**ECTS TRAINING COURSE:**

**BONE HISTOMORPHOMETRY AND RELATED APPROACHES TO THE STUDY OF BONE**


# Bone Mineralization Density Distribution (BMDD)
# -
# Computer Modeling of Mineralization Kinetics


Richard Weinkamer

Max Planck Institute of Colloids and Interfaces
Department of Biomaterials, Potsdam, Germany



# why do bones break?

- low bone mineral density
- low bone quality

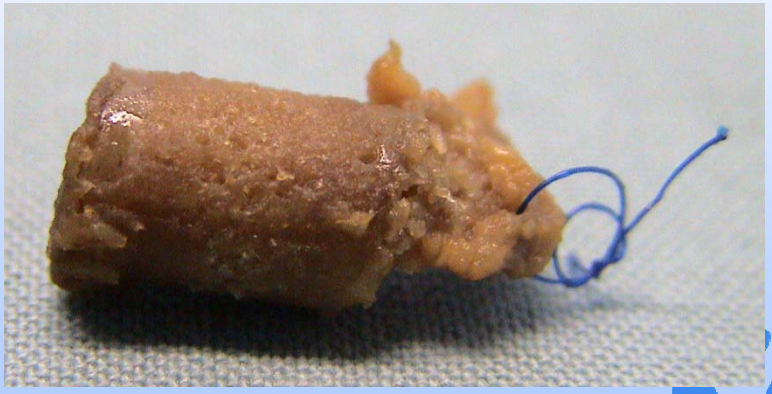
# what is bone quality?

all factors that mediate bone mechanical competence at constant BMD

<u>research task:</u>

- define quantities of bone quality
- measure these quantities

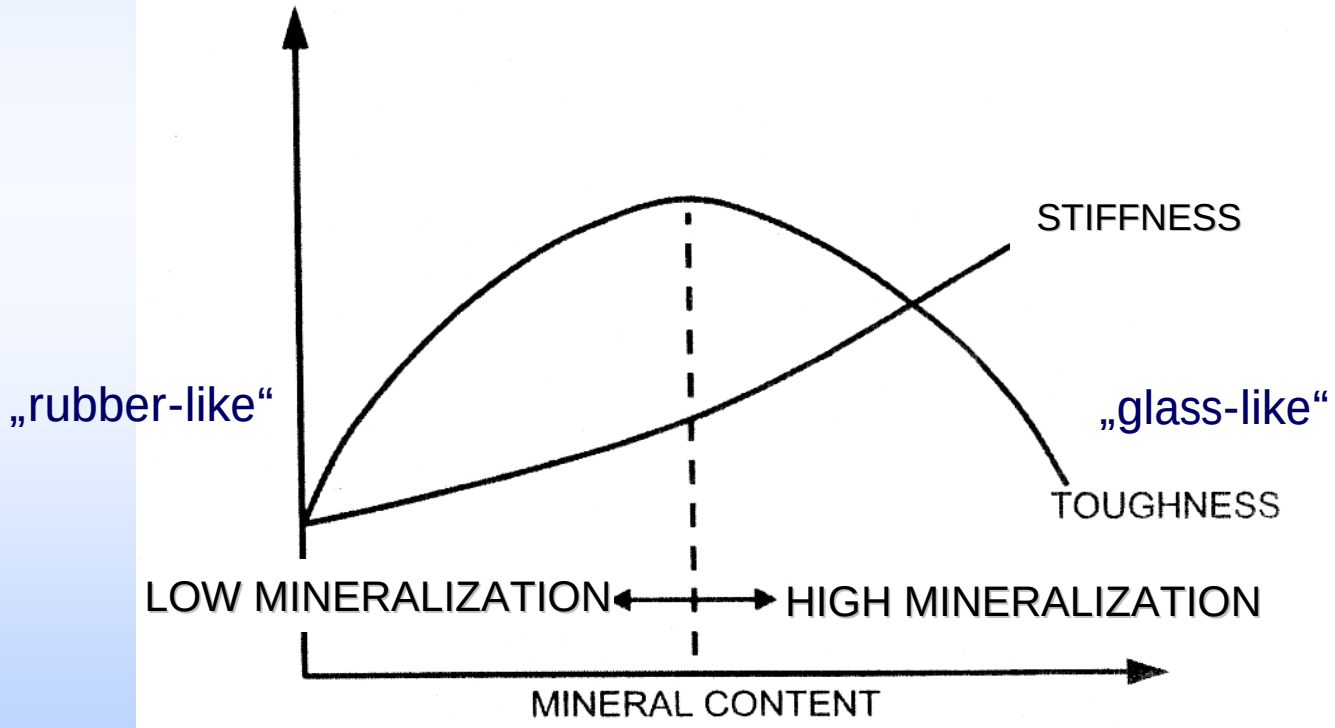
measurement typically requires a bone biopsy



# mechanical competence

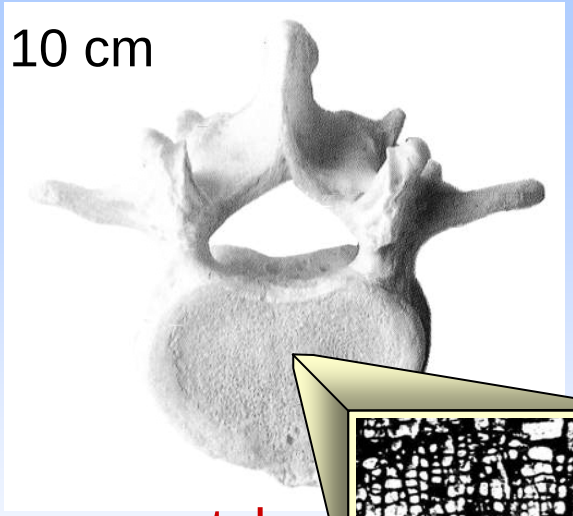
- stiffness: resistance to deformation
- toughness: resistance to fracture

mineral content determines stiffness and toughness of the bone material




after S.A. Wainwright et al. (1976)

# material bone: a hierarchical structured material




human vertebra

bone architecutal quality

bone material quality

10 mm

trabecular bone

500 μm

trabecula

20 μm

lamellar structure

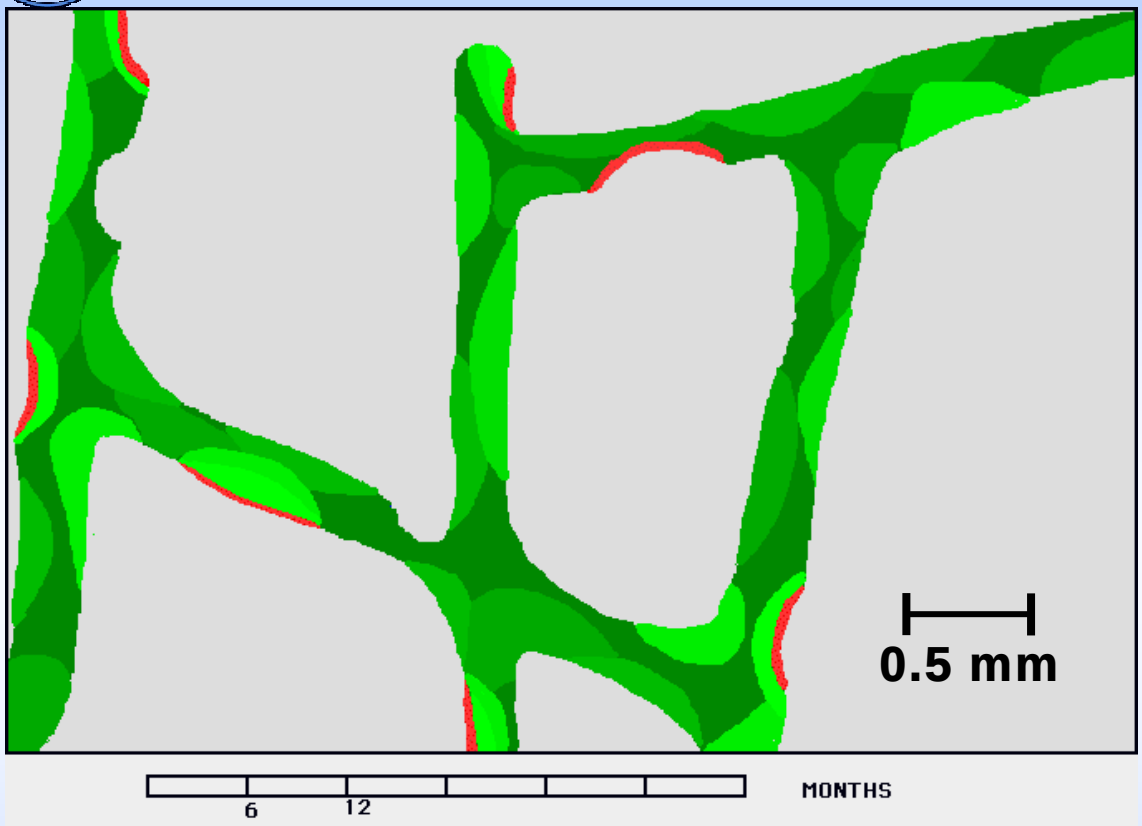
100 nm

nano-composite: collagen fibrils + mineral crystals

part 1

- what is the BMDD?
- how is the BMDD measured?
- basic definitions
- first examples

