Bone Remodelling

Lecture 8

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AMME4981/9981
Week 9
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Mechanical Responses of Bone

- Bone microstructure
  - Descriptions
  - Imaging
- Bone constitutive models and relationships
  - Stiffness and apparent density
- Bone remodelling mechanisms
  - Physiological responses to mechanical stimuli
- Models of bone responses
  - Simple example calculations

Body kinematics

Biomaterial mechanics

Biomaterial responses
Bone microstructure
Description and clinical imaging
Description of bone microstructure and composition

- Five major functions: load transfer; muscle attachment; joint formation; protection; hematopoiesis
- Composition and structure of bone heavily influences its mechanical properties
  - Collagen fibres
  - Bone mineral (hydroxyapatite)
  - Bone cells (osteoblasts, osteoclasts, osteocytes)
- Two classes of bone structure
  - Cancellous (or spongy) bone
  - Cortical (or compact) bone
Description of cortical bone microstructure

(a) Compact bone consists mainly of osteons, which are concentric lamellae surrounding blood vessels within central canals. The outer surface of the bone is formed by circumferential lamellae, and bone between the osteons consists of interstitial lamellae. 

(b) Photomicrograph of an osteon.
Bone imaging modalities

- **DXA** – Dual energy X-ray Absorptiometry
  - Provides bone mineral density *(BMD)*
  - Commonly used to diagnose osteoporosis (based on BMD)
  - Two beams are used and soft tissue absorption is subtracted
- **MRI** – Magnetic Resonance Imaging
  - Ideal for soft tissues
  - Commonly used to examine joints for soft tissue injuries
  - fMRI for brain studies
- **CT** – X-Ray Computed Tomography.
  - Ideal for hard tissues.

MRI scan of the knee joint
DXA – Dual Energy X-Ray Absorptiometry

The only way to do this is to measure bone mineral density. Low measurements on DXA predict the risk of fractures of the spine and hip, analogous to the relationship between high serum cholesterol and the risk of myocardial infarction, or between high blood pressure and the risk of stroke.

Driving the demand for DXA is the availability of proven, FDA-approved therapies for osteoporosis, ie, alendronate (Fosamax), risedronate (Actonel), calcitonin (Miacalcin), raloxifene (Evista), estrogen replacement therapy, and parathyroid hormone (Forteo).

DXA uses x-rays at two energy levels to determine the bone mineral content. This is accomplished by subtracting the difference of absorption of x-rays between soft tissue and calcium bone. The scanner software calculates the bone mineral density, dividing the bone mineral content by the area of the region of interest. The bone mineral density is compared to reference data specific to the scanner, and the results are expressed as the T score and the Z score (see below).

Although DXA could be used to measure bone density at many skeletal sites, two sites are typically measured: the first four vertebrae of the lumbar spine posteroanteriorly, and the proximal femur (“hip”), including the femoral neck and the trochanteric areas and total hip measurement (FIGURE 1). Opportunities for error

Several aspects of the bone density measurements should be evaluated before a study is accepted as accurate.

Placement and sizing of the “regions of interest.” Changes in placement can significantly affect the results. Proper positioning is crucial for accurate measurement.

FIGURE 1. Left, normal positioning for DXA of the hip. The lesser trochanter is minimally visualized or not visualized, the diaphysis is parallel to the table edge. The hip is not abducted. Center, external rotation results in visualization of the lesser trochanter, shortening the femoral neck. The hip is also abducted. Improper positioning results in poor precision on follow-up studies because it is difficult to reproduce the positioning. The exam data are also less reliable since the reference database was presumably collected with proper positioning. Right, loss of joint space from degenerative joint disease results in cortical thickening of the medial femoral neck region, falsely increasing bone mineral density measurement. Eccentric placement of the femoral neck region of interest does not affect bone mineral density analysis. Reproducibility on subsequent scans is difficult, especially as degenerative changes progress.

