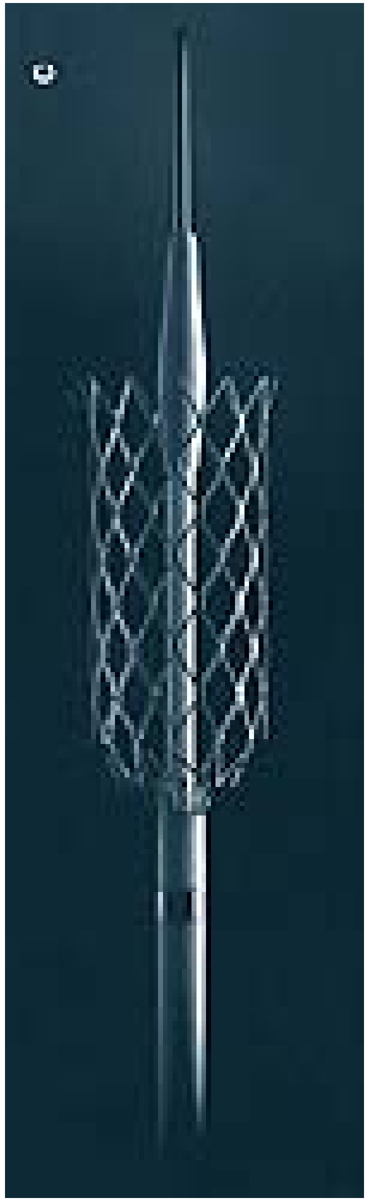


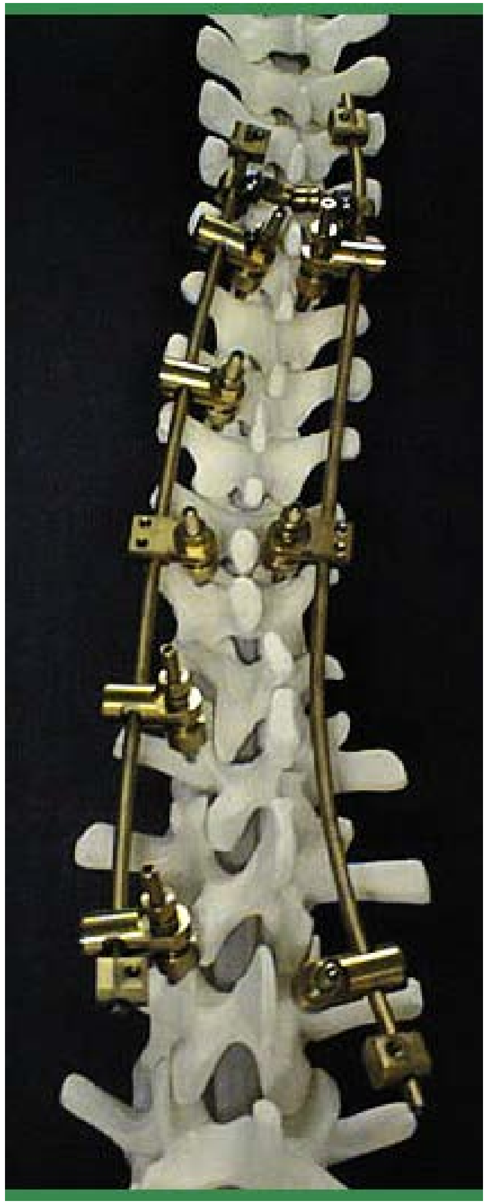
Θέρμανση > $100^{o}C$



Μνήμη Σχήματος







- Compresssive strength
- Tensile strength
- Bending strength
- E-Modulus
- Coefficient of thermal expansion
- Coefficient of thermal coductivity
- Surface tension
- Hardness and density
- Hydrophobic/philic
- Water aborption/solubility
- Surface friction
- Creep
- Bonding properties

What is the main difference of the human anatomy to any other engineering system?

Which of these properties are important for implants and why?

If an implant initiates a chemical bonding between itself and human tissue (e.g. bone), then it is accepted to have ***Bioactive properties*** (e.g. Hydroxylapatite).

If a direct contact between implant and bone is formed under light microscope, then it achives ***osterintegration***.

Why is this expected of titanium (Ti) implants?

Is this why Ti implants are popular?

Blood-material interactions *trigger a complex series of events including protein adsorption, platelet adhesion and activation, coagulation, and thrombosis i.e.:*

- Hemolysis is the is the rupturing of the cytoplasmic membrane of red cells (erythrocytes). Red cell destruction probably results from the mechanical effects of altered circulatory dynamics in which abnormal velocity and turbulence of flow are generated.
- Coagulation also known as clotting, is the process by which blood changes from a liquid to a gel, forming a blood clot (prevalent to Platelets, a small colourless disc-shaped cell fragment without a nucleus, found in large numbers in blood)

The immune system will sense an implant as a foreign body and respond in a variety of ways, ranging from a simple inflammatory reaction to complex immune responses against the biomaterials at hand.

Biocompatibility: The ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, *but generating the most appropriate beneficial host response (cellular or tissue) in that specific situation, and optimizing the clinically relevant performance of that therapy.*

Host response: the reaction of a living system to the presence of a material.

Implant type	Annual cases worldwide	Typical problems
Joint replacements	2.500.000	10-15 year life spam
Heart valves	400.000	Calcification/thrombosis
Pace makers	600.000	Electrode encapsulation
Stents	1.500.000	Clotting/closure
Dental implants	120.000.000	Bone resorption/osteointegration
Orthopedic implants	140.000	Stress shielding/loosening
Catheters	1.000.000.000	Thrombosis/infections
Contact lenses	150.000.000	Discomfort/eye injury

Deterioration of Biomaterials

- Corrosion
- Degradation
- Calcification
- Peri-implant complications due to mechanical loading
- But the worst is always…

Cell/tissue reaction to implant

- Soft tissue
- Hard tissue
- Blood cells

The biological milieu

- Atomic scale
- Molecular scale
- Cellular level
- Tissue
- Organ

But the human body differs in many other aspects as well… e.g. what is pH in humans?

The right question is "what is the pH where in the human body?"

- Gastric content 1.0
- Urine 4.5-6.0
- Intracellular 6.8
- Interstitial 7.0
- Blood 7.17-7.35

Sequence of local events following implantation in soft tissue

- Injury
- Actute inflammation
- Granulation tissue
- Foreign body reaction
- Fibrosis → e.g. new bone at a fracture point

Soft tissue response to an implant

- Actut (mins to hrs) - Cell type: Leukocytes - Function: Recognition, engulfment and degradation (killing)
- Chronic (days to months) - Cell types: Macrophages, monocytes and lymphocytes.
- Granulation tissue formation (3-5 days) - Cell types: Endothelial cells (forming blood vesssels), fibroblasts (forming connnective tissue)
- Foreign body reaction (days to life time) - Cell types: Foreign body giant cells, Macrophages, fibroblasts
- Fibrosis & Fibrous encapsulation - Cell type: Fibroblasts

Test Hierarchies (for blood-contacting device)

- Cell culture, cytotoxicity (Mouse L929 cell line)
- Hemolysis (rabbit or human blood)
- Mutagenicity (Ames test)
- Systemic injection, acute toxicity (Mouse)
- Sensitization (Guinea pig)
- Pyrogenicity (Rabbit)
- Intramuscular implantation (Rat, rabbit)
- Blood compatibility
- Long-term implantation.