# static view on trabecular bone




... osteoid

... low mineral content

... medium mineral content

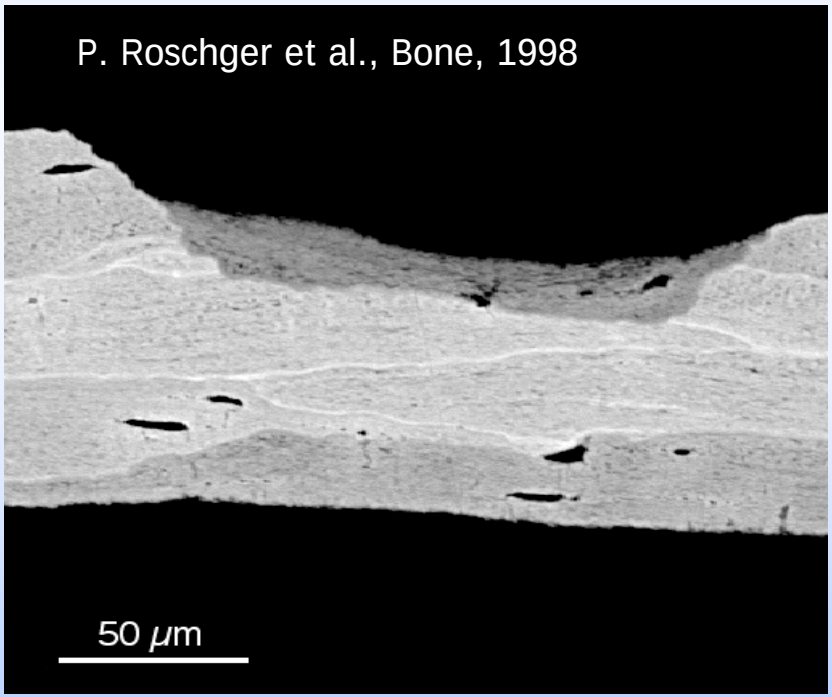
... high mineral content

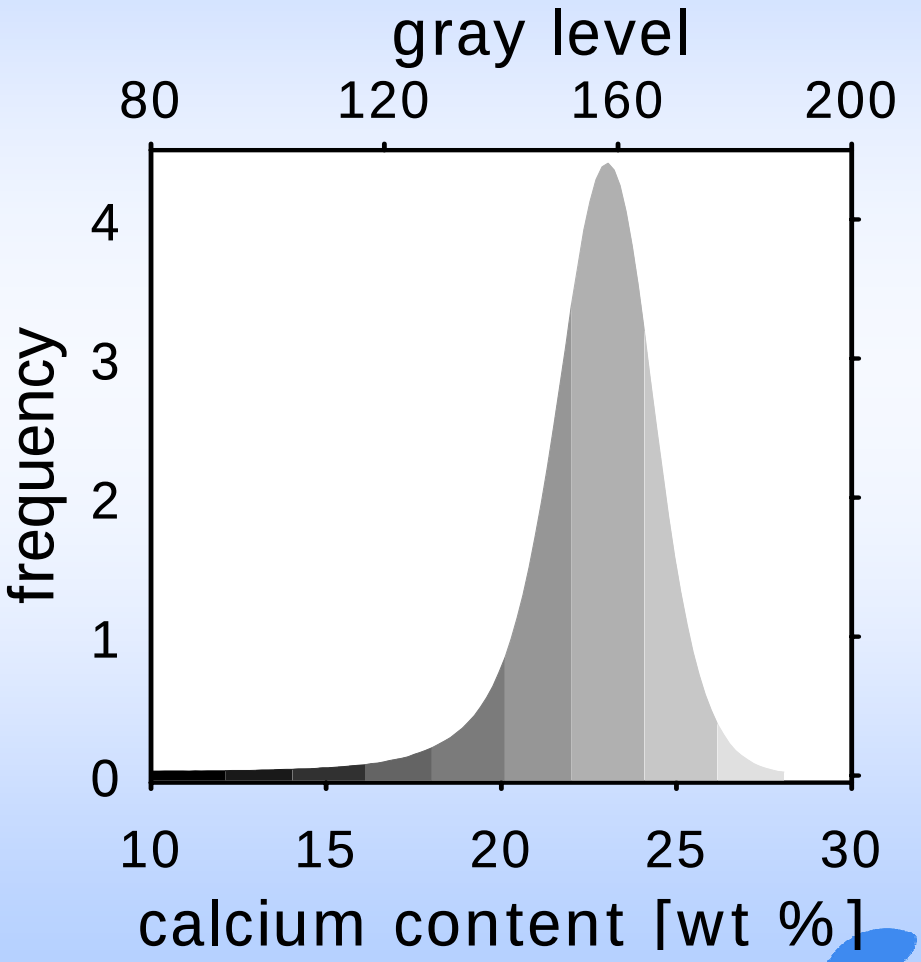
patchwork of different bone packets
(or bone structural units – BSU)
with different mineral content

# how to describe the heterogeneous mineral content?

## Bone Mineralization Density Distribution (BMDD)

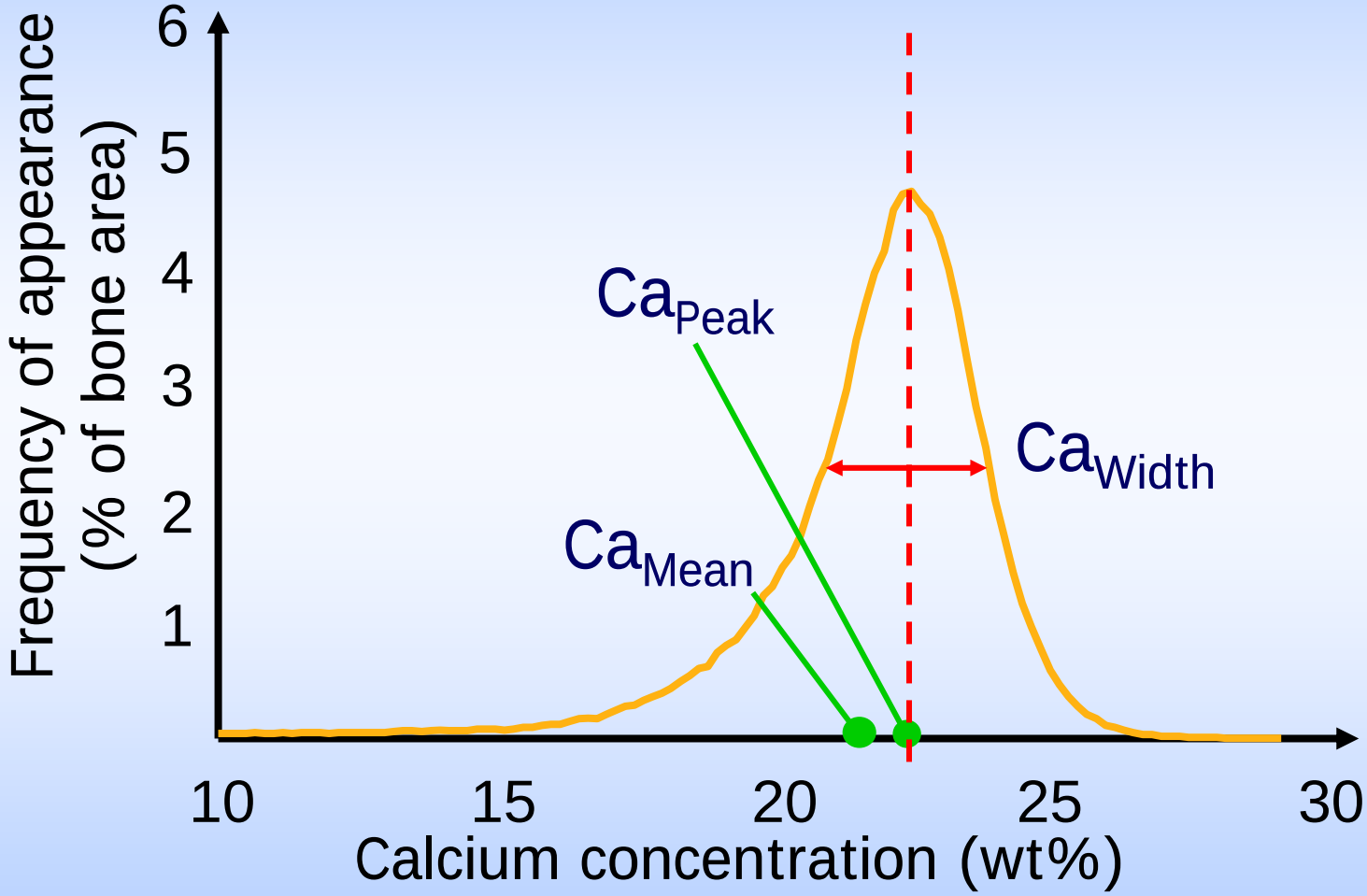
measurable quantity
(quantitative Backscattered Electron Imaging (qBEI))




