

Knowledge  
Based  
Materials

19th-29th August, 2008,  
Trest, Czech republic

## bone and wood as intelligent materials - adaptation and healing

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Department of Biomaterials  
Potsdam



Max Planck Institute  
of Colloids and Interfaces



### outline

#### first presentation (last Thursday):

- structure of bone and wood
- bone and wood as cellular solids
- building with fibers
- bone and wood as nanocomposites
- fluid flow in bone

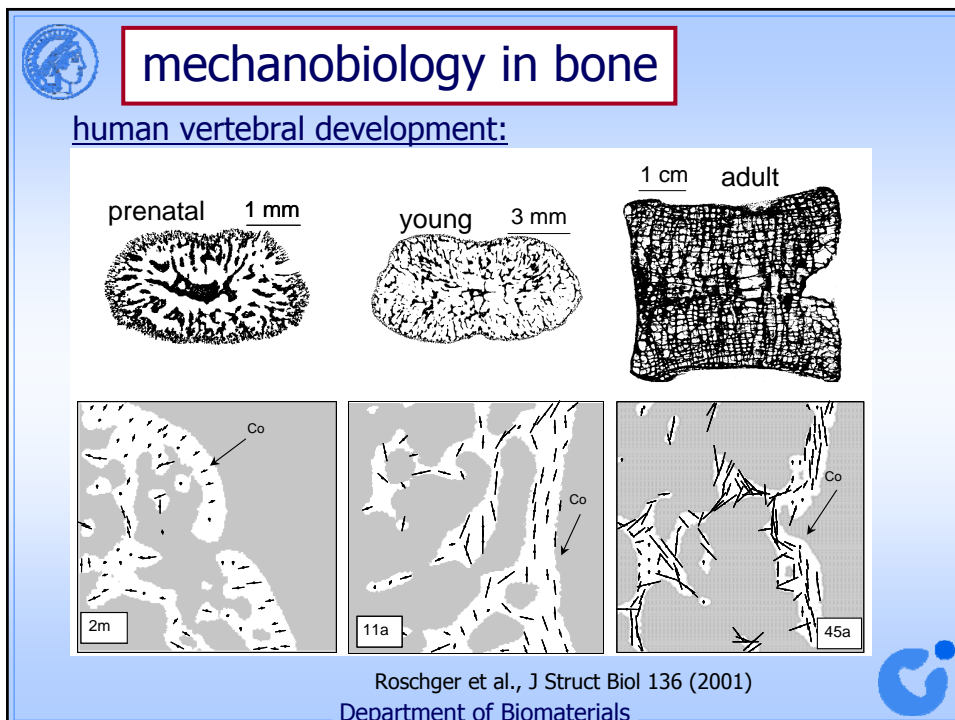
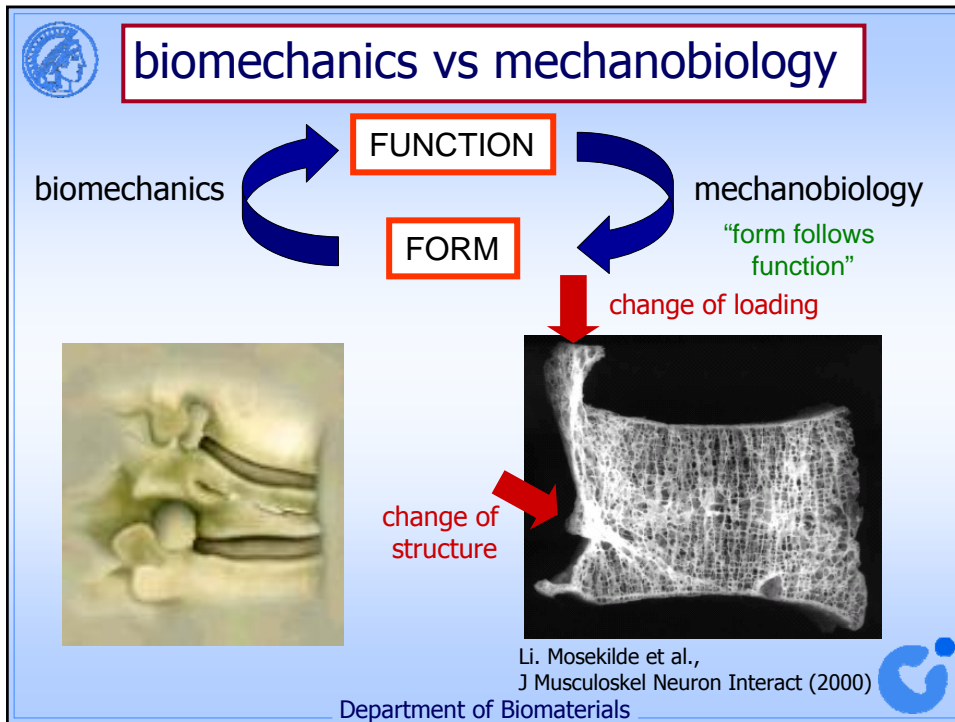
#### second presentation (today):

- bone remodeling
- bone mineralization
- bone fracture healing


static  
dynamic



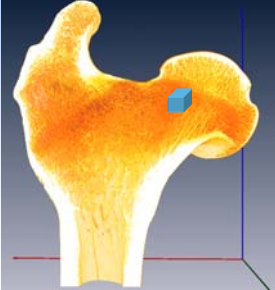
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**trabecular bone architecture – Wolff's law**