Images courtesy of GE Lunar Medical Systems

GE Lunar DEXA Systems
Imaging of bone microstructure

- To examine the bone microstructure, high resolution scanning is required
- Micro-CT and Nano-CT options have high resolution that allows visualisation of bone microstructure

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Max. Resolution (in-vivo) in microns</th>
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<tbody>
<tr>
<td>Medical CT</td>
<td>200 x 200 x 200</td>
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<tr>
<td>3D-pQCT</td>
<td>165 x 165 x 165</td>
</tr>
<tr>
<td>MRI</td>
<td>150 x 150 x 150</td>
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<tr>
<td>Micro-MRI</td>
<td>40 x 40 x 40</td>
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<tr>
<td>Micro-CT</td>
<td>5 x 5 x 5</td>
</tr>
<tr>
<td>Nano-CT</td>
<td>0.05 x 0.05 x 0.05</td>
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</table>
Micro-CT of bone microstructure

- MicroCT Scanner (SkyScan 1172).
- Micro-CT scan → sectional image → segmentation → 3D image (STL)
- Limited field of view
Microstructural changes in cancellous bone

- **Right:** decreasing bone density with age as indicated.
- **Bottom:** comparison of bone density between a healthy 37-year-old male (L) and a 73-year-old osteoporotic female (R).

32-year-old male

59-year-old male

89-year-old male
Bone constitutive models
Stiffness and apparent density relationships
Power law relationship for cancellous bone stiffness

- Well-established relationship between apparent density ($\rho$) and cancellous bone Young’s modulus ($E$)
- $a, p$ are empirically determined constants

$$E = a\rho^p$$

<table>
<thead>
<tr>
<th>References</th>
<th>$p$</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carter and Hayes (1977), J Bone Joint Surg Am, 59:954</td>
<td>3.00</td>
<td>0.74</td>
</tr>
<tr>
<td>Rice et al. (1988), J Biomech 21:155</td>
<td>2.00</td>
<td>0.78</td>
</tr>
<tr>
<td>Hodgkinson and Currey (1992), J Mater Sci Mater Med 3:377</td>
<td>1.96</td>
<td>0.94</td>
</tr>
<tr>
<td>Kabel et al. (1999), Bone 24:115</td>
<td>1.93</td>
<td>0.94</td>
</tr>
</tbody>
</table>
Power law models for cancellous bone

- Hodgkinson – Currey model (1992) \( E_{\text{mean}} = 0.003715 \rho^{1.96} \)
- Kabel isotropic model (1999)
  \[
  E = E_{\text{tissue}} 813 \phi^{1.93} = E_{\text{tissue}} 813 \left( \frac{\rho}{1800} \right)^{1.93} = E_{\text{tissue}} 0.000424 \rho^{1.93}
  \]
  \[
  E_{11} = E_{\text{tissue}} (1240 \phi^{1.8}), \quad E_{22} = E_{\text{tissue}} (885 \phi^{1.89}), \quad E_{33} = E_{\text{tissue}} (529 \phi^{1.92})
  \]
  \[
  G_{23} = E_{\text{tissue}} (533.3 \phi^{2.04}), \quad G_{13} = E_{\text{tissue}} (633.3 \phi^{1.97}), \quad G_{12} = E_{\text{tissue}} (972.6 \phi^{1.98})
  \]
  \[
  \nu_{23} = 0.256 \phi^{-0.086}, \quad \nu_{13} = 0.316 \phi^{-0.191}, \quad \nu_{12} = 0.176 \phi^{-0.248}
  \]

\( \phi \) – volume fraction and \( \rho \) – 1800\( \phi \) kg/m\(^3\)
Orthotropy of bone

- Material possesses symmetry about three orthogonal planes
- **9 independent components**
- 3 Young’s moduli: \( E_1, E_2, E_3 \)
- 3 Poisson’s ratios:
  \[ \nu_{12} = \nu_{21}, \nu_{23} = \nu_{32}, \nu_{31} = \nu_{13} \]
- 3 shear moduli:
  \[ G_{12}, G_{23}, G_{31} \]