spatial resolution: 1 – 4 μm
penetration depth < 1.5 μm

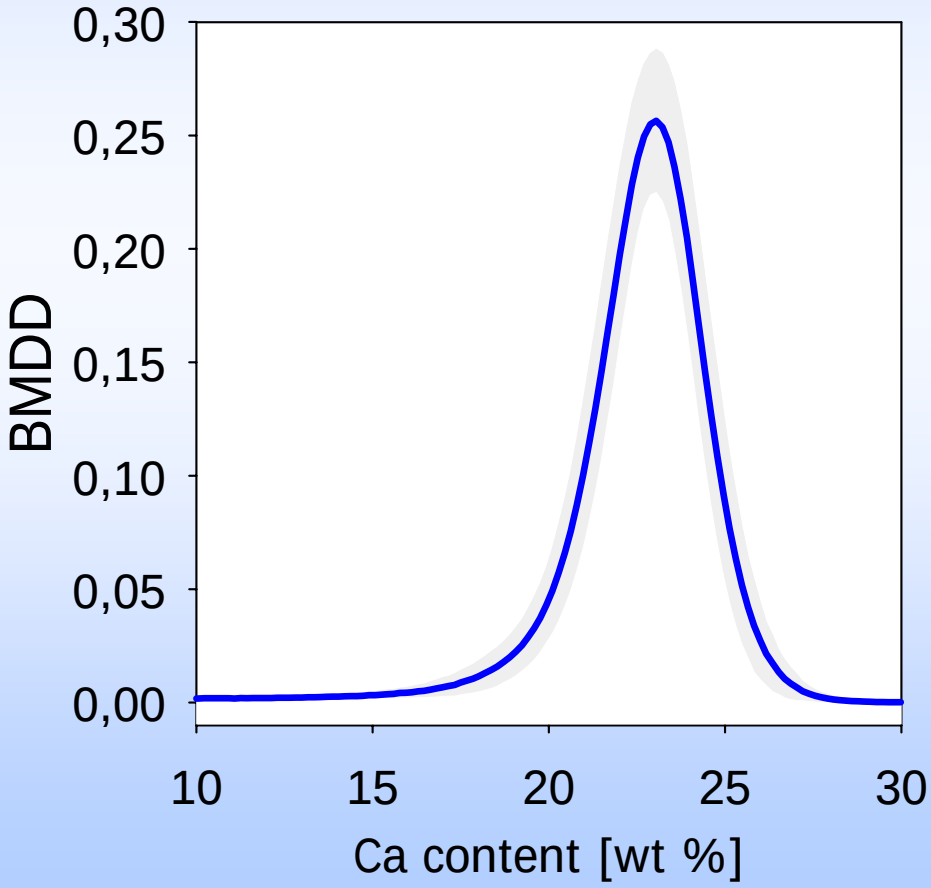
# BMDD is a frequency distribution which quantifies the heterogeneous Ca content in bone




histogram bin width= 0.17 wt% Ca

# definition of a reference BMDD

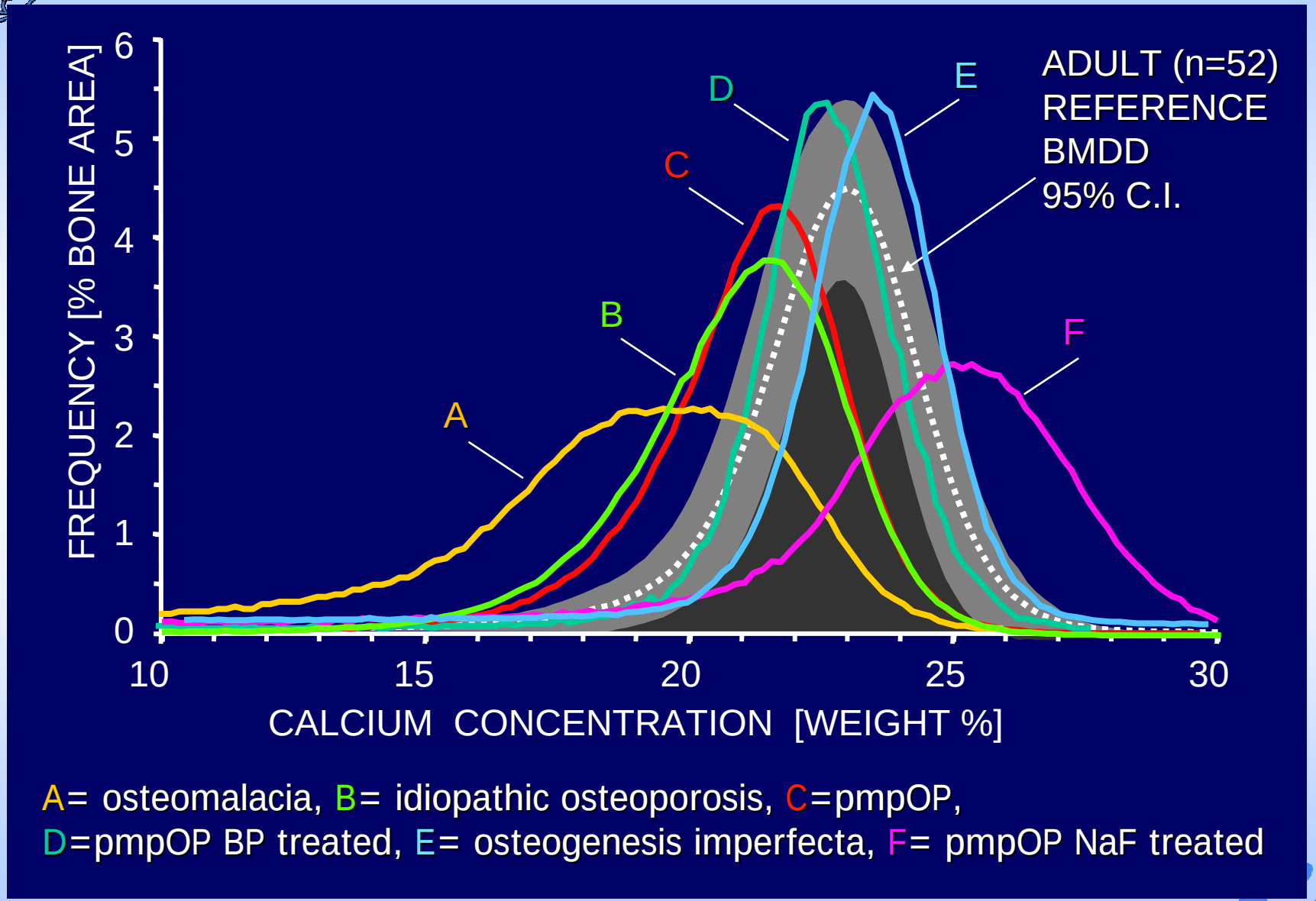
the BMDD of trabecular bone in healthy adults is independent of sex, ethnicity, skeletal site and age




$Ca_{Mean}$ = 22.20 wt% Ca (0.45)
$Ca_{Peak}$ = 22.94 wt% Ca (0.39)
$Ca_{Width}$ = 3.35 wt% Ca (0.34)

Roschger, Gupta, Berzlanovich, Ittner, Dempster, Fratzl, Cosman, Parisien, Lindsay, Nieves, Klaushofer (2003) Bone, 32, 316-323

# BMDD in disease/treatment




A= osteomalacia, B= idiopathic osteoporosis, C=pmpOP,
D=pmpOP BP treated, E= osteogenesis imperfecta, F= pmpOP NaF treated