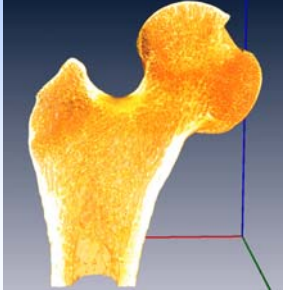



**Papio**  
**WALKER**



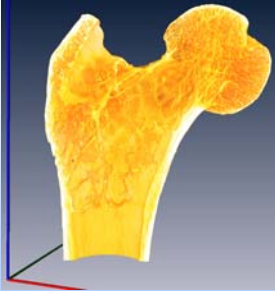


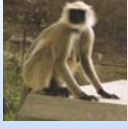
**Hylobates**  
**HANGER**



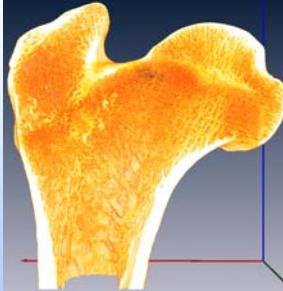


**Alouatta**  
**CLIMBER**





**Presbytis**  
**SPRINGER**

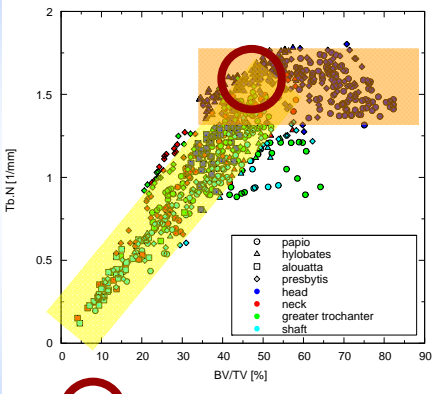


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**mechanisms of trabecular bone adaptation**

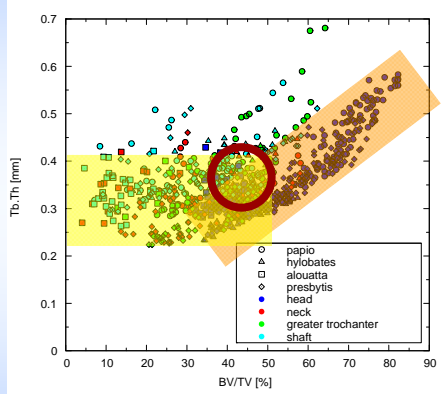
**mathematical tool: image analysis**

**RESULTS**



Tb.N [1/mm]

BV/TV [%]



Tb.Th [mm]

BV/TV [%]

newly created trabeculae

decrease in BV/TV by removing trabeculae

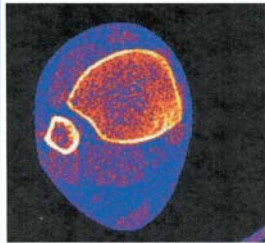
increase in BV/TV by thickening existing trabeculae

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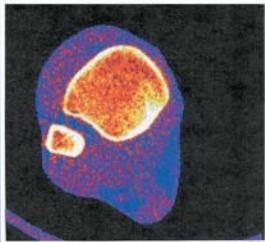


## mechanobiology in bone

further examples:



human distal tibia:



Heinonen et al., Bone 29 (2001)

greyhounds:



Johnson et al., Bone 27 (2000)

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## BONE vs WOOD

resorption/deposition  
of material

adaptation on  
the tissue level

only deposition of  
new material

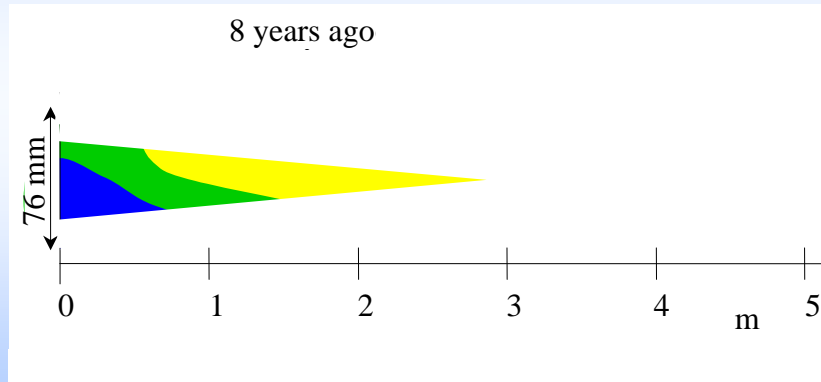
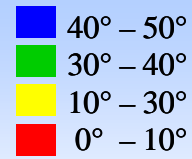
adaptation on  
the material level

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## microfibril angle distribution in the vertical section of a spruce branch



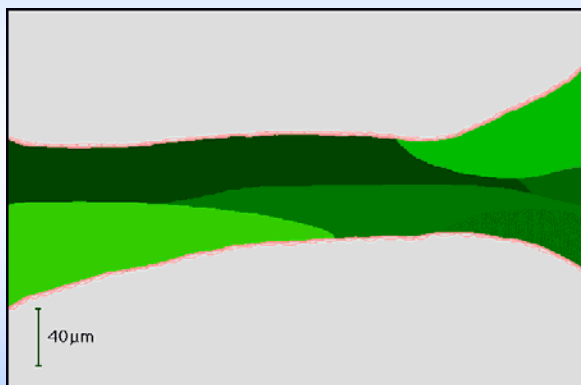
J. Färber et al., J. Mater. Sci. (2001)

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## bone: a living material

### BONE REMODELING:



### BONE CELLS:

- **osteoclasts:**  
bone resorption  
(at the surface)
- **osteoblasts:**  
bone formation  
(at the surface)
- **osteocytes:**  
mechanical sensors  
(inside of bone)

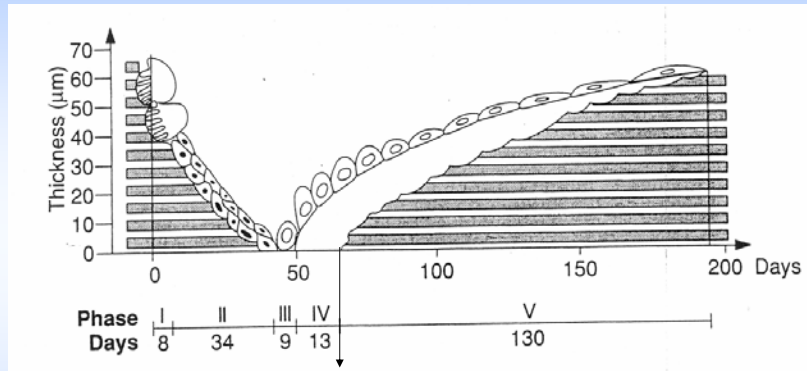
<http://courses.washington.edu/bonephys/opmovies.html>

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## remodeling sequence



start of mineralization

- bone remodeling occurs at about 1 to 2 million microscopic sites per adult skeleton
- 25% of trabecular bone volume is renewed each year



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## bone: an intelligent material



### Wolff-Roux law:

(Roux: Der Kampf der Teile im Organismus, 1881  
Wolff: Das Gesetz der Transformation der Knochen, 1892)

“Bone is deposited wherever mechanically needed and is resorbed where it is not needed”

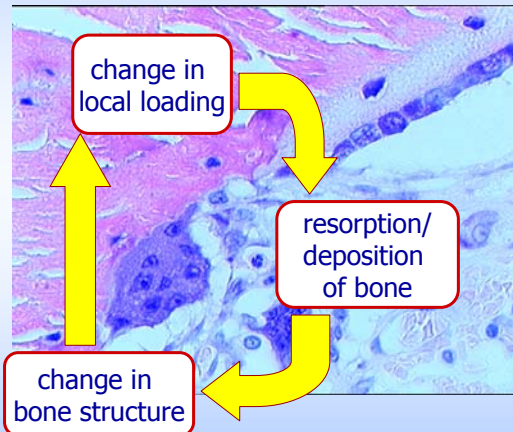


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## how does the remodeling system work?