Standards

Test methods, Materials standards, Device standards, Procedure standards

- ISO 10993-1 (or EN 30993): Guidance on selection of tests
- ISO 10993-2: Animal welfare requirements
- ISO 10993-3: Test for genotoxicity, carcinogenicity and reproductive toxicity
- ISO 10993-4: Selection of tests for interactions with blood
- ISO 10993-5: Tests for cytotoxicity: In vitro methods
- ISO 10993-6: Test for local effects after implantation
- ....

Testing of Biomaterials

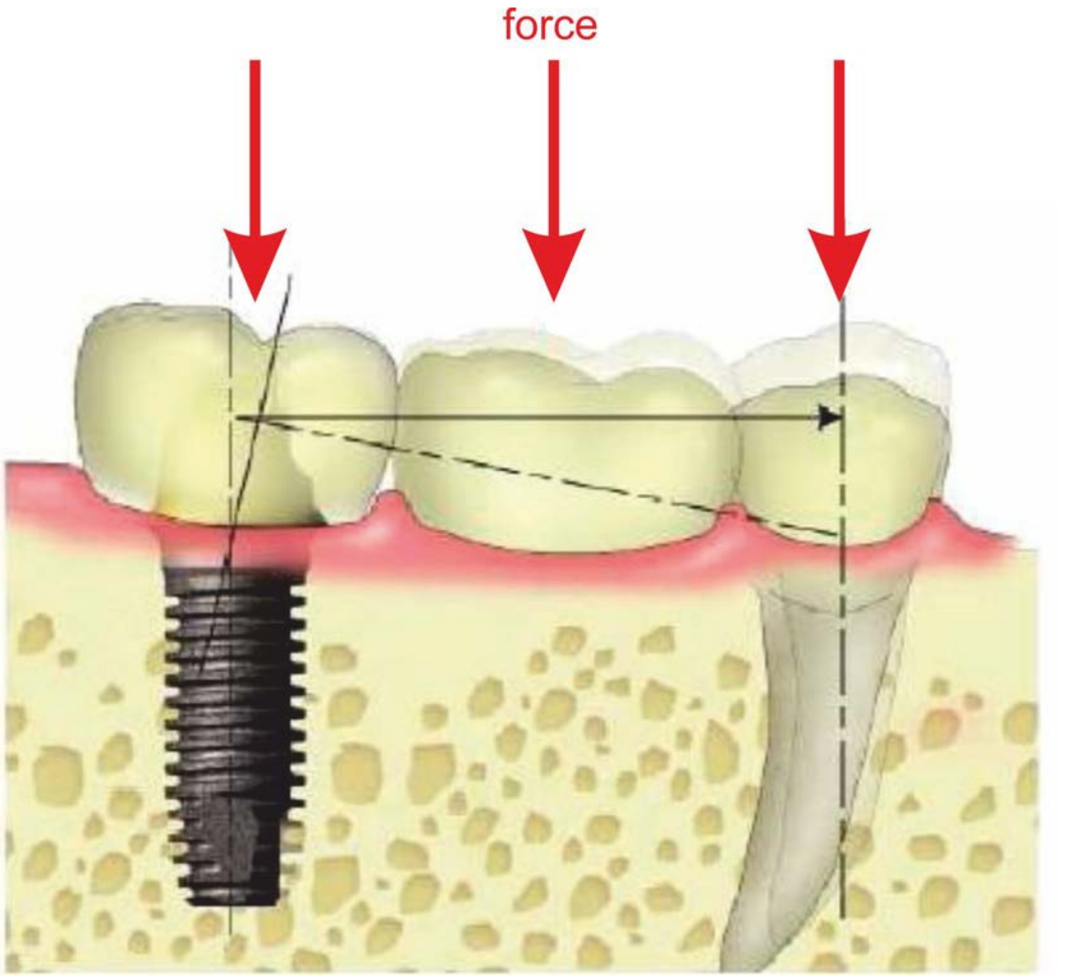
- Physical and mechanical
- Biological (In vitro, in vivo, in ovo, Functional and Clinical assessment)

3-principles in dental implant design

- Initial retention
- Anti-rotation mechanics
- No sharp-edges

General criteria for tooth filling materials

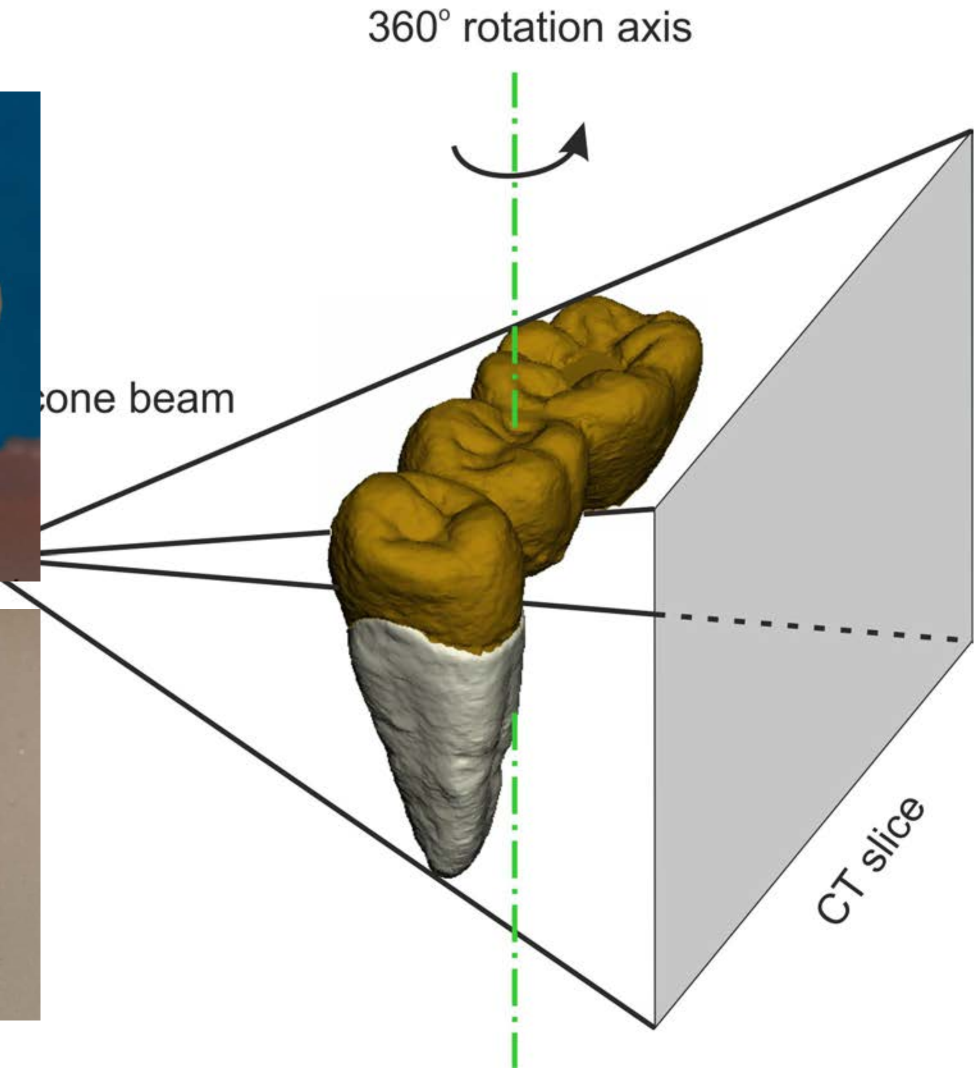
- Non-irritation to pulp and gingival
- Low systemic toxicity
- Cariostatic
- Bonding to tooth substance without marginal leakage
- Not dissolved or erode in saliva
- Mechanical strength, wear resistance, modules matching… implant failure?
- Good aesthetic properties
- Thermal properties (expansion & conductivity)
- Minimal dimensional changes on setting and adequate working time and radio opacity
- Functional aspects/implant mechanics