Roschger, Paschalis, Fratzl, Klaushofer (2008) Bone 42:456-466

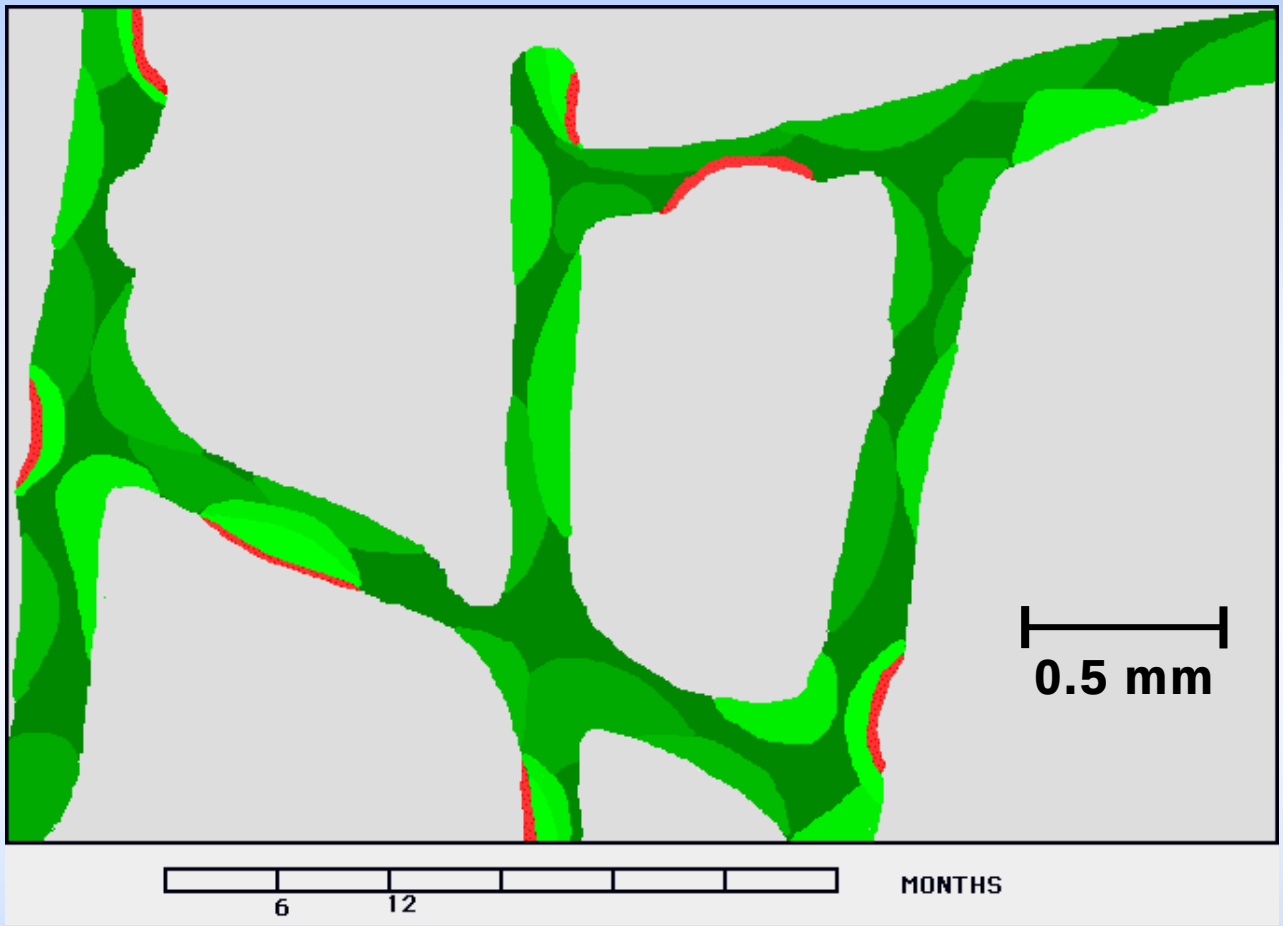
# part 1 in a nutshell

- the BMDD is a frequency distribution quantifying the non-homogeneous Ca content in bone
- the BMDD is experimentally accessible using bone biopsies
- the BMDD for healthy adults is the same, but is different in diseased or treated bone

## part 2

- what information can be extracted from the BMDD?
- how can computer modeling help?
- examples

# dynamic view on trabecular bone

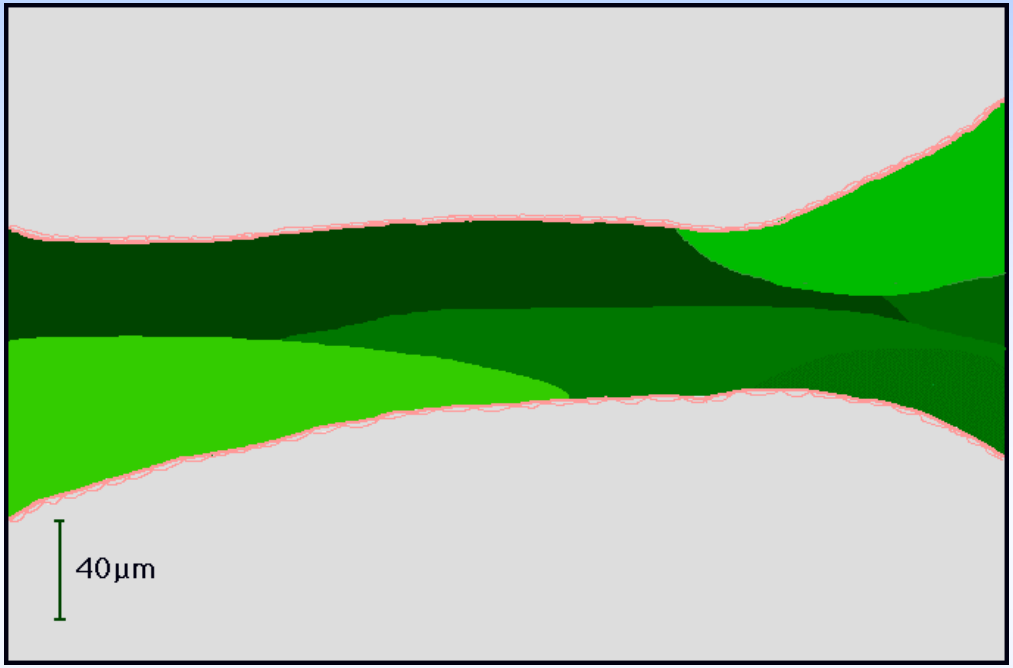



heterogeneous mineral content due to:

- remodeling process
- mineralization process

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

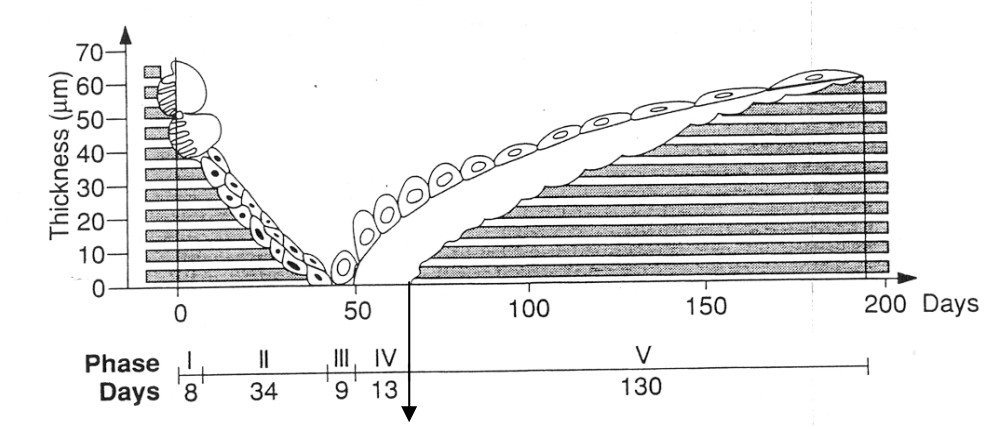
# remodeling process




basic multicellular unit (BMU)
performs a remodeling cycle

BMU imbalance:
difference between resorbed
and deposited bone volume
in a remodeling cycle

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




start of mineralization

remodeling process characterized by:

- **bone turnover time**

OR

- **origination frequency of new BMUs**

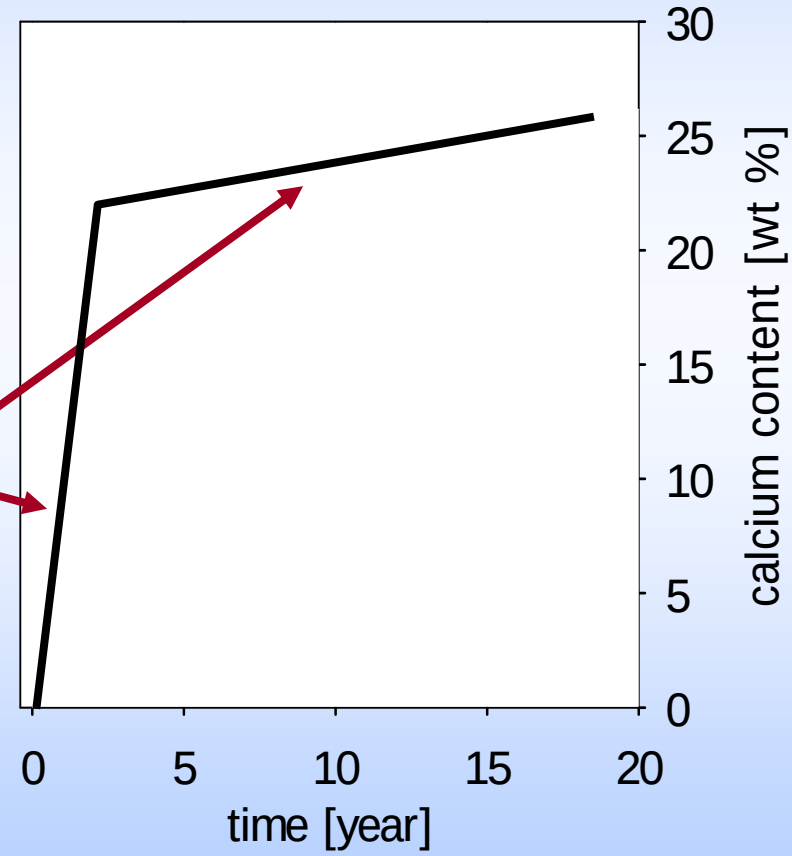
# mineralization process

mineralization process characterized by:

- **mineralization law**:

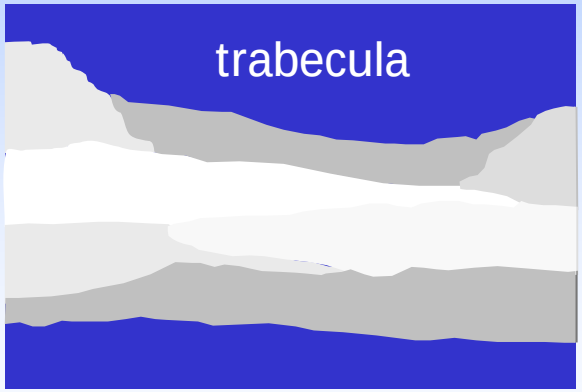
describes the increase in mineral content in a newly formed bone packet

- primary mineralization (fast initial increase)
- secondary mineralization (slower increase at later times)