LOAD



„mechanostat“  
(H. Frost)

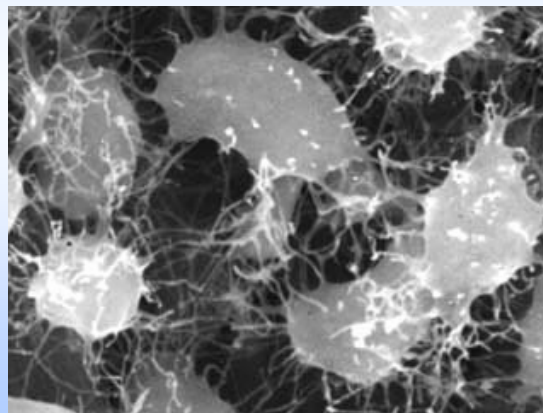
mechanical regulatory cycle (feedback loop)

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## open questions

- reason for bone remodeling?
- the nature of the signal?
- what is the mechanical stimulus the cells are reacting to?
- what is the connection between dysfunctions of the control system and bone diseases like osteoporosis?



osteocytes  
inside bone

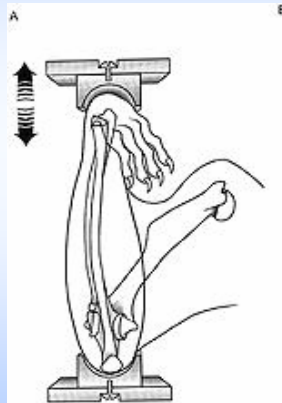
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## in vivo experiments:

mechanical loading → structure

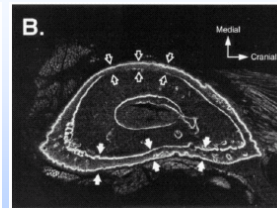
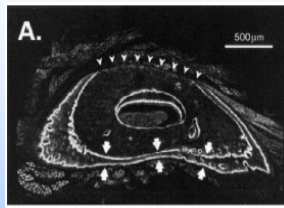


### increased loading:

- exercise
- osteotomy
- devices to apply controlled loading

### decreased loading:

- casting
- hindlimb suspension
- space flight
- bedrest



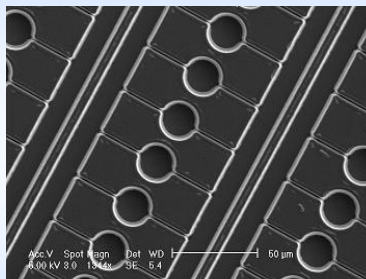
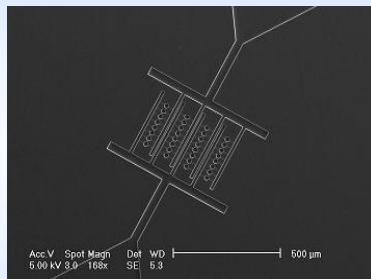
Mosley and Lanyon, Bone 23 (1998)

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## in vitro experiments:

3D microfabricated flow system:



Jacobs et al., The Cell and Molecular Biomechanics Laboratory at Stanford University

→ response of the osteocyte processes to fluid flow

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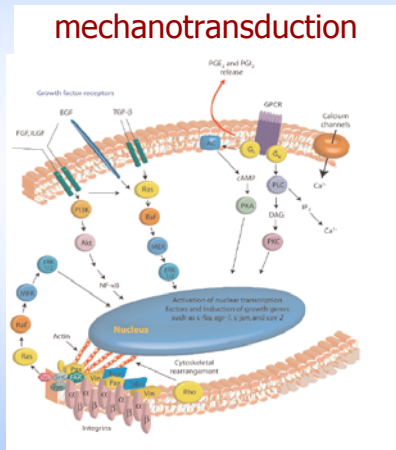




## computer experiments

„realistic“ description:

mechanical  
stimulus



cell reaction  
local bone  
resorption/depositon

Hughes-Fulford,  
*Science's STKE* (2004)



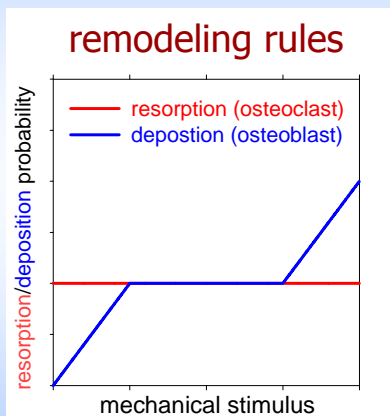
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## computer experiments

phenomenological description:

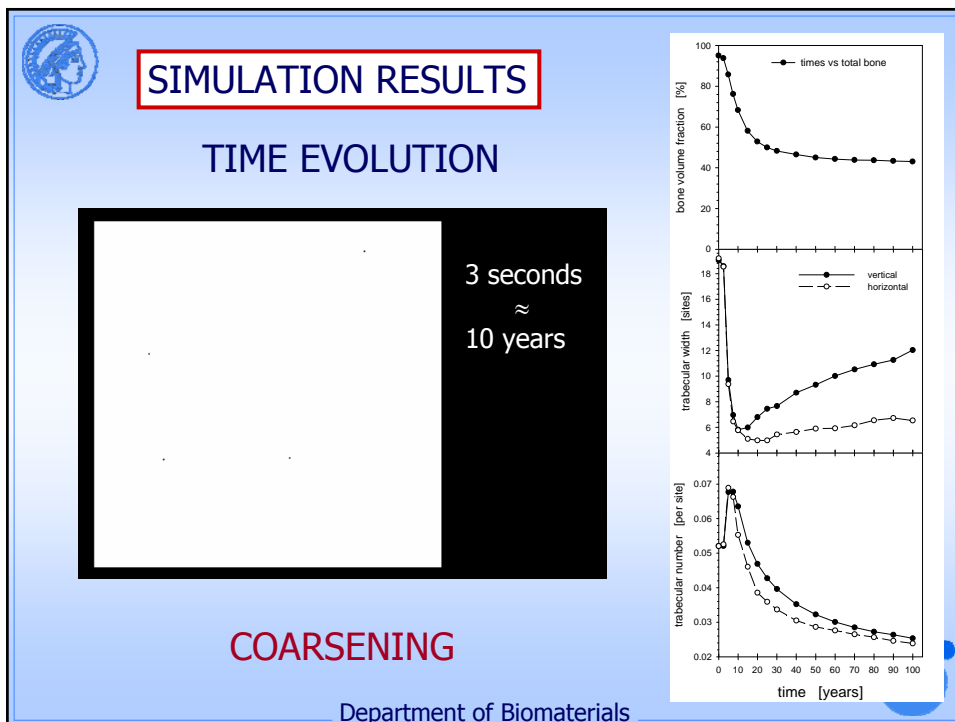
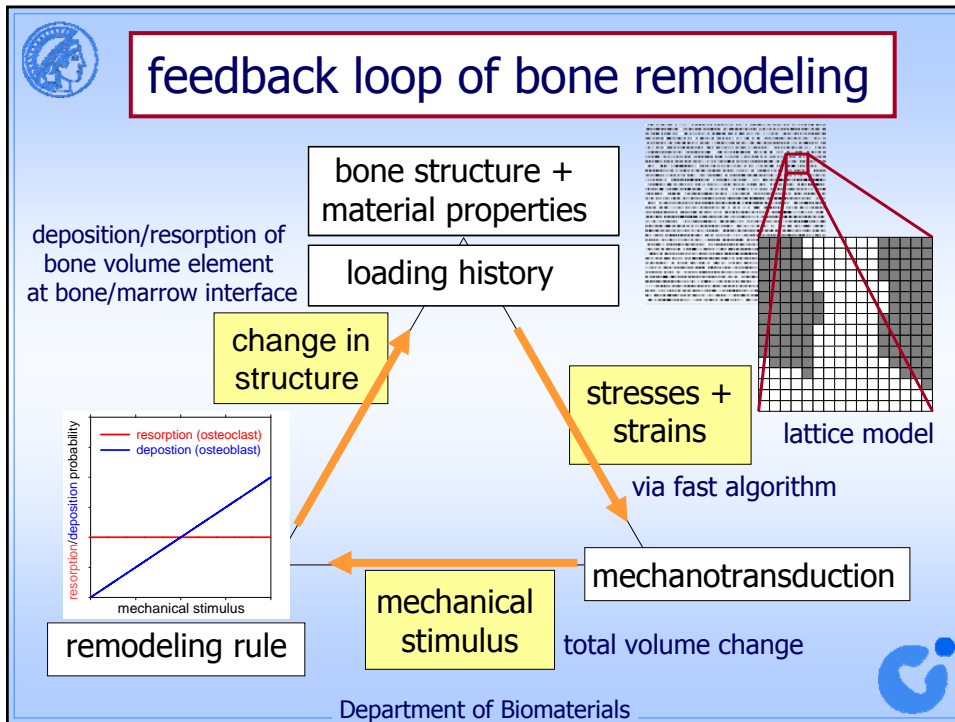
mechanical  
stimulus

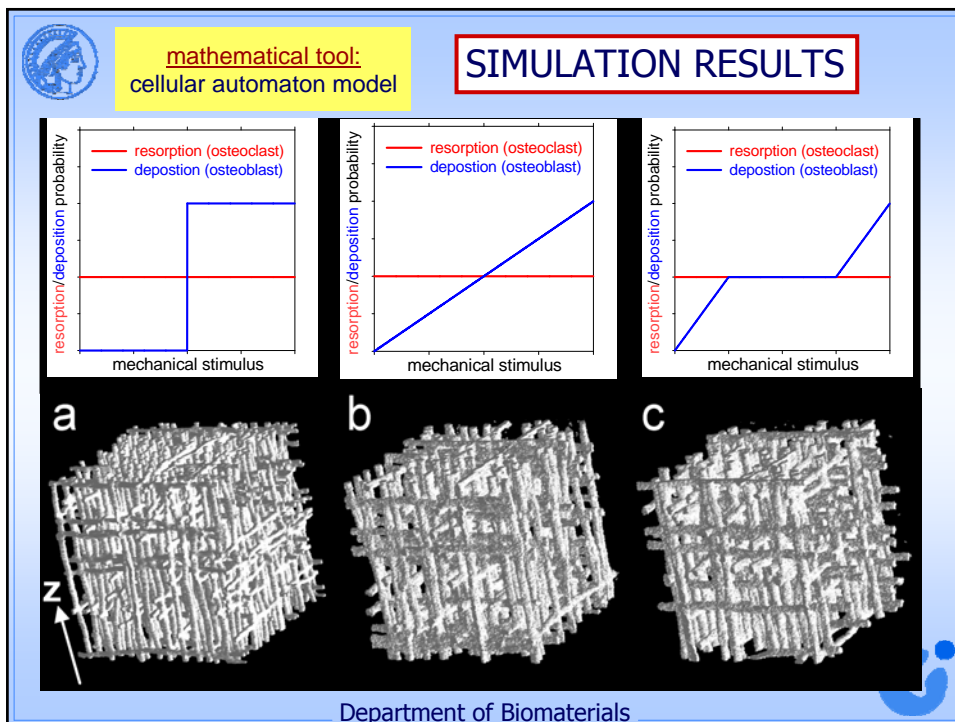
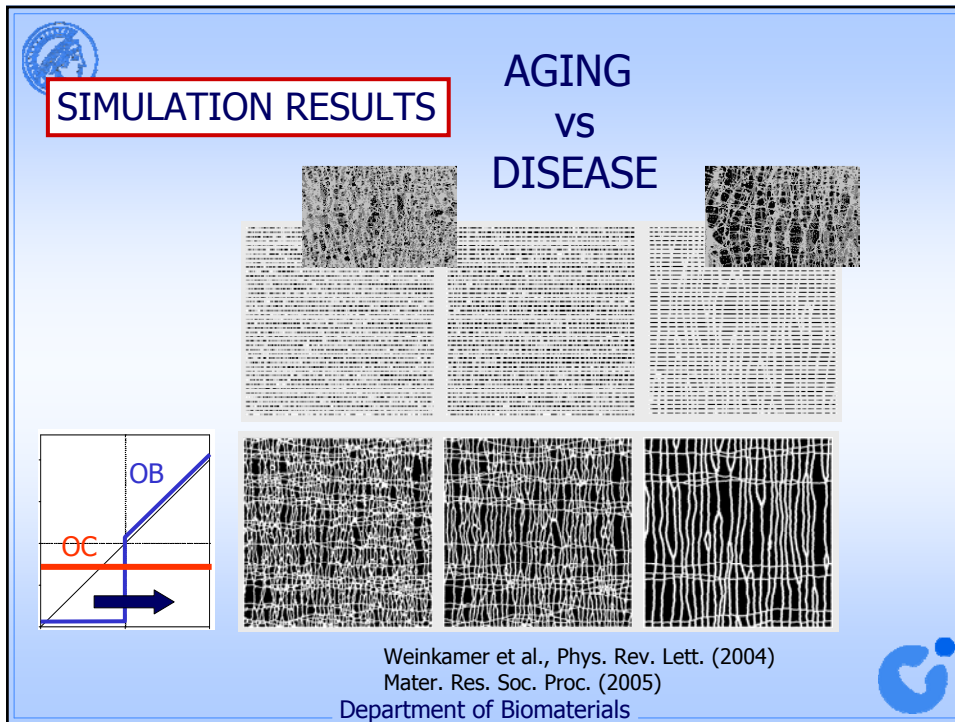