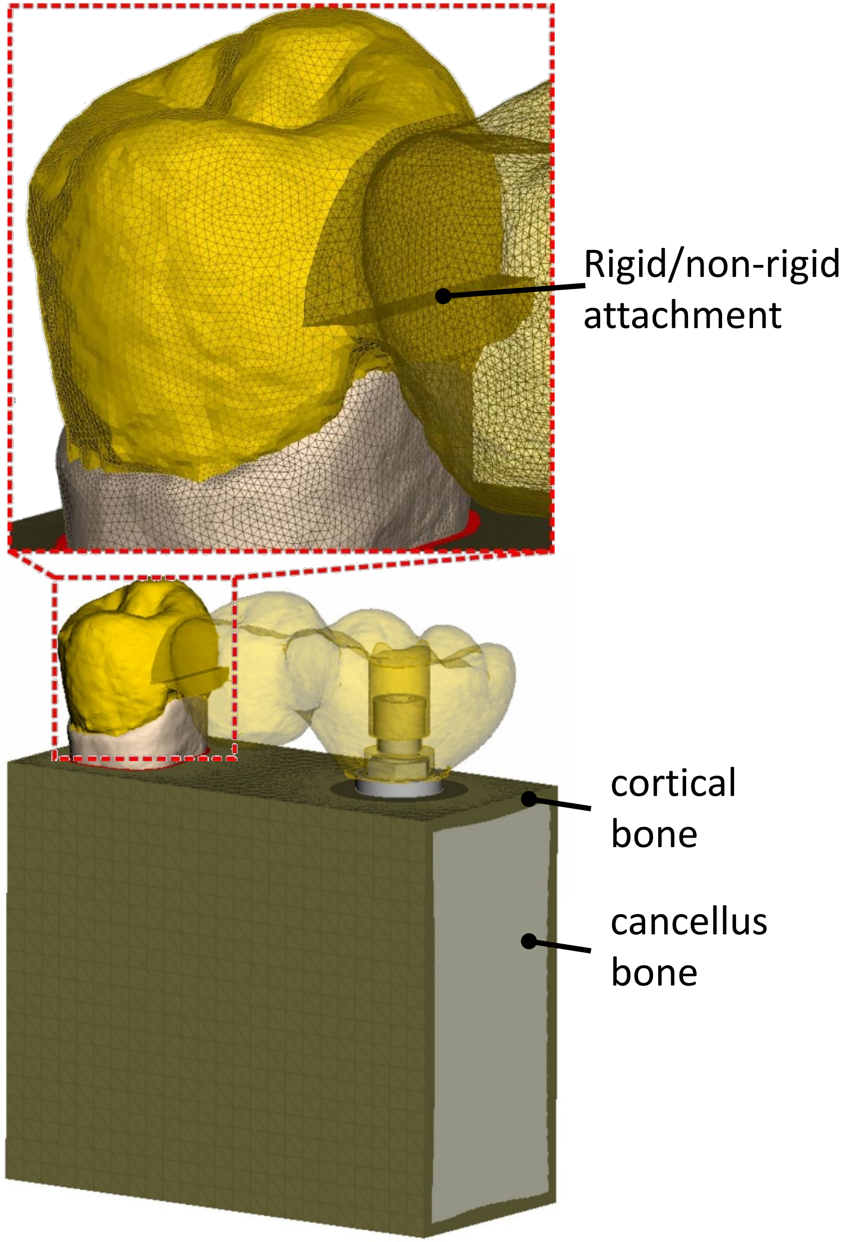
Does bone quality have an effect on the biomechanical behavior of a tooth connected to an implant, when a rigid and a non-rigid attachment is used ?

Yes, rigid vs. non-rigid connection is a preoperative decision which should be taken with respect to bone quality.
Although we would suggest avoiding this type of connection altogether!

A. Tsouknidas et al. (2016) Int J Oral Maxillofac Implants. 31(6):e143-e154

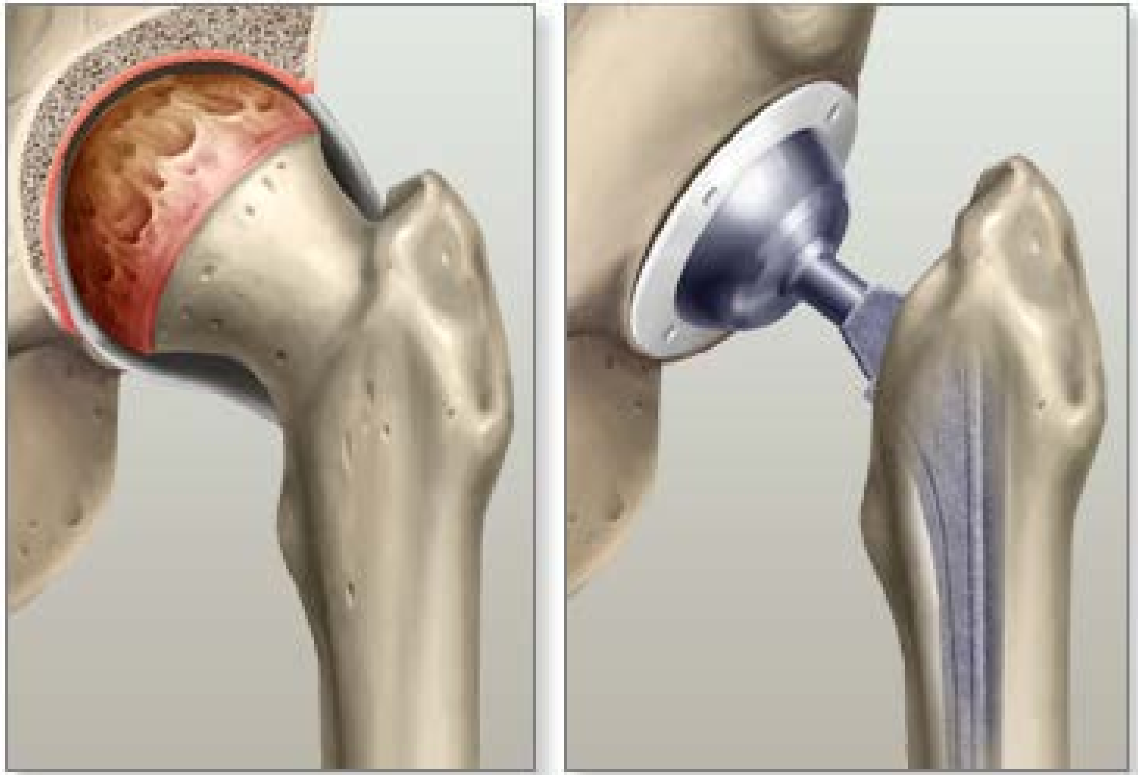

360° rotation axis
cone beam
CT slice


abutment screw
4.3 mm
externally-hexed implant
4.0 × 13 mm (Biomet 3i)