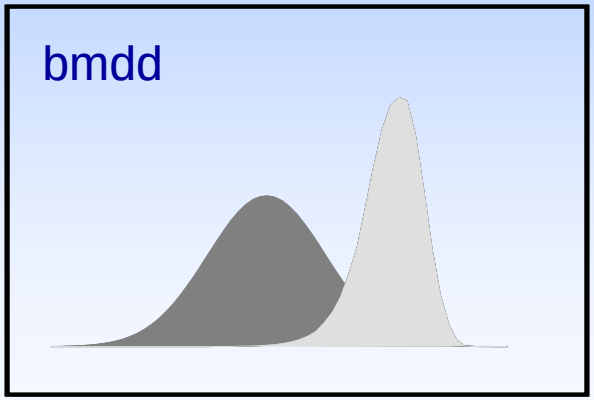
# BMDD changes due to mineralization and remodeling

mineralization only

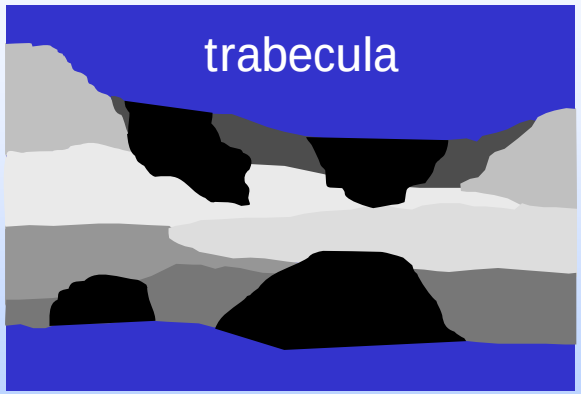



young bone
(low Ca)

old bone
(high Ca)

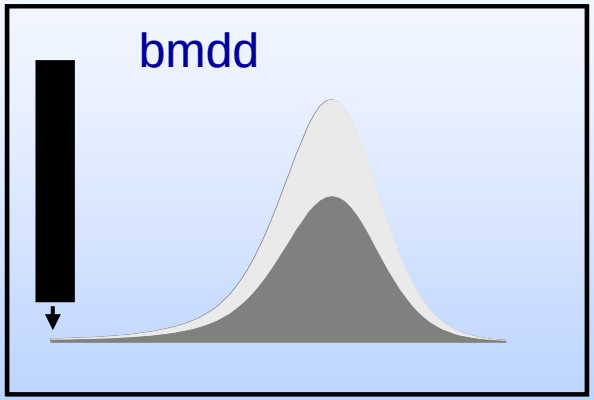



remodeling only




young bone
(low Ca)

old bone
(high Ca)



# computer simulation

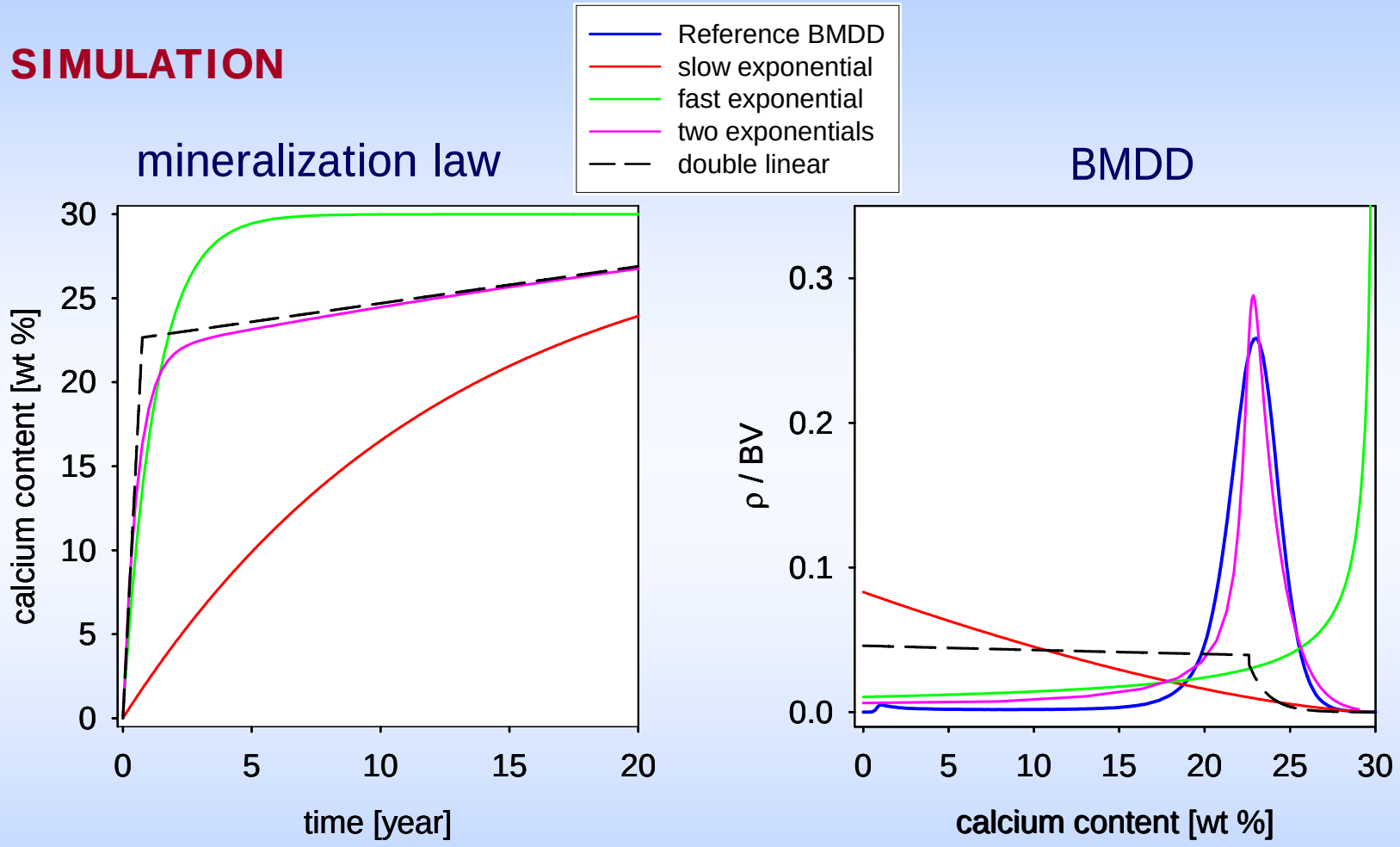
- quantify these considerations
- transfer into the language of mathematics and implementation in the computer
- never forget: it is only a model – but we also think in models
- computer results are much more trustworthy than human reasoning
- what are limitations/assumptions of the model

# model to describe BMDD behavior

- bone remodeling is described by the action of BMUs
- bone mineralization is described by a mineralization law
- assumption: bone resorption is independent of the Ca content