cell reaction  
local bone  
resorption/depositon



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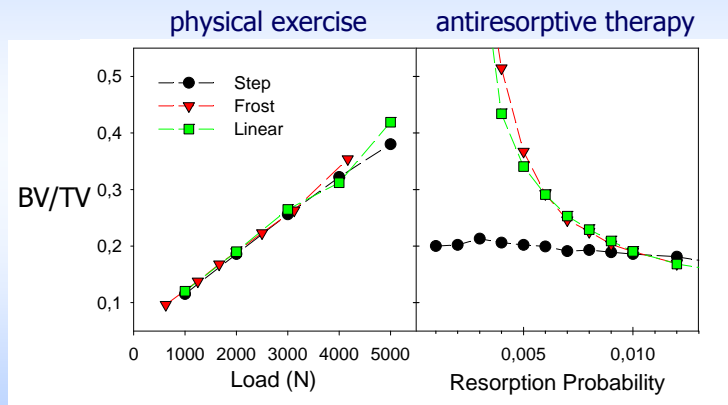






### QUESTION:

what is the effect of different therapies on the virtual bone with different remodeling rules?



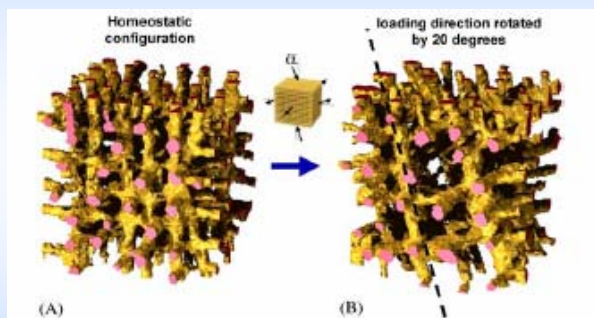
Dunlop et al., submitted

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### SIMULATION RESULTS

adaptation to alternative loading directions:  
(bone modeling)




Ruimerman et al., J Biomechanics 38 (2005)

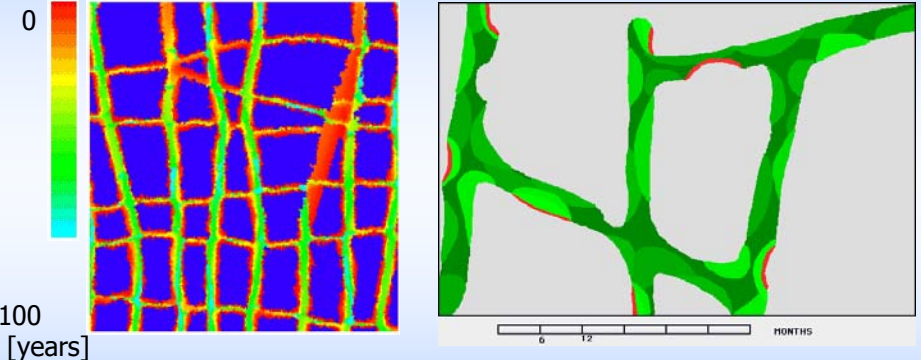
reorientation of the trabecular structure  
after 12 simulated years still not completed !

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 dynamics of the architecture → dynamics of the material

**AGE DISTRIBUTION** **BONE REMODELING**




0  
100 [years]


0 12 MONTHS

heterogeneous mineralization due to:

- remodeling process
- mineralization process

<http://courses.washington.edu/bonephys/opmovies.html>

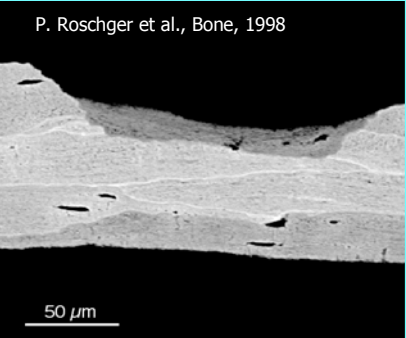
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 how to describe the heterogeneous mineralization?