Rigid/non-rigid
attachment
cortical
bone
cancellus
bone

Hip joint prosthesis

What materials do we use in hip joint prosthesis to account for local bone complexity and joint mechanics?



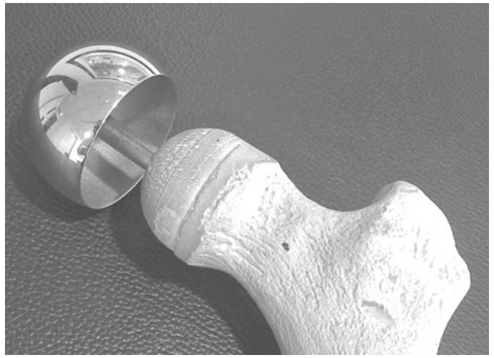
Typical indicators for hip surgery

- Due to fracture
- Due to arthritis

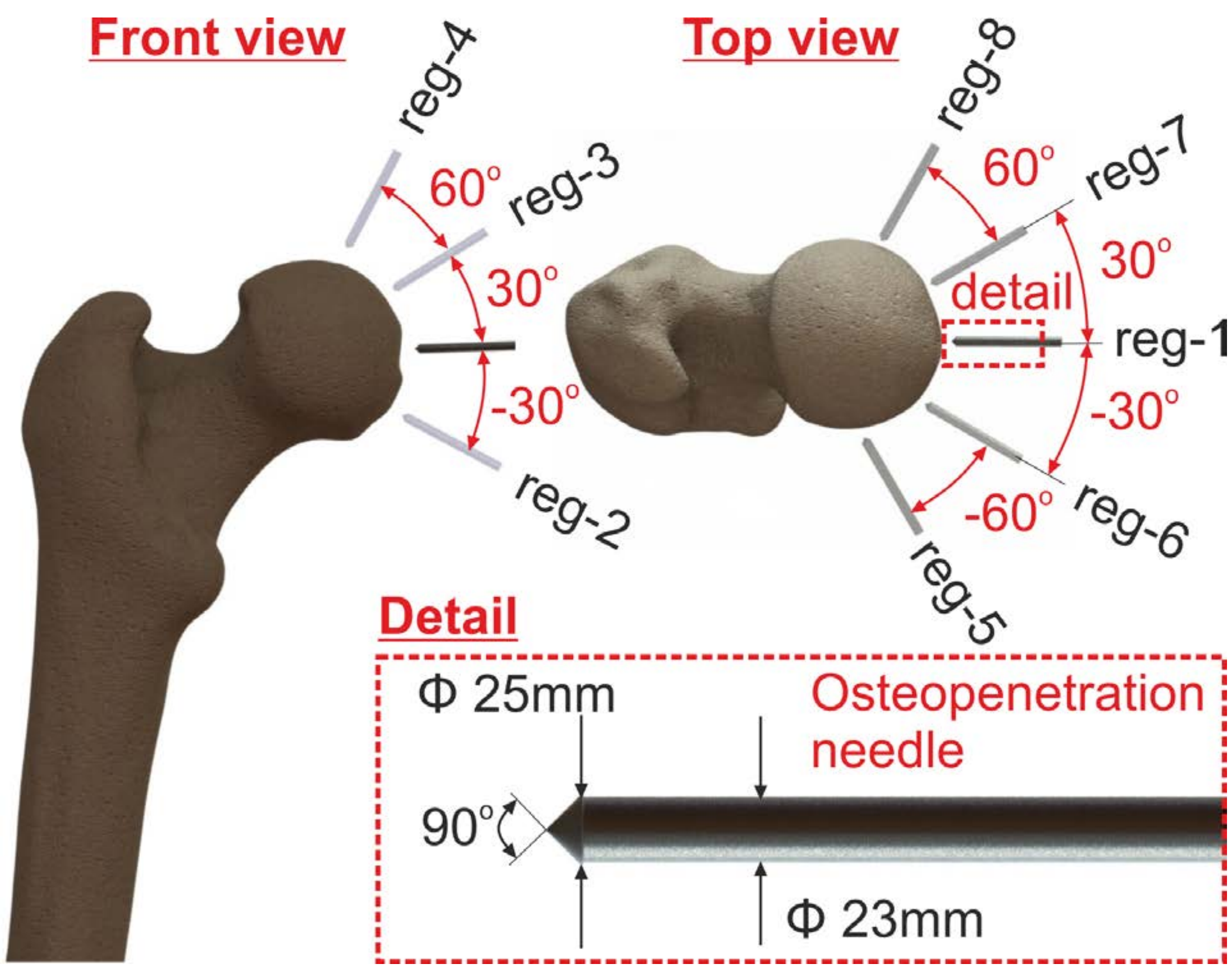
Aspects to consider

- *Life spam ≈ 10-15 years*
- *Stressed higher in young patients*

The solution



The new problem… bone anisotropy!



A. Tsouknidas et al. (2015) Clin. Biomech. 30(5):418-23.

Aspects to consider

(during experimental planning)

- *Age?*
- ~~*Gender?*~~
- *Osteoarthritis*
- *Osteoporosis*

Osteopenetration energy

- Higher in osteoarthritic samples
- Lower in Osteoporotic ones
- Why?

What could we change to facilitate better anchorage?

Stem material or treatment (e.g. thermal)!

Introduced in 1958 by Sir John Charnley (for secure fixation of the femoral & acetabular components), PMMA was the first and still remains the most commonly used bone cement in orthopedics.

PMMA has an elasticity modulus inbetween hyperelastic bone and Ti, thus mediating stress shielding phenomena. Which one is correct $E_{titanium}<E_{PMMA}<E_{bone}$ or $E_{titanium}>E_{PMMA}>E_{bone}$?

The main advantage of PMMA is…

Popular Additives are:

- Chlorophyllin, adds a distinctive green colour, aiding visualisation and correct placement
- Barium sulphate, aiding visualisation on postoperative radiographs to assess implant quality
- and of course… antibiotics! *Stay tuned for a relevant experiment…*

PMMA cement is packaged in the form of a liquid monomer & a powder copolymer. These are mixed together at the time of use and undergo polymerisation to form a viscous material which can be moulded and inserted into the required location. The transition from liquid to a useable paste is quick, and PMMA sets as a solid in ≈ 9 min.