# mineralization law ➡ BMDD

**SIMULATION**

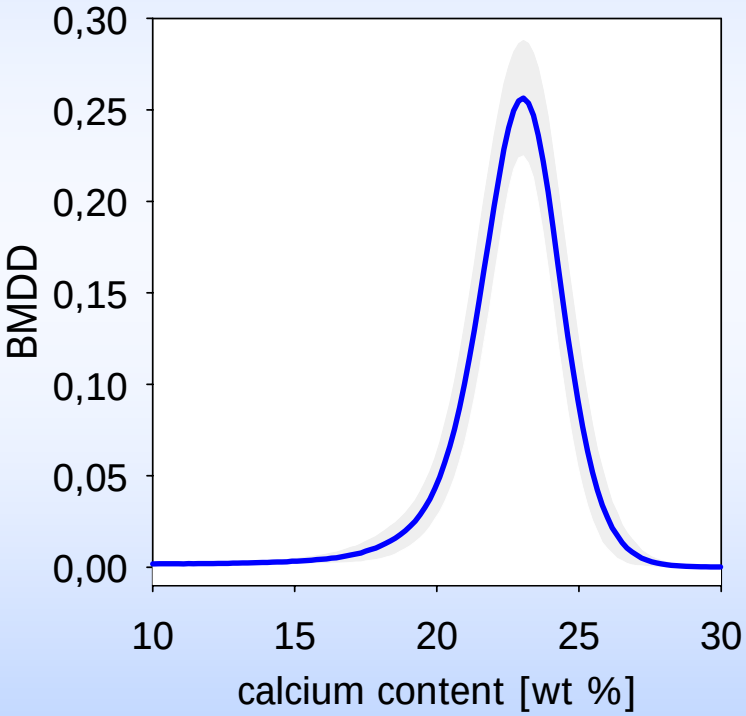



peaked BMDD ➡ biphasic mineralization law

# BMDD ➡ mineralization law

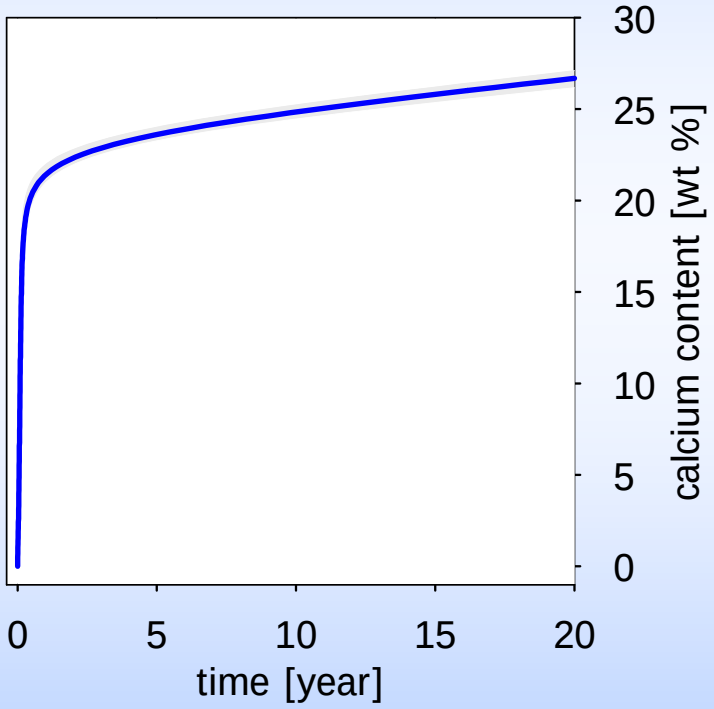
**healthy adult humans:**

starting point: reference BMDD




**MEASUREMENT**

**mineralization law for healthy adults**



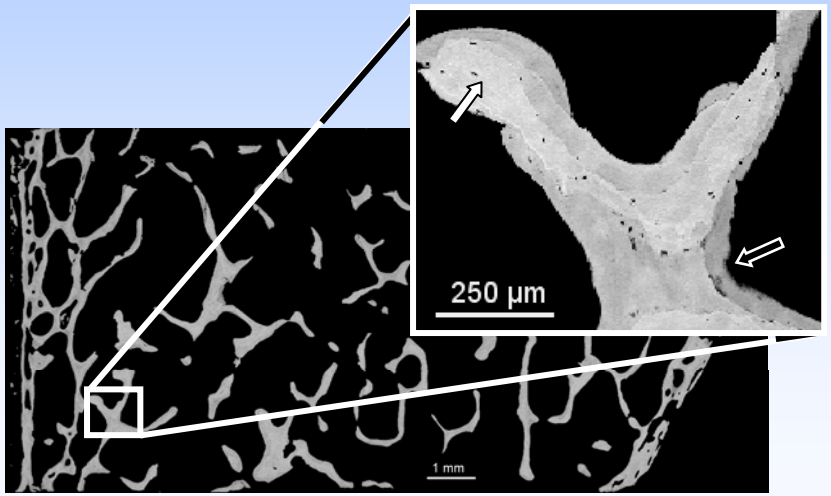

**SIMULATION**

Ruffoni, Fratzl, Roschger, Klaushofer, Weinkamer (2007) Bone 40:1308-1319

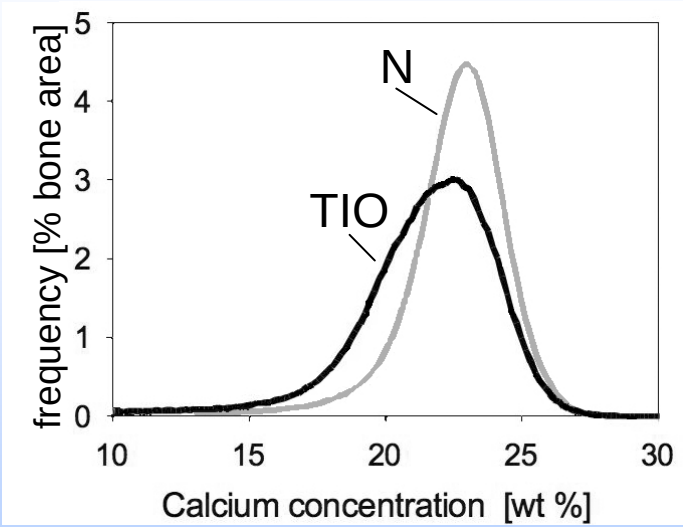
# change in mineralization law

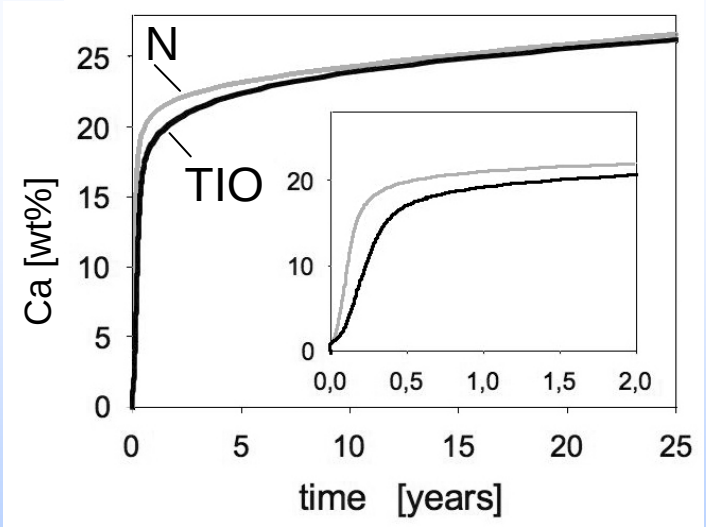
**tumor induced osteomalacia (TIO):**

- tumor produces FGF23
- FGF23 disturbs phosphate metabolism
- hypophosphatemia disturbes mineralization process




**MEASUREMENT**



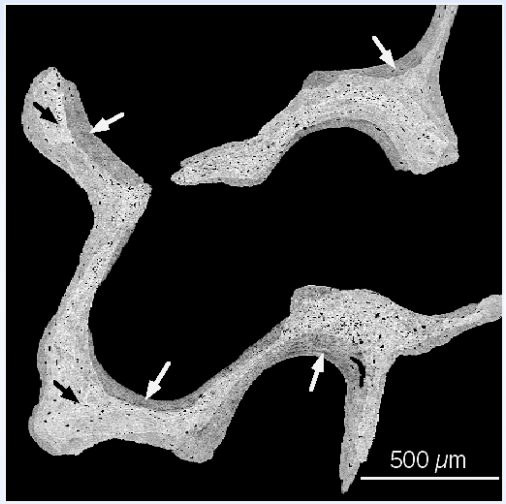

**SIMULATION**

Nawrot-Wawrzyniak, Varga, Nader, Roschger, Sieghart, Zwettler, Roetzer, Lang, Weinkamer, Klaushofer, Fratzl-Zelman (2009) CTI 84: 313-323