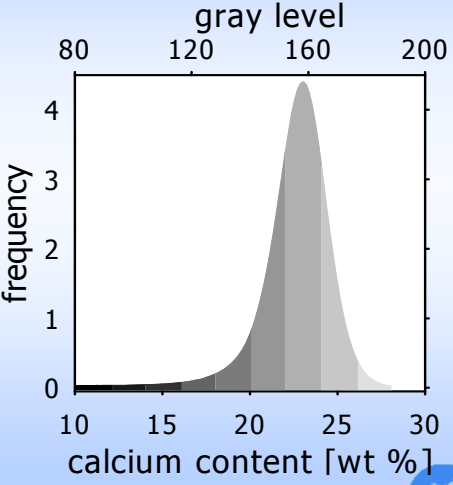
**Bone Mineralization Density Distribution (BMDD)**

measurable quantity  
(quantitative Backscattered Electron Imaging (qBEI))

P. Roschger et al., Bone, 1998



50 μm



gray level


80 120 160 200

frequency

4  
3  
2  
1  
0

10 15 20 25 30

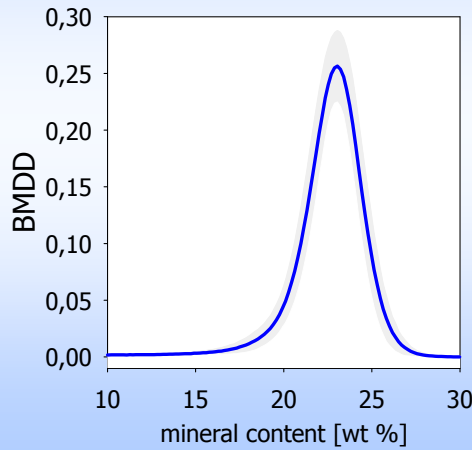
calcium content [wt %]

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## experimental result

the BMDD of trabecular bone in healthy humans is independent of gender, ethnicity, skeletal site and age



P. Roschger et al., Bone 32 (2003)

steady-state  
reference BMDD

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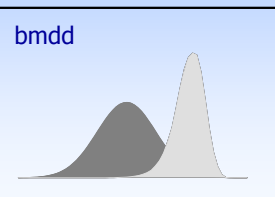


## BMDD changes due to mineralization and remodeling

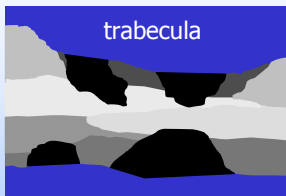
mineralization



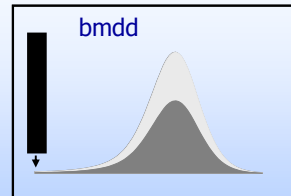
young bone  
(low Ca)  
old bone  
(high Ca)



remodeling




young bone  
(low Ca)  
old bone  
(high Ca)



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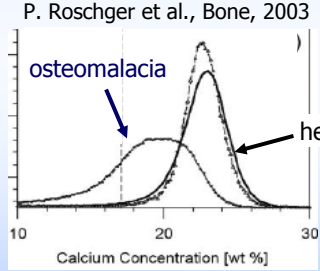


 **modeling with the**


**AIM** mineralization law ↔ **BMDD**  
turnover rate


**MOTIVATION**

implications for bone quality

 P. Roschger et al., Bone, 2003

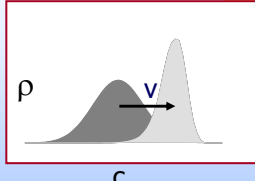
mechanical properties: **SOFT DUCTILE** ↔ **STIFF BRITTLE**

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 **THE MODEL** continuity equation

|                                            | MINERALIZATION                                  | REMODELING                       |
|--------------------------------------------|-------------------------------------------------|----------------------------------|
| $\frac{\partial \rho}{\partial t}(c, t) =$ | $\frac{\partial}{\partial c} [\rho(c, t) v(c)]$ | $- \omega_{oc}(c, t) \rho(c, t)$ |
| rate of change of bone                     | mineralization process                          | bone removal due to osteoclasts  |
|                                            |                                                 | $\rho(0, t) v(0) = j_{ob}(t)$    |
|                                            |                                                 | bone addition due to osteoblasts |

$\rho$ ... BMDD  
 $c$ ... mineral content  
 $t$ ... time



Ruffoni et al., Bone 40 (2007)

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## THE MODEL

continuity equation

$$\frac{\partial \rho}{\partial t}(c, t) = \frac{\partial}{\partial c} [\rho(c, t) v(c)] - \omega_{oc}(c, t) \rho(c, t)$$

steady state solution:  $\frac{\partial \rho}{\partial t} = 0$

$\omega_{oc}(c) = \omega_{oc} = \text{const}$  bone removal is independent of the mineral content

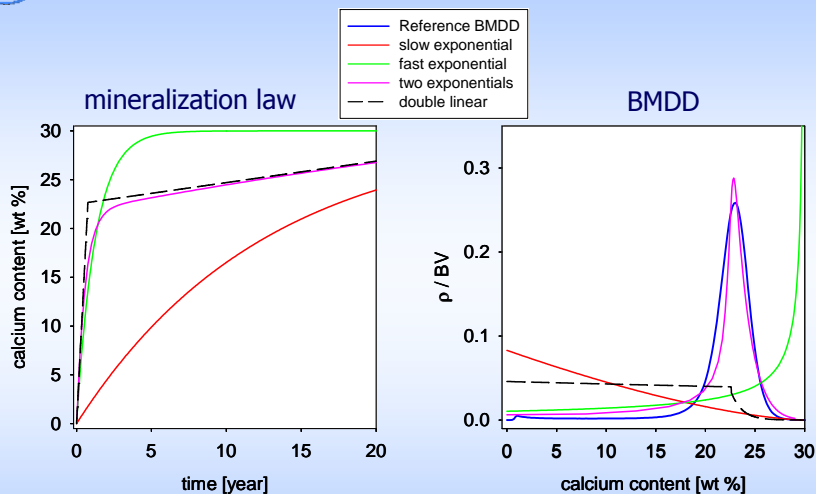
$\tau = t / t_{\tau 0}$  dimensionless time – time rescaled in units of turnover time

$$\frac{\rho(c)}{BV} = -\frac{d}{dc} [\exp(-\tau(c))] \iff \tau(c) = -\ln \int_c^{c_{\max}} \frac{\rho(c')}{BV} dc'$$

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## mineralization law $\rightarrow$ BMDD