PMMA's most common applications are:

- Joint reconstruction (hip, knee and shoulder arthropiasties)
- Oncology (as an allograft bone filler)
- Spinal surgery (Vertebral crush fractures)

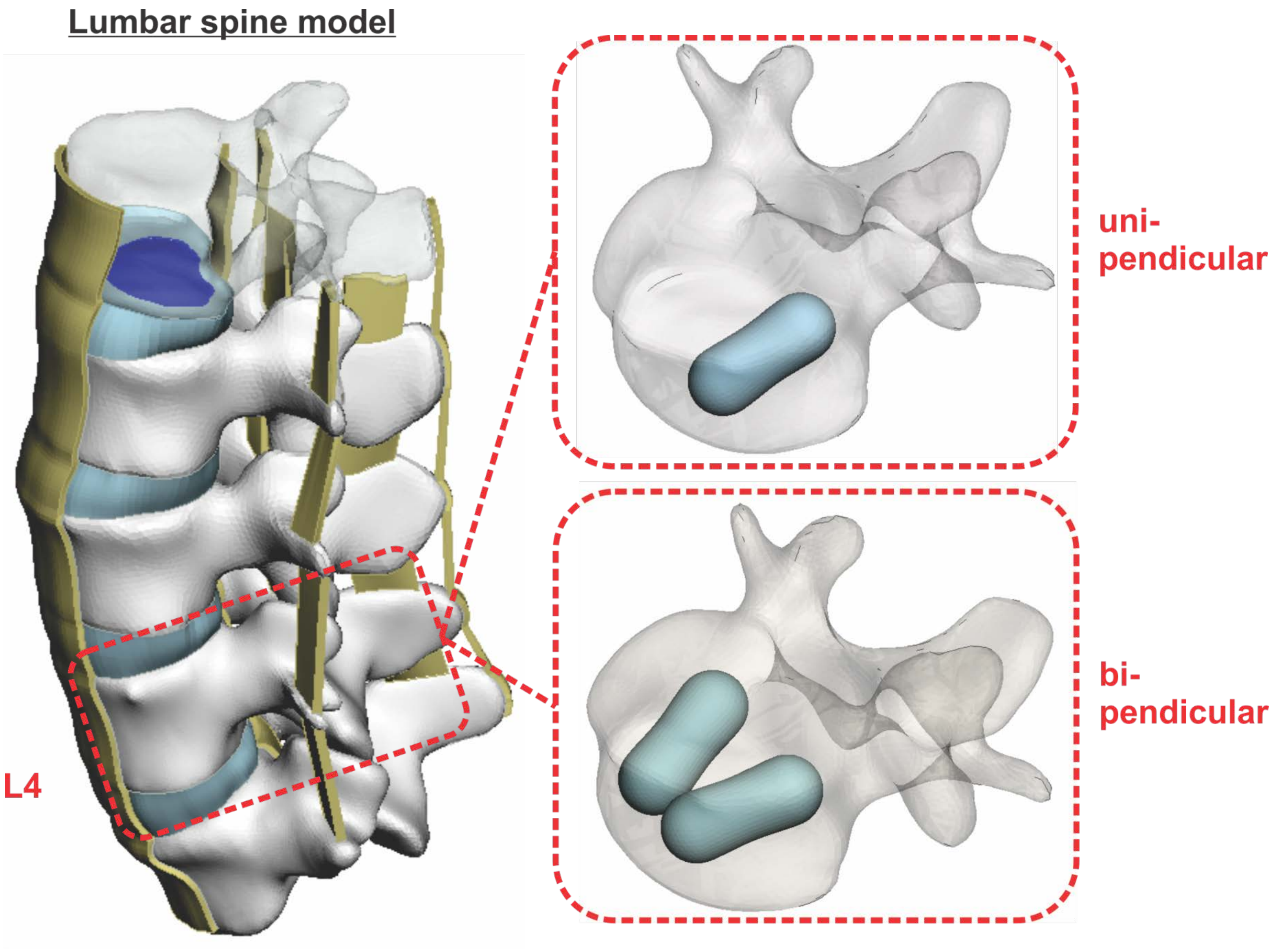
Complications:

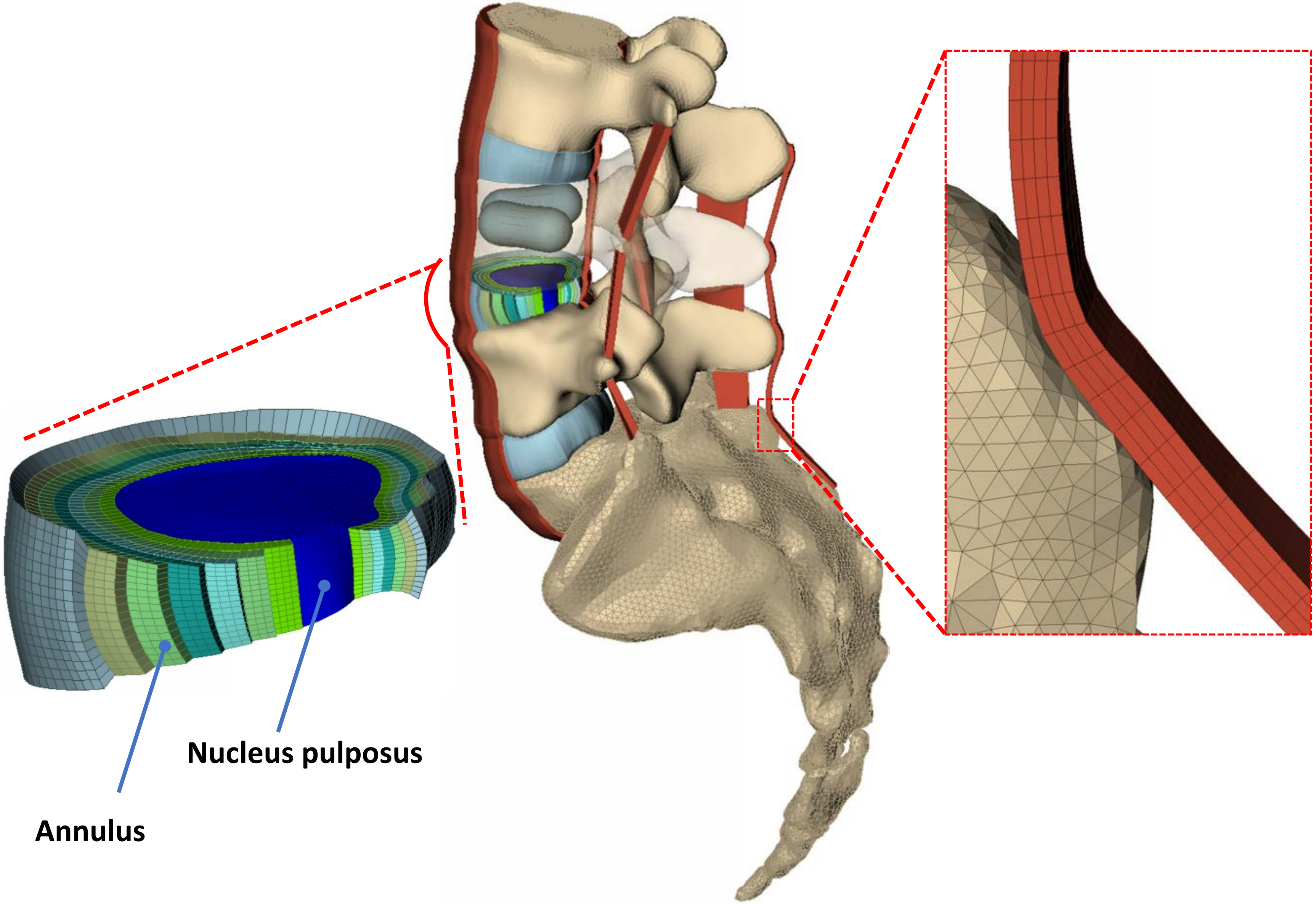
- Bone cement implantation syndrome (BCIS)