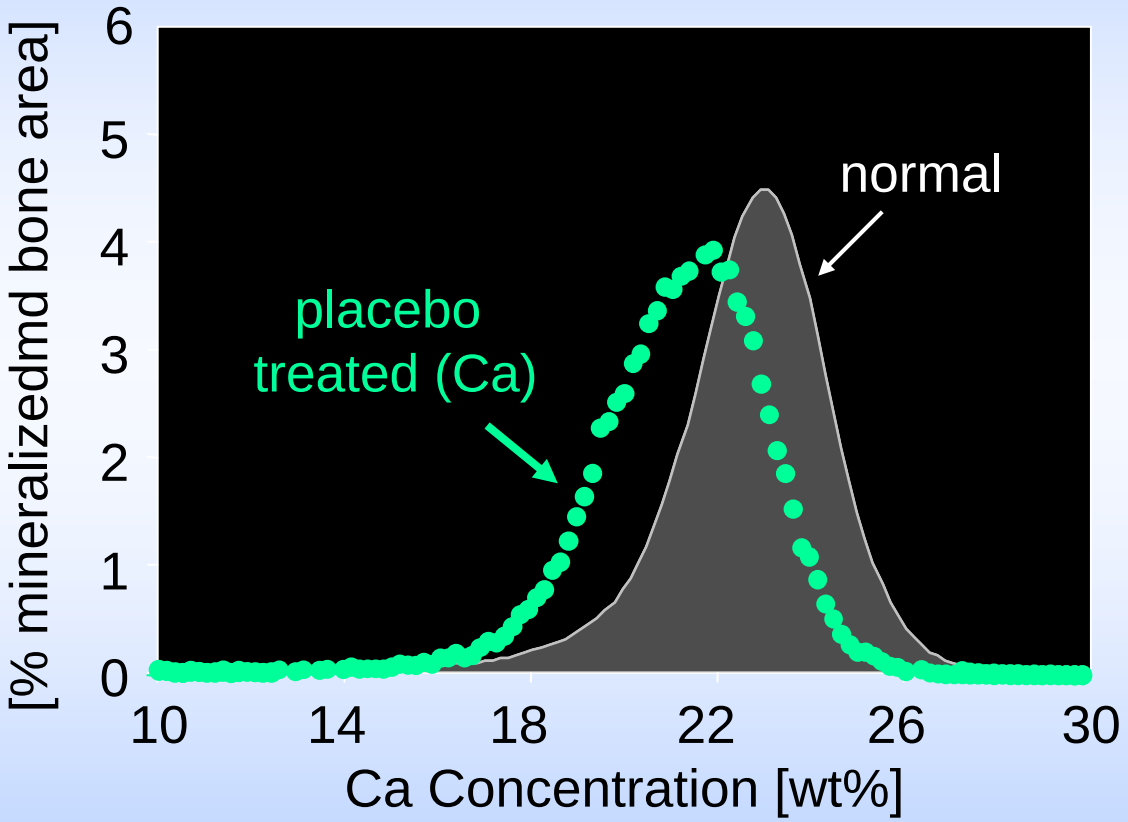
# increase in bone turnover

**postmenopausal osteoporosis (pmp OP):**

Iliac bone, female




qBEI image




Roschger, Rinnerthaler, Yates, Rodan, Fratzl, Klaushofer (2001) Bone 29:185-191

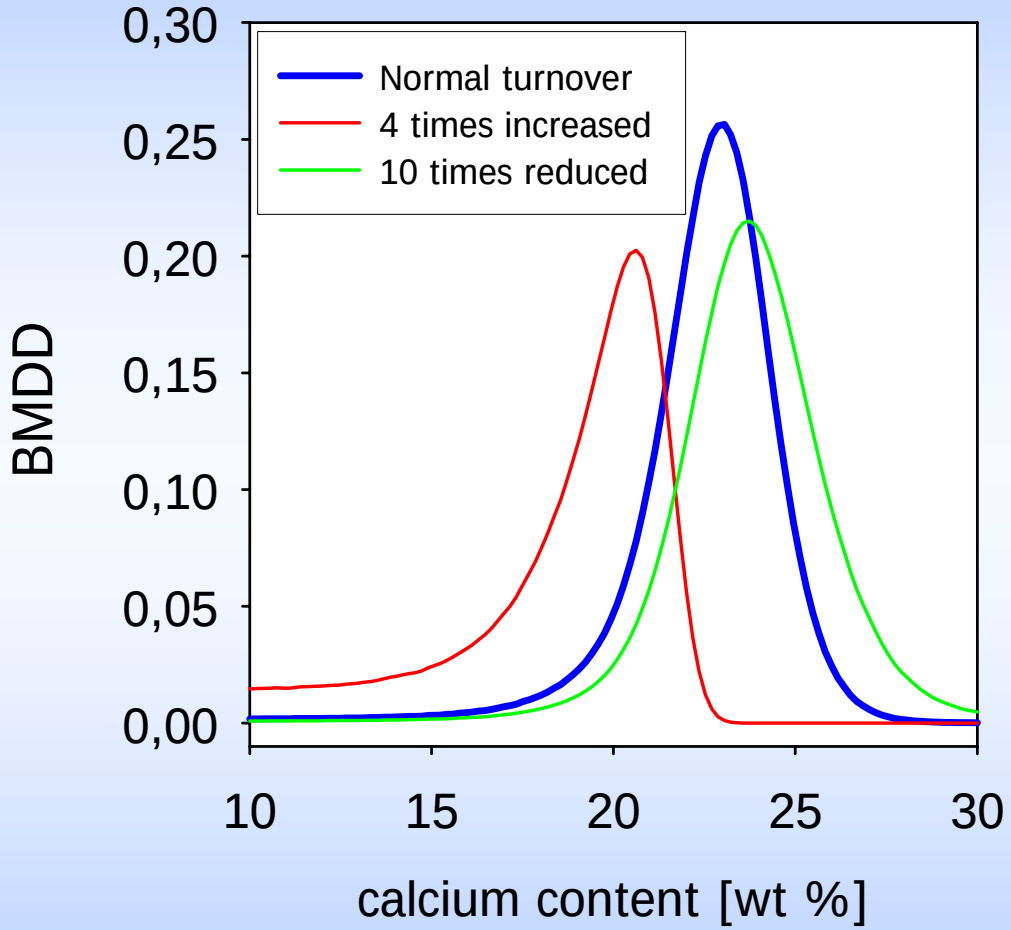
# change in turnover rate

assuming a fixed mineralization law

**SIMULATION**

**steady-state BMDD**

(BMDD long time after turnover change)




Ruffoni, Fratzl, Roschger, Klaushofer, Weinkamer (2007) Bone 40:1308-1319

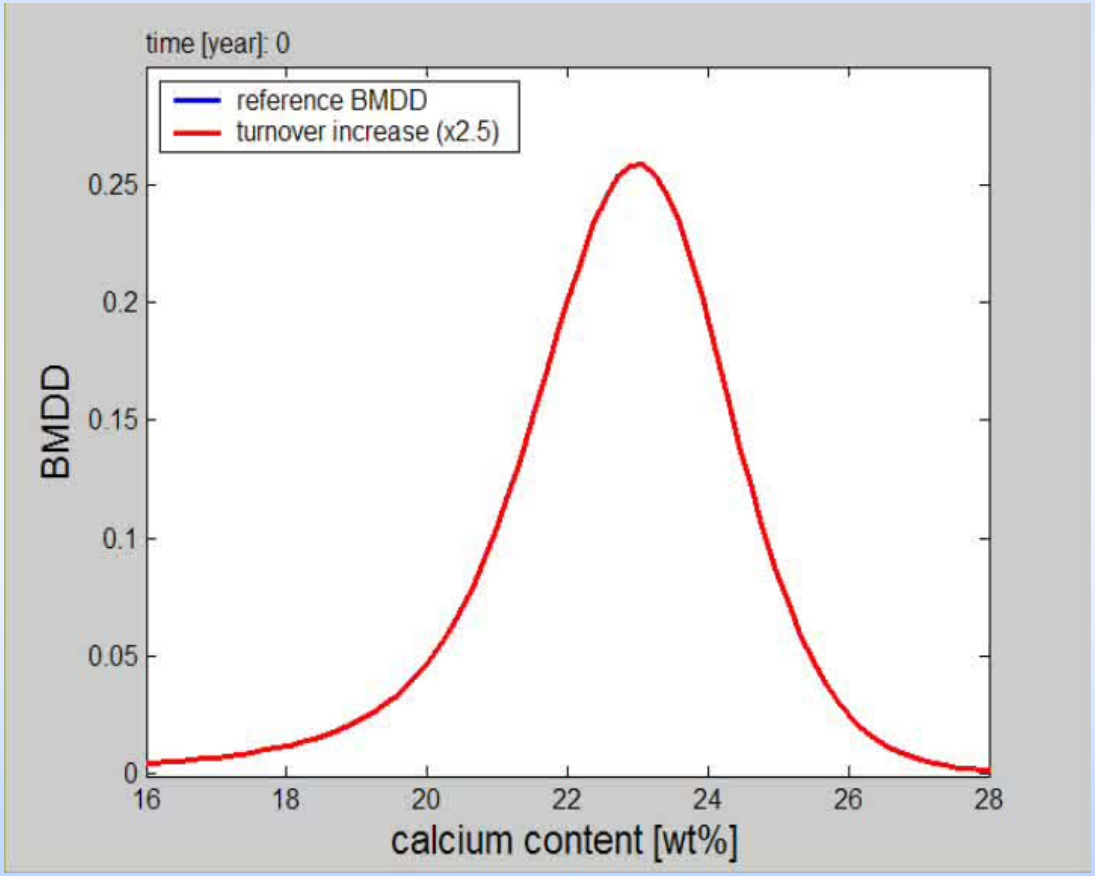
# increase in bone turnover

## postmenopausal osteoporosis (pmp OP):

### SIMULATION

**time evolution of the BMDD**

starting configuration:
- reference BMDD
- 2.5 times increase in bone turnover




Ruffoni, Fratzl, Roschger, Klaushofer, Weinkamer (2008) JBMR 23:1905-1914

# increase in bone turnover

## postmenopausal osteoporosis (pmp OP):

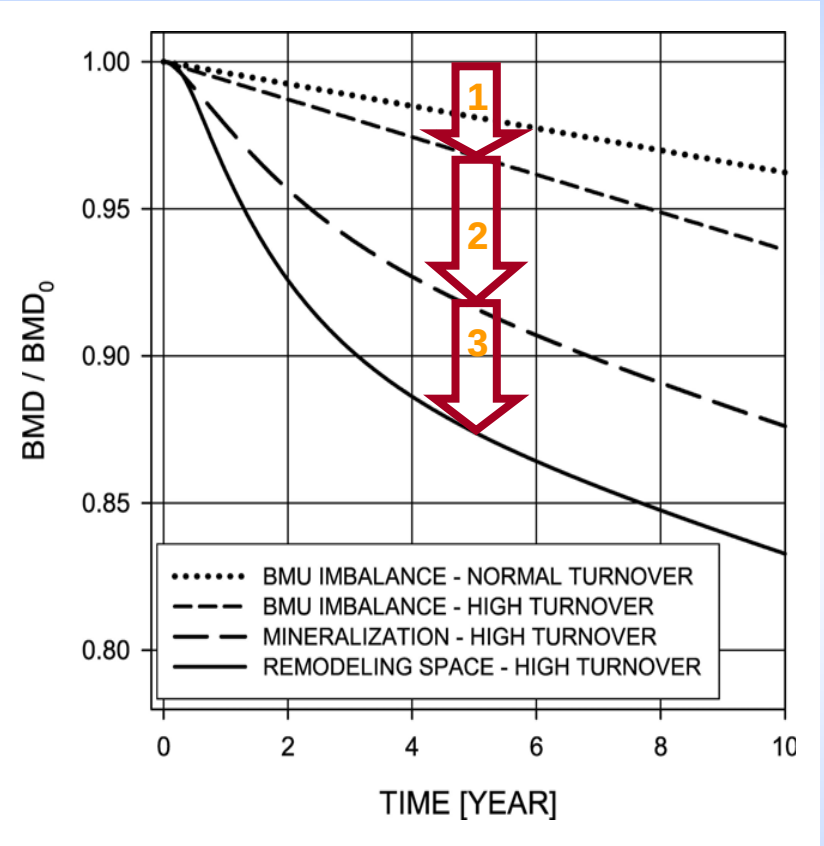
**SIMULATION**

**decrease in bone mineral density (BMD) due to increase in bone turnover only:**

**contributions to vBMD:**
- bone volume
- mean mineral content ($Ca_{Mean}$)

**increase turnover leads to a decrease in BMD due to:**

1) more number of remodeling cycles with negative balance between resorbed and deposited bone (BMU imbalance)
2) decrease in the mineral content (BMDD shift to smaller Ca values)
3) more BMUs originate starting with resorption (increase in remodeling space)