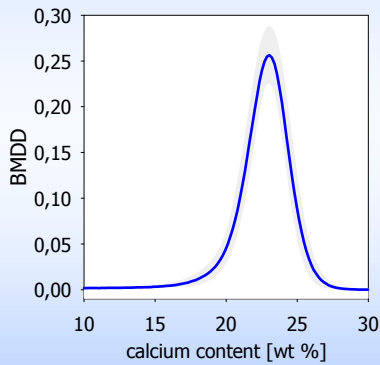
peaked BMDD  $\rightarrow$  biphasic mineralization law

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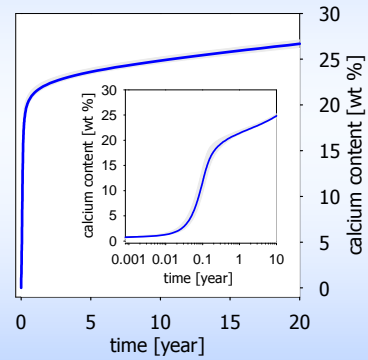


## BMDD → mineralization law

starting point  
experimental reference  
BMDD for healthy humans



mineralization law



Ruffoni et al., Bone 40 (2007)

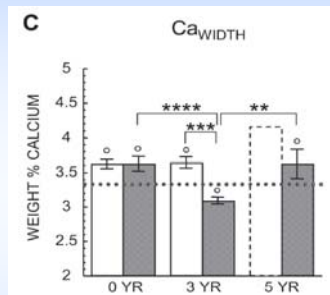
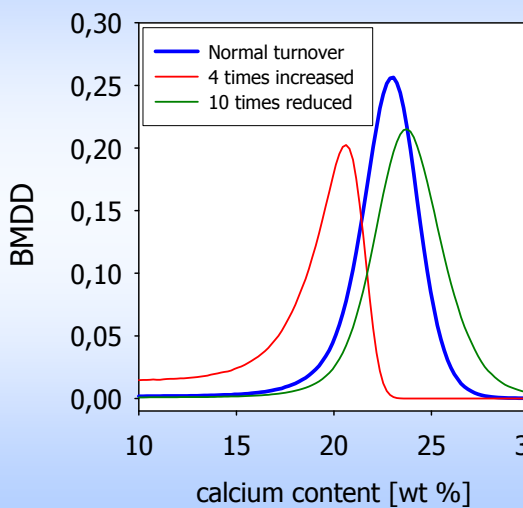
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## effect of turnover rate

assuming a fixed  
mineralization law

bisphosphonate treatment:



□ PLACEBO (0 AND 3 YR / N=8, 5 YR / N=2)  
■ RISEDRONATE (0 AND 3 YR / N=10, 5 YR / N=8)  
..... NORMAL REFERENCE (N=52)

Zoehrer et al., J Bone Min Res 21 (2006)

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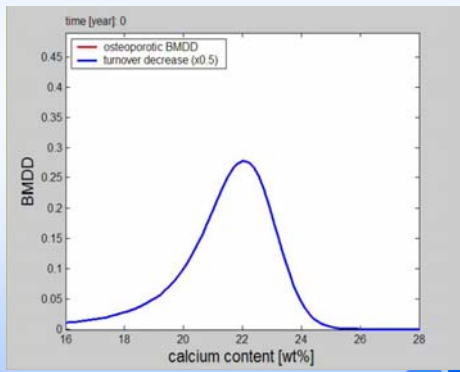
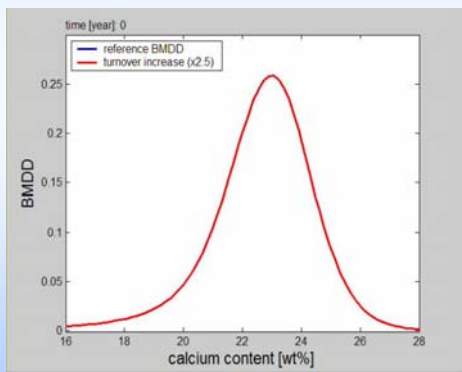




**QUESTION:**  
how does the BMDD change when the rate of bone remodeling changes?

example: menopause  
increase of the rate of bone remodeling

example: osteoporosis treatment with bisphosphonates (risedronate)  
reduction of the rate of bone remodeling



soft, tough

stiff, brittle

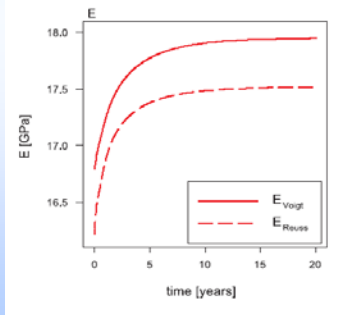
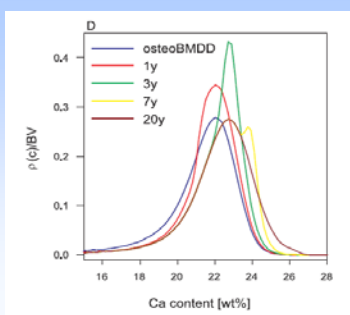
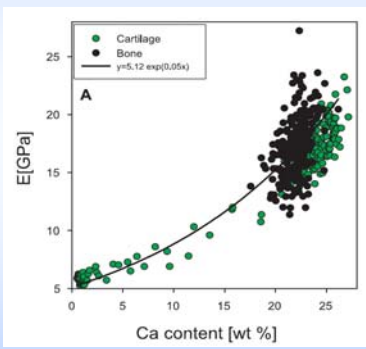
Ruffoni et al., J Bone Min Res, accepted

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**mechanical implications**

relation between mineral content and Young's modulus:



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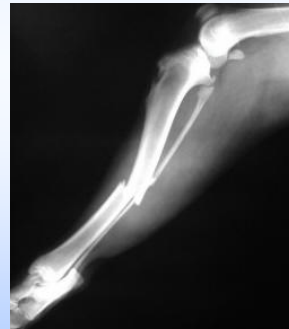


## bone: a self-healing material

limb regeneration  
in salamanders:



bone is capable of healing  
without the formation  
of scar tissue



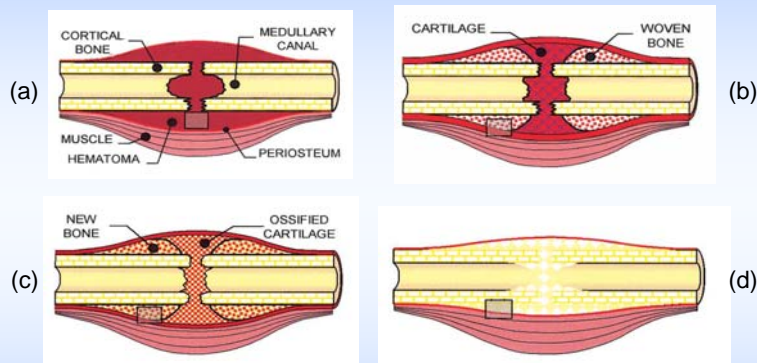
Max-Planck-Institut für  
Molekulare Zellbiologie und Genetik