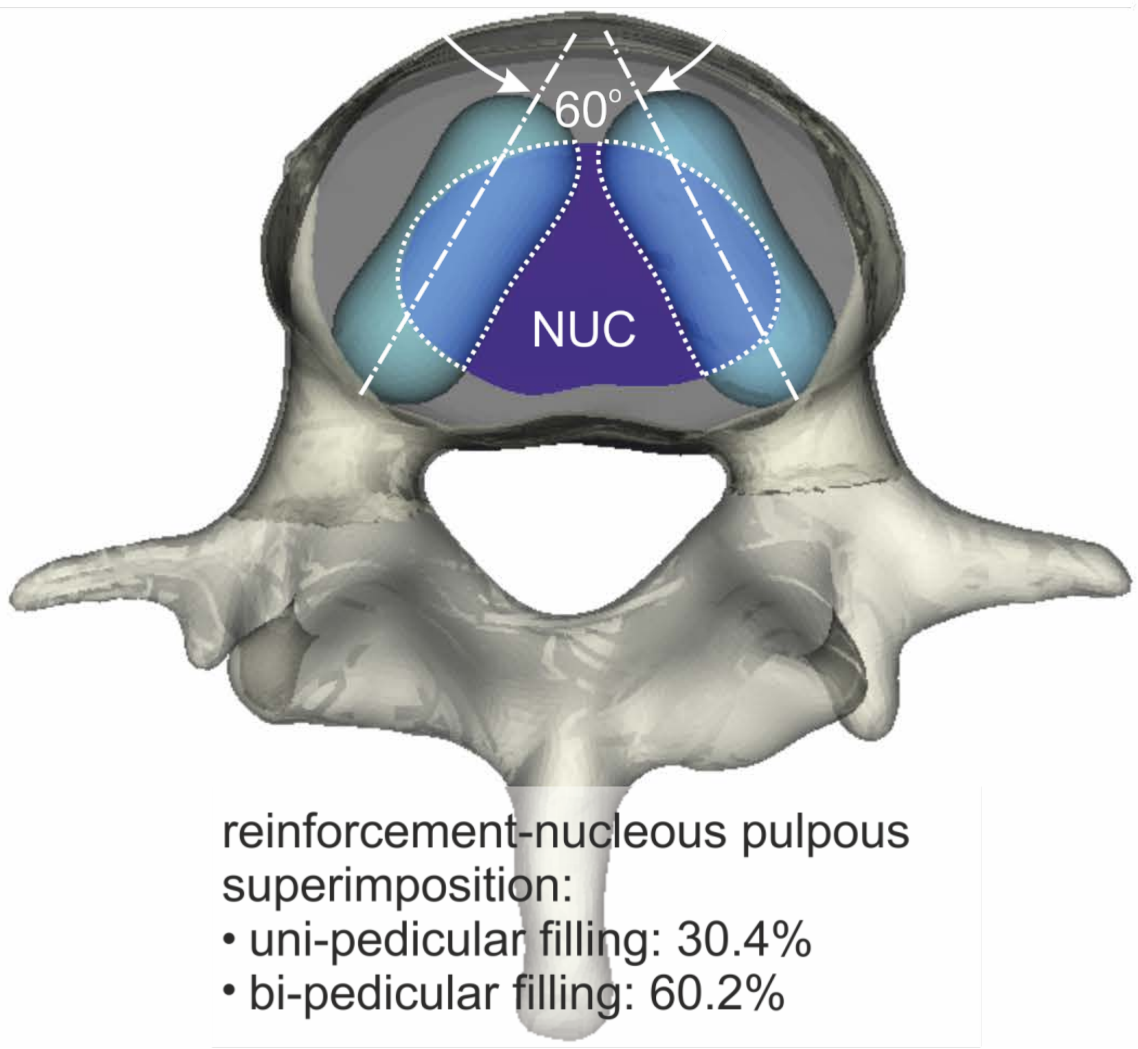
  Ought to toxicity of the cement monomer (MMA) on the cardiovascular system, or microemboli into the systemic circulation
- Thermal injury!

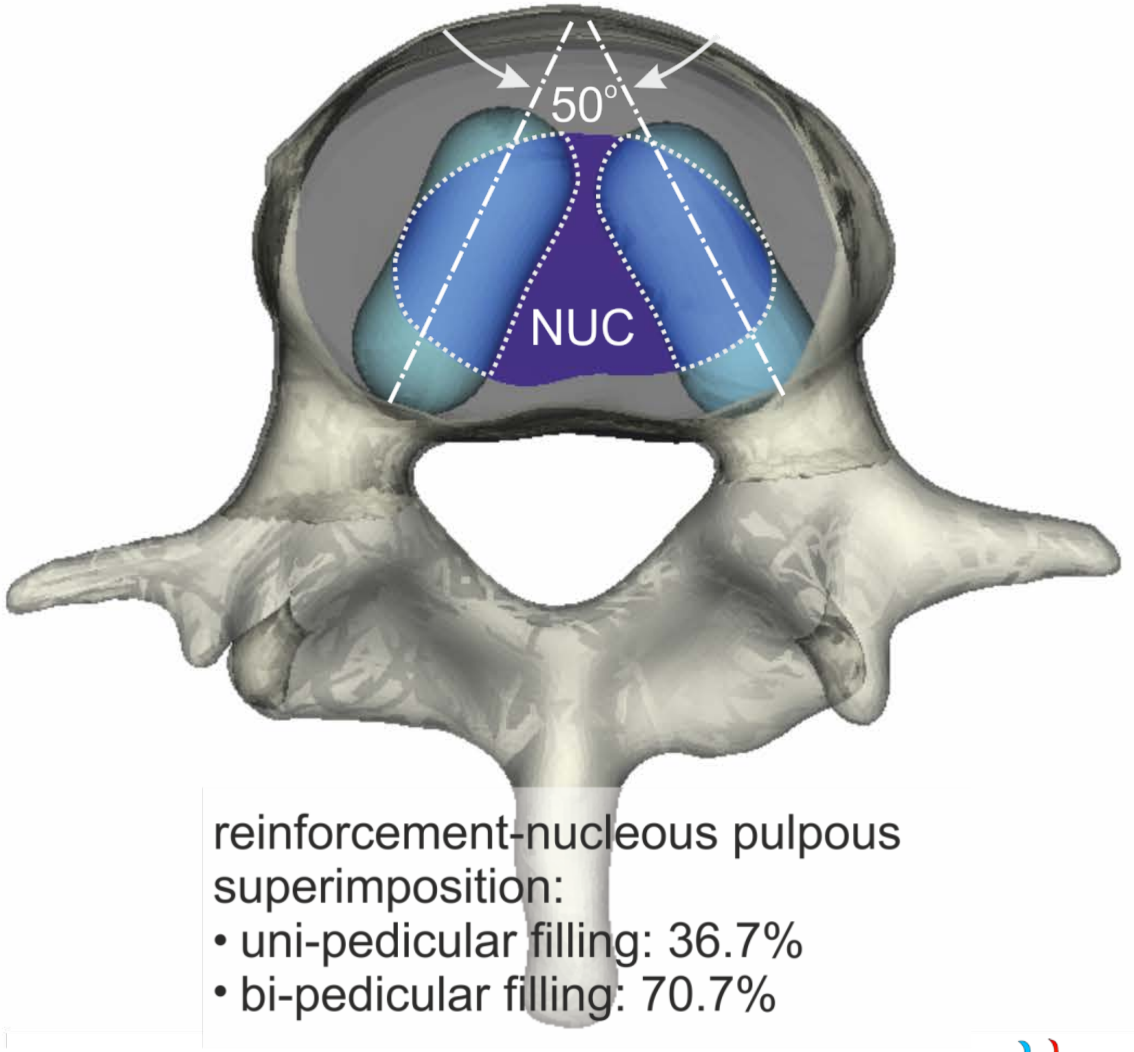
  PMMA polymerization is highly exothermic and temperatures can reach as high as 110°C
- Leakage