Ruffoni, Fratzl, Roschger, Phipps, Klaushofer, Weinkamer (2008) JBMR 23:1905-1914

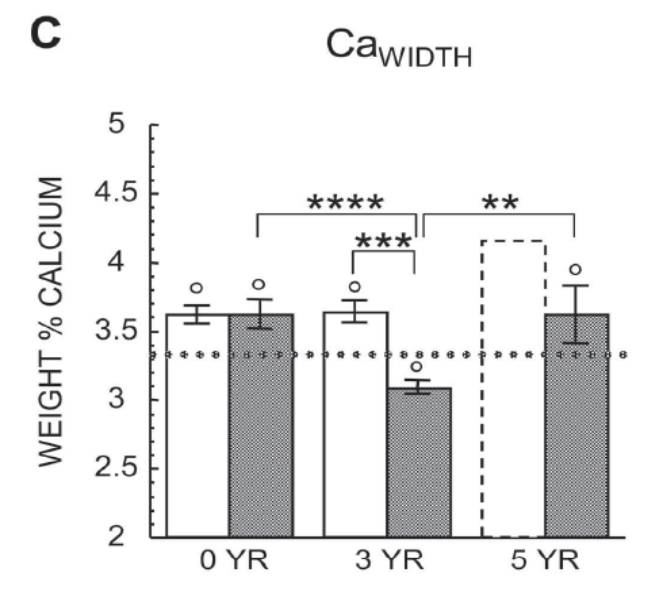
# decrease in bone turnover

**osteoporosis treatment with bisphosphonates (risedronate):**

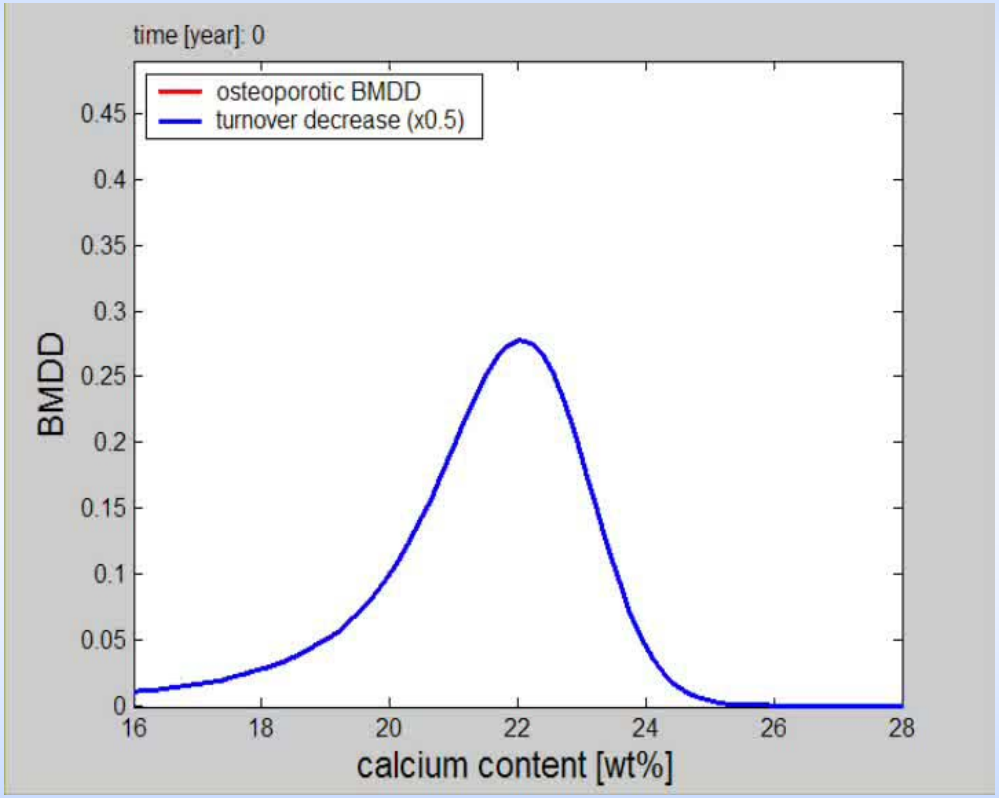
**SIMULATION**

starting configuration:
- osteoporotic BMDD
- 2 times decrease in bone turnover

**MEASUREMENT**




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, Roschger, Paschalis, Hofstaetter, Durchschlag, Fratzl, Phipps, Klaushofer (2006), J Bone Min Res 21, 1106-1112

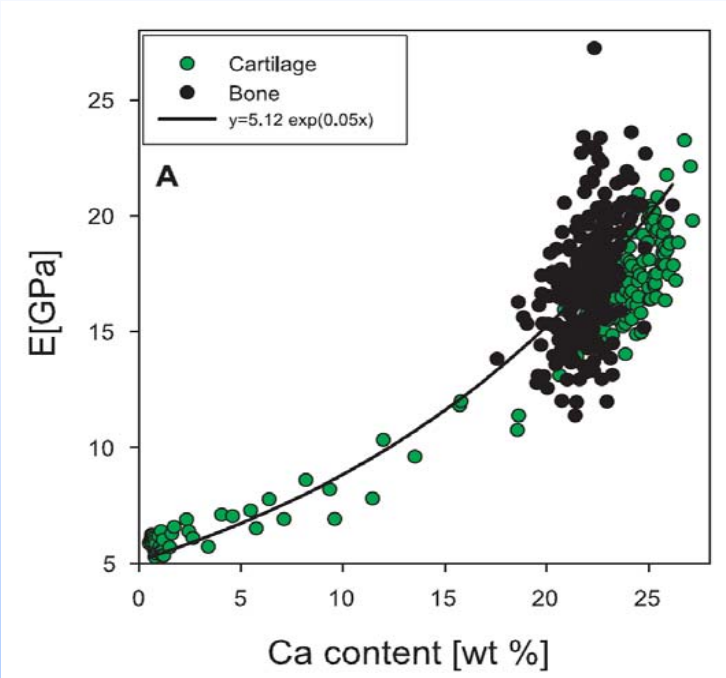
Ruffoni, Fratzl, Roschger, Phipps, Klaushofer, Weinkamer (2008) JBMR 23:1905-1914

# mechanical implications of BMDD changes

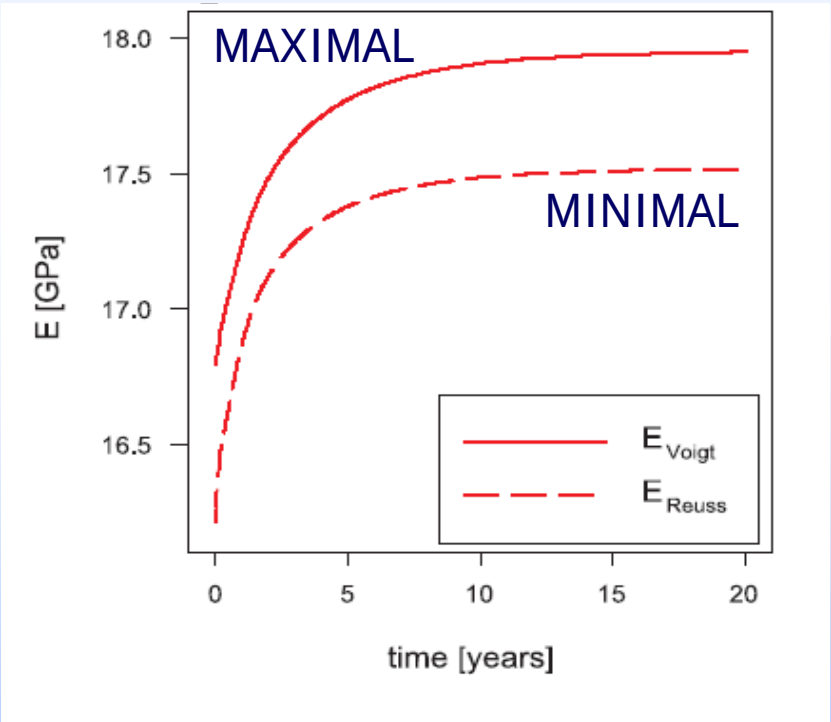
**osteoporosis treatment with bisphosphonates (risedronate):**

- very hard to give quantitative predictions
- result depends on the exact arrangement of the bone packets

relation between
mineral content and E-modulus
(experimental data):




estimation of the change in stiffness:




Carolin Lukas, diploma thesis

# part 2 in a nutshell

- the BMDD contains information about both the remodeling and mineralization process
- the measurement of the BMDD in combination with computer simulation provides a diagnostic tool to differentiate between diseases affecting bone turnover and mineralization process.
- computer simulations help in separating factors which influence BMDD and BMD, and allow a prediction of their time evolution

# Acknowledgments

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THANK YOU