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## secondary fracture healing

via a geometrical and material detour:



Li et al., J Bone Min Res 16 (2001)

Urist and Johnson, (1943)

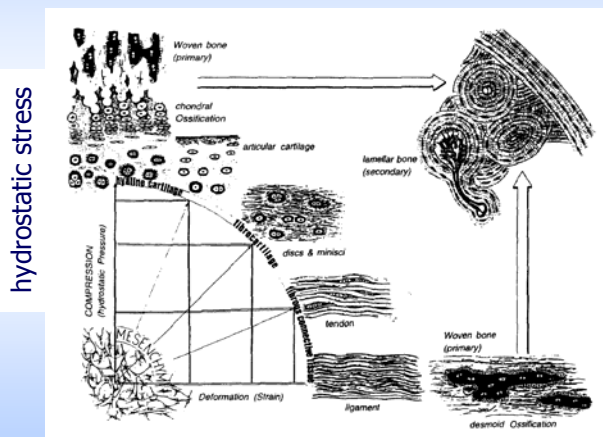
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## tissue differentiation is a mechano-regulated process

phase diagram of tissue differentiation:



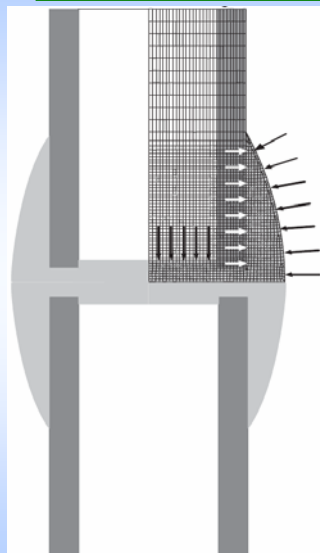
distortional stress

Weinans et al., Bone 19 (1996)

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## mechanobiological model for bone fracture healing



lattice model with voxels of different tissue type (stiffness)

two different stimuli:

- **mechanical** (long-range)
- **biological** (short-range)

tissue differentiation regulation rules as a function of the mechanical and biological stimulus

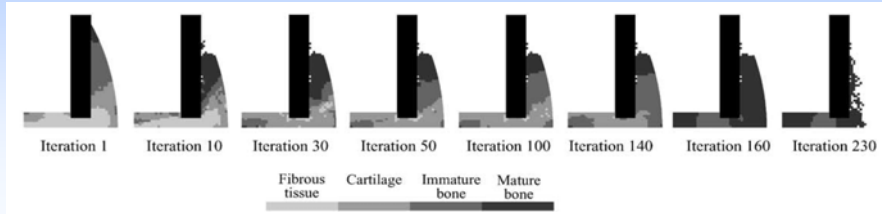
Lacroix et al., J Biomech 35 (2002)

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## bone healing simulations



Lacroix et al.,  
J Biomech 35 (2002)

„simulations in agreement with experiments“

BUT

**QUESTION:**  
how does the “normal” healing path look like?

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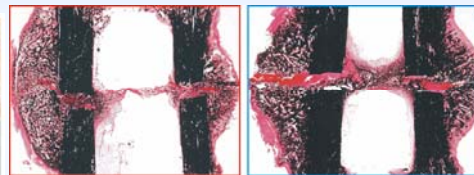
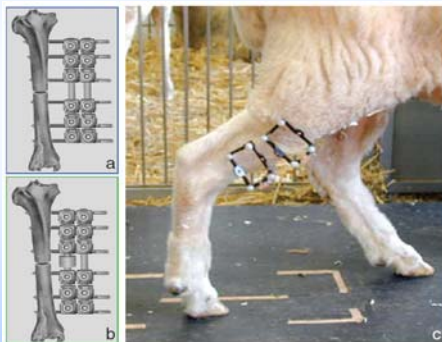


## bone healing: experiments

animal experiments (sheep):

- osteotomy of the tibia
- fixation of the bone fracture ends

longitudinal histological sections:



rigid fixation

semi-rigid fixation

Schell et al., J Orthop Res 23 (2005)

Epari et al., Bone 38 (2006)

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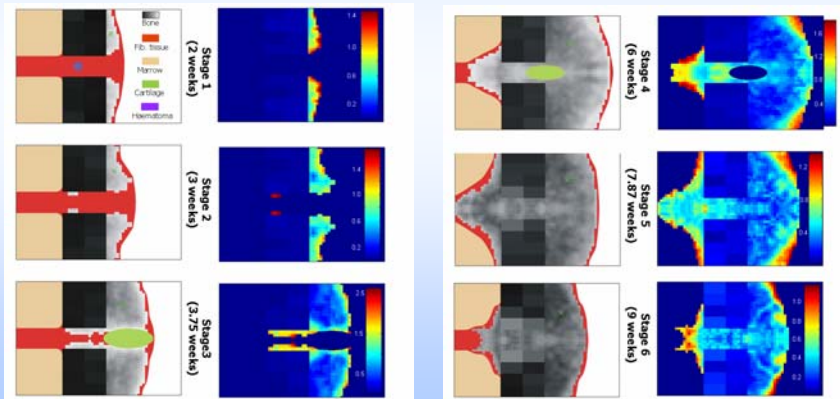


## bone fracture healing

problem of interindividual variability



normal healing path:



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## Acknowledgments

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"mechanobiology"

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 Peter Saporin (postdoc)  
 Caro Lukas (diploma)

Peter Fratzl



cooperation partners:

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 Robin Seidel  
 Devakara Epari

Paul Roschger  
 Klaus Klaushofer

Heike Scherf  
 Jean-Jacques Hublin

Andreas Fery

Angelo Valleriani  
 Maarten Biesheuvel

Yves Brechet

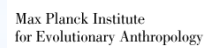
Franz Dieter Fischer



Charité,  
Berlin



Vienna,  
Austria



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