  If placed prior to reaching its past-like state it may leak into the surrounding anatomy and cause significant surgical complications.


Lumbar spine model
L4
uni-
pendicular
bi-
pendicular

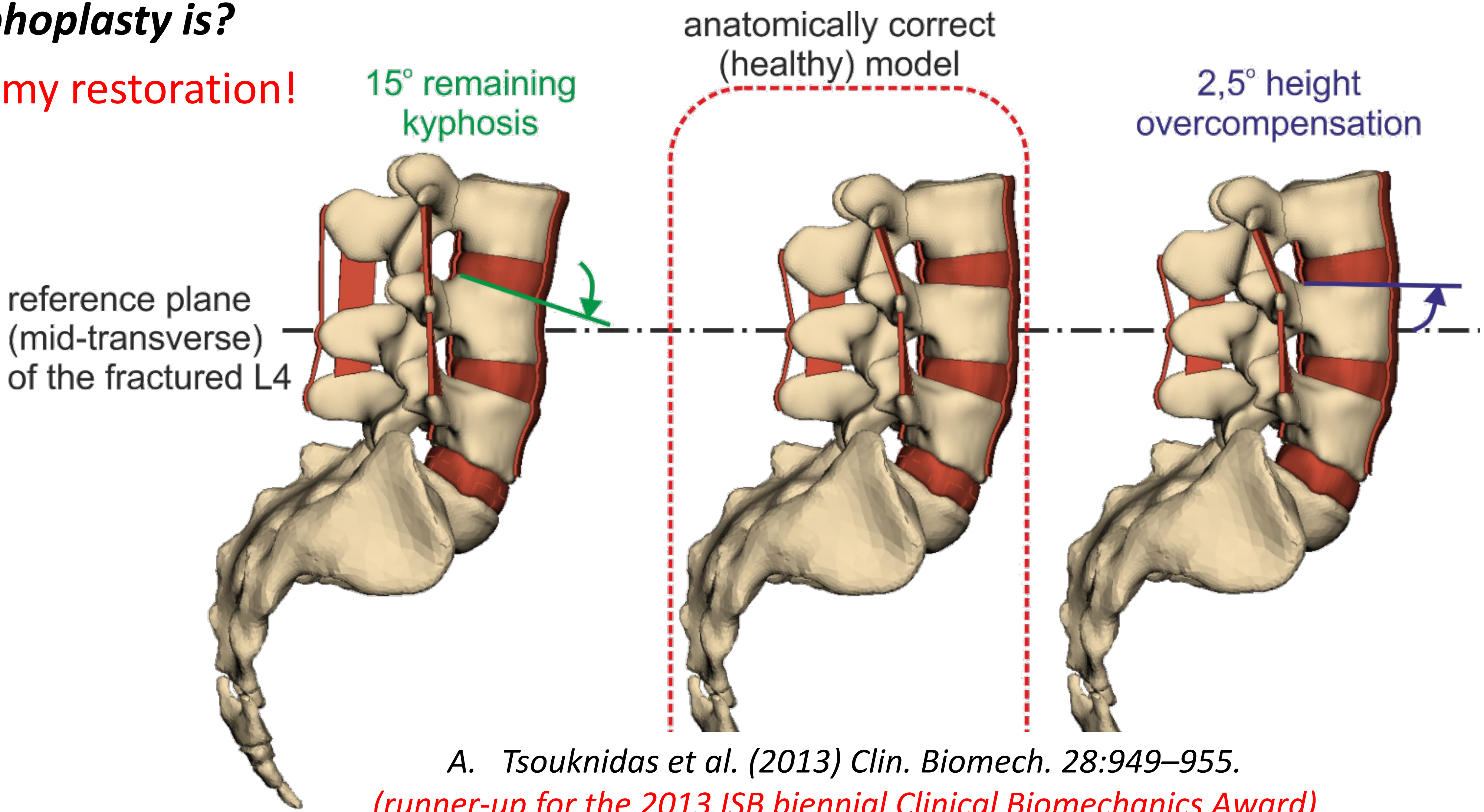

Nucleus pulposus
Annulus


60°
NUC
reinforcement-nucleous pulpous superimposition:
• uni-pedicular filling: 30.4%
• bi-pedicular filling: 60.2%


50°
NUC
reinforcement-nucleous pulpous superimposition:
• uni-pedicular filling: 36.7%
• bi-pedicular filling: 70.7%

Anyone care to guess what the simple most important factor for positive surgical outcome in kyphoplasty is?

Anatomy restoration!



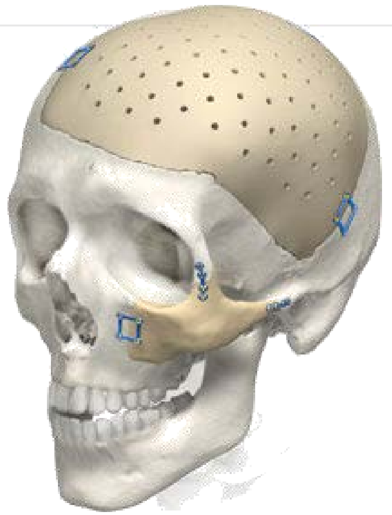
A. Tsouknidas et al. (2013) Clin. Biomech. 28:949–955.