\[
\begin{bmatrix}
\epsilon_{11} \\
\epsilon_{22} \\
\epsilon_{33} \\
2\epsilon_{23} \\
2\epsilon_{13} \\
2\epsilon_{12}
\end{bmatrix} = \begin{bmatrix}
\frac{1}{E_1} & -\frac{\nu_{12}}{E_1} & -\frac{\nu_{13}}{E_1} & 0 & 0 & 0 \\
-\frac{\nu_{12}}{E_2} & \frac{1}{E_2} & -\frac{\nu_{23}}{E_2} & 0 & 0 & 0 \\
-\frac{\nu_{13}}{E_3} & -\frac{\nu_{23}}{E_3} & \frac{1}{E_3} & 0 & 0 & 0 \\
0 & 0 & 0 & 1/G_{23} & 0 & 0 \\
0 & 0 & 0 & 0 & 1/G_{31} & 0 \\
0 & 0 & 0 & 0 & 0 & 1/G_{12}
\end{bmatrix} \begin{bmatrix}
\sigma_{11} \\
\sigma_{22} \\
\sigma_{33} \\
\sigma_{23} \\
\sigma_{13} \\
\sigma_{12}
\end{bmatrix}
\]
Orthotropic constitutive models of cortical bone

(Humpherey and Delange, An Introduction to Biomechanics, 2004)

Tibia

<table>
<thead>
<tr>
<th>Young's modulus</th>
<th>Poisson's ratio</th>
<th>Shear modulus</th>
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</thead>
<tbody>
<tr>
<td>$E_1=6.9 \text{ GPa}$</td>
<td>$\nu_{12}=0.49$, $\nu_{21}=0.62$</td>
<td>$G_{12}=2.41 \text{ GPa}$</td>
</tr>
<tr>
<td>$E_2=8.5 \text{ GPa}$</td>
<td>$\nu_{13}=0.12$, $\nu_{31}=0.32$</td>
<td>$G_{13}=3.56 \text{ GPa}$</td>
</tr>
<tr>
<td>$E_3=18.4 \text{ GPa}$</td>
<td>$\nu_{23}=0.14$, $\nu_{32}=0.31$</td>
<td>$G_{23}=4.91 \text{ GPa}$</td>
</tr>
</tbody>
</table>

Femur

<table>
<thead>
<tr>
<th>Young's modulus</th>
<th>Poisson's ratio</th>
<th>Shear modulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_1=12.0 \text{ GPa}$</td>
<td>$\nu_{12}=0.376$, $\nu_{21}=0.422$</td>
<td>$G_{12}=4.53 \text{ GPa}$</td>
</tr>
<tr>
<td>$E_2=13.4 \text{ GPa}$</td>
<td>$\nu_{13}=0.222$, $\nu_{31}=0.371$</td>
<td>$G_{13}=5.61 \text{ GPa}$</td>
</tr>
<tr>
<td>$E_3=22.0 \text{ GPa}$</td>
<td>$\nu_{23}=0.235$, $\nu_{32}=0.350$</td>
<td>$G_{23}=6.23 \text{ GPa}$</td>
</tr>
</tbody>
</table>
Homogenisation techniques for bone microstructure

Voxel-based FE model
(element size: 25 microns)
- Directly transfer voxel to element (Grid mesh)
- Large number of elements
- Stress concentration

Solid-based FE model
(element size: 150 microns)
- Segmentation process
- Smoothing, creation of geometry
- Control of meshing algorithms

Perform static FEA under simple loading to determine the effective stiffness of these structures
Bone remodelling mechanisms
Physiological responses to mechanical stimuli
Concept of bone remodelling

- Living tissues are subject to remodelling/adaptation, where the properties change over time in response to various factors
- “every change in the function of bone is followed by certain definite changes in internal architecture and external conformation in accordance with mathematic laws.”
  – Julius Wolff (1892)
- Cancellous bone aligns itself with internal stress lines
Structural remodelling in bones

- Remodelling or adaptation can occur when there are changes in tissue environment, such as:
  - Stress/strain/strain energy density
  - Loading frequency
  - Temperature
  - Formation of micro-cracks

- A good example is to look at the growth of trees around external structures
  - Thickening of branches near fences/gates
  - Natural optimisation

Mattheck (1998)
Variations in bone remodelling responses

- Bone remodelling is thought to be mediated by osteocytes
- Site dependency
  - Different bones provide different mechanical function
  - Different sites have different biological environment
  - Results in different remodelling equilibrium
- Time dependency
  - High frequency (25 Hz) vs low frequency
  - Large load and low frequency can prevent mass loss
  - At higher frequencies, substantial bone growth is possible
  - Fading memory effects, i.e. adaptation of tissue to mechanical stimulation
Mechanical signal transduction in bones

- Bone transduces mechanical strain to generate an adaptive response
  - Piezoelectric properties of collagen
  - Fatigue micro-fracture damage-repair
  - Hydrostatic pressure of extracellular fluid influences on bone cell
  - Hydrostatic pressure influences on solubility of mineral and collagenous component, e.g. change in solubility of hydroxyapatite
  - Creation of streaming potential
  - Direct response of cells to mechanical loading

These are all mechanisms which may allow mechanical strain to be detected by bone
Bone remodelling by micro-fracture repair

Increased stress causes cracks in bone microstructure

Triggers osteoclast formation to remove broken tissue

Osteoblasts are then recruited to help form new bone

Osteoblasts become osteocytes and maintain bone structure

Indirect osteoblast-osteoclast coupling through mechanics

Mechanical load

Homeostasis

Microdamage triggers osteoclasts

Osteocytes recruit Osteoblasts

New bone with new OCY's

Recruitment stimuli

Region of elevated mechanical signals

The University of Sydney
Bone remodelling by dynamic loading

- Dynamic loading is much more effective at stimulating bone growth.
- Burr et al. (2002) found that dynamic loading forces fluids through canalicular channels, stimulating osteocytes by increased shear stresses.
Models of bone responses
Bone remodelling calculations
**Mechanical stimuli - \( \psi \)**

- Strain energy density
  \[
  \psi = U = \frac{1}{2} \{\sigma\}^T \{\varepsilon\} = \frac{1}{2} [\sigma_{11} \varepsilon_{11} + \sigma_{22} \varepsilon_{22} + \sigma_{33} \varepsilon_{33} + \sigma_{12} \varepsilon_{12} + \sigma_{13} \varepsilon_{13} + \sigma_{23} \varepsilon_{23}]
  \]

- Energy stress – linearise the quadratic nature of \( U \)

\[
\psi = \sigma_{\text{energy}} = \sqrt{2E_{\text{avg}} U}
\]

- Mechanical intensity scalar
  (volumetric shrinking/swelling)

- von Mises stress (\( \sigma_1, \sigma_2, \sigma_3 \) – principal stresses)

\[
\psi = \sigma_{\text{vm}} = \sqrt{\frac{1}{2} [ (\sigma_1 - \sigma_2)^2 + (\sigma_2 - \sigma_3)^2 + (\sigma_3 - \sigma_1)^2 ]}
\]

- Daily stresses (\( n_i = \) number of cycles of load case \( i \), \( N = \) number of different load cases, \( m = \) exponent weighting impact of load cycles)

\[
\psi = \sigma_d = \left( \sum_{i=1}^{N} n_i \bar{\sigma}_i^m \right)^{1/m}
\]
Continuum model of bone remodelling

- **Surface remodelling** — changes in external geometry of bone (cortical surface) over time, e.g. radius of bone

  \[ \Psi(t) \] — Mechanical stimulus. It may also change with time.
  \[ \Psi^*(t) \] — Reference stimulus

- **Internal remodelling** — changes in a material property over time, e.g. apparent density

  \[ [S] = [S(t)] \]
  \[ [C] = [C(t)] \]
Surface remodelling

- **Stimulus Error**: deviation of stimulus from some baseline/ref. value.
  \[ e = \psi(t) - \psi^*(t) \]

- **Surface Remodelling Rate**: \( c_s \) is a given constant.
  \[ \frac{ds}{dt} = \dot{s} = c_s [\psi(t) - \psi^*(t)] = c_s e \]

- **Surface Remodelling Rule with Lazy Zone**: \( w_s \) defines the lazy zone.
  \[ \dot{s} = \begin{cases} 
    c_s [\psi(t) - \psi^*(t) - w_s] & \text{for } \psi(t) - \psi^*(t) > w_s \\
    0 & \text{for } -w_s < \psi(t) - \psi^*(t) < w_s \\
    c_s [\psi(t) - \psi^*(t) + w_s] & \text{for } \psi(t) - \psi^*(t) < -w_s 
  \end{cases} \]
The lazy zone model for surface remodelling

Surface remodelling rate ($\dot{S}$) vs. Mechanical stimulus ($\psi$)

Lazy zone

Alternative remodelling rule without lazy zone: $\dot{S} = c_s \left[ \frac{\psi(t) - \psi^*(t)}{\psi^*(t)} \right]$
The lazy zone model for internal remodelling

Alternative remodelling rule without lazy zone: 
\[ \dot{s} = c_\rho \left[ \frac{\psi(t) - \psi^*(t)}{\psi^*(t)} \right] \]
Calculations!
Example: Bone loss in space

Human spaceflight to Mars could become a reality within the next 15 years, but not until some physiological problems are resolved, including an alarming loss of bone mass, fitness and muscle strength.