(runner-up for the 2013 ISB biennial Clinical Biomechanics Award)

The rise of PEEK (Polyether ether ketone):

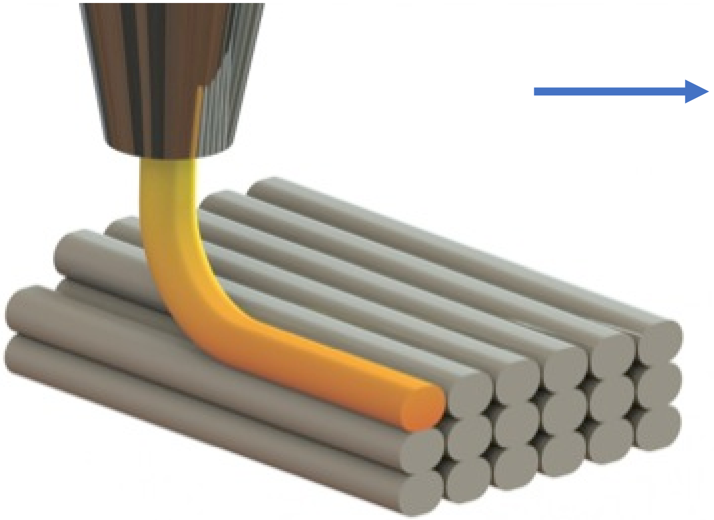
Initially used in spine and hip surgery, PEEK is rapidly becoming the implant material of choice not only for orthopedic surgeons but also dentists. PEEK is:

- highly biocompatible,
- Can become Bioactive e.g. through the incorporation of hydroxyapatite,
- resistant to thermal and ionizing radiation,
- biomechanically resembles cortical bone,
- Requires minimal to no intraoperative adjustments (CAD/CAM manufacturing)
- Exceptional cost to performance ratio



The exceptional potential of PEEK lies in its thermoplastic properties and low melting point (jet higher than most polymers)!

- SLS (Selective Laser Sintering)
- FDM (Fused Deposition Modelling)



Cost efficient additive manufacturing (FDM)

Sunday 14th of April

Medical imaging & Modeling

Quick intro to next semester's Bio-printing lab

with Prof. E. Varitis and MSc. N. Ntinas

Endless capabilities

3D-printed

Bionic prostheses

Bionic implants differ from mere prostheses by mimicking the original function very closely, or even surpassing it. What to be need?

- Biomaterials
- Design and Optimization techniques
- Customizable manufacturing (RP)
- Bio-sensors… so biomaterials again!

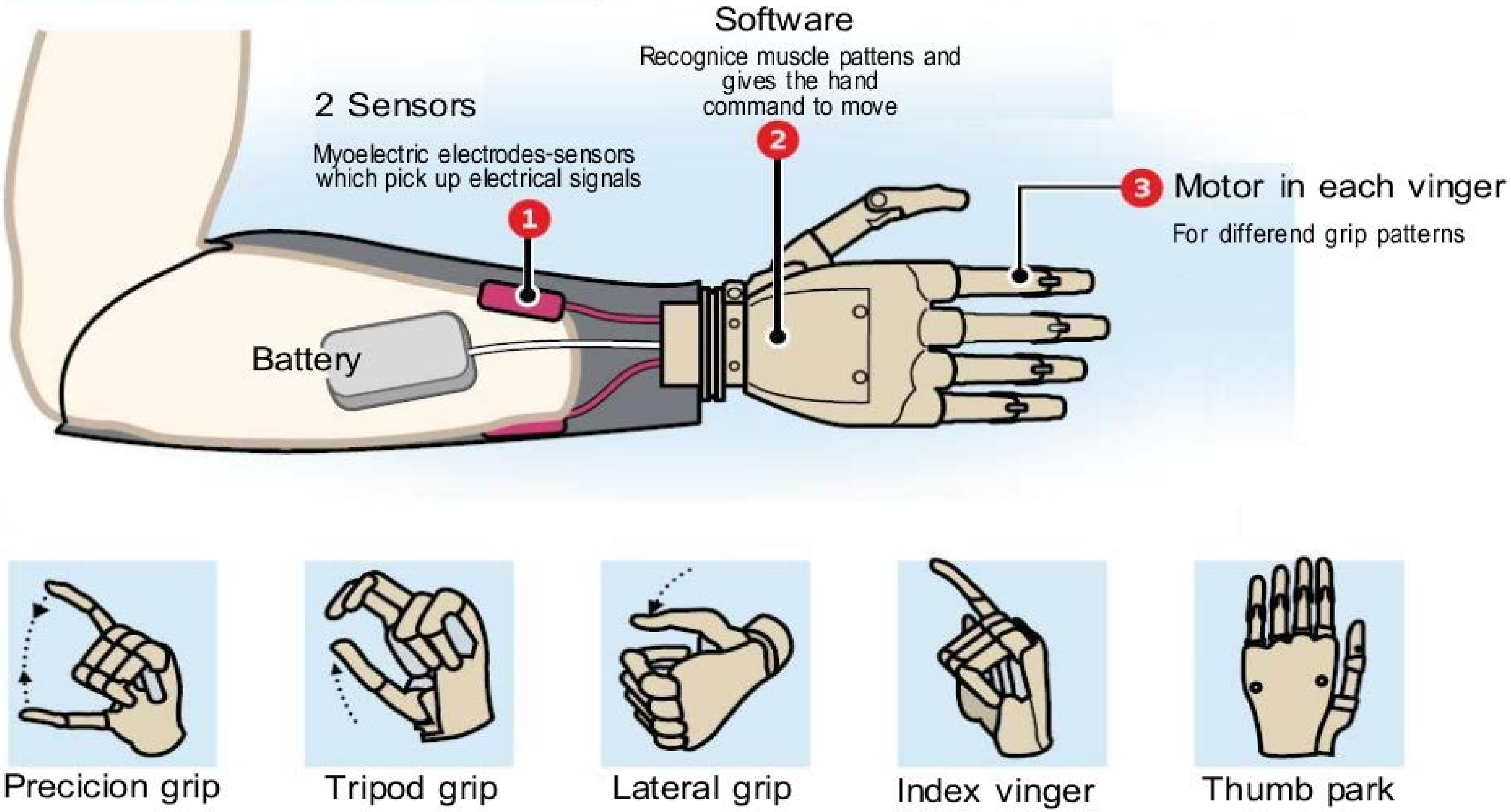
Saturdy 6th of April

Experimental Biomechanics (in Serres), Introduction to multichannel EMG (next semester's "Bio-Sensors") with Prof. F. Arabatzi and MSc. M. Papagiannaki

i-Limb Ultra (18.000$ Functional prosthetic hand)

- Fingers that move independently & bend at natural joints.
- Manually rotatable thumb.
- Multi-flex wrist option or manually rotatable.
- skin coverings (both active and natural).
- Variety of automated grips along with custom gestures.

Bionic hand



EMG sensor records the electrical impulse generated during a movement of the existing limb and translates it into intended movement, driving the bionic hand (AI)

In order to utilize these concepts we need…
basic material science knowledge!

Imperfections in Crystals, *Thermal & Mechanical treatment, Diffusion,*
Fracture & Fatigue, Tribology & Wear