**Gravity at Mars' surface is about 38% of that on Earth.** With lower gravitational forces, bones decrease in mass and density. The rate at which we lose bone in space is 10-15 times greater than that of a postmenopausal woman and there is no evidence that bone loss ever slows in space. NASA has collected data that humans in space lose bone mass at a rate of \( c = 1.5\% / \text{month} \).

Further, it is not clear that space travelers will regain that bone on returning to gravity. During a trip to Mars, lasting between 13 and 30 months, unchecked bone loss could make an astronaut's skeleton the equivalent of a 100-year-old person.
Bone loss in space: derivation of bone density changes

- Bone remodelling sans lazy zone

\[ \dot{\rho} = \frac{d\rho}{dt} \approx \frac{\Delta \rho}{\Delta t} = \frac{\rho_{n+1} - \rho_n}{\Delta t} = c_\rho \left[ \frac{\psi(t) - \psi^*(t)}{\psi^*(t)} \right] \]

\[ \rho_{n+1} = \rho_n + c_\rho \left[ \frac{\psi(t) - \psi^*(t)}{\psi^*(t)} \right] \Delta t \]

- \( \psi \) is the Mars stress level, \( \psi^* \) is the Earth stress level

\[ \frac{\psi}{\psi^*} = 0.38, \quad c_\rho = 0.015\rho_n \]

\[ \rho_{n+1} = \rho_n - (0.015\rho_n)(0.62)\Delta t = \rho_n(1 - 0.0093\Delta t) \]
Critical bone loss in space

- How long could an astronaut survive in space if we assume the critical bone density to be 1.0 g/cm³? Initial bone density on Earth is ~1.79 g/cm³.
Example: simply loaded femur

- Take strain energy density as mechanical stimulus, $\psi$

$$\psi = U = \frac{1}{2} \{\sigma\}^T \{\varepsilon\} = \frac{1}{2} [\sigma_{xx}\varepsilon_{xx} + \sigma_{yy}\varepsilon_{yy} + \sigma_{zz}\varepsilon_{zz} + \sigma_{xy}\varepsilon_{xy} + \sigma_{yz}\varepsilon_{yz} + \sigma_{zx}\varepsilon_{zx}]$$

- Surface remodelling rate equation with lazy zone

$$\dot{s} = \begin{cases} 
    c_s[\psi(t) - \psi^*(t) - w_s] & \text{for } \psi(t) - \psi^*(t) > w_s \\
    0 & \text{for } -w_s < \psi(t) - \psi^*(t) < w_s \\
    c_s[\psi(t) - \psi^*(t) + w_s] & \text{for } \psi(t) - \psi^*(t) < -w_s 
\end{cases}$$
Spreadsheet calculation for simply loaded femur

Assume lazy zone half-width is 10% of $\psi^*$, so: $\psi - \psi^* > 0.1 \times \psi^*$

Modelled for 18 months, bone growth slows and equilibrium is reached
Spreadsheet calculation for dynamically loaded femur

Force is increased by 10 N every month: \( F(m+1) = F(m) + 10 \);
Reference stimulus increased by 5% per month: \( \Psi^*(m+1) = 1.05\Psi^*(m) \)
Static vs dynamic loading cases in the femur
FEA!
Finite element model workflow

- Update FEA Model
- Compute stress/strain tensor?
- Equilibrium
  - No
    - $e = |\psi(t) - \psi^*(t)| > w$
  - Yes
    - Apply remodeling rule
- Update Geometry or Material Property
- Modify surface or Bone density
Subroutines

- Many classic FE solvers have components written in Fortran
- Custom behaviour by the development of Fortran subroutines
- Subroutines are executed during the solution

```fortran
*deck,userfld USERDISTRIBUT parallel rjayasee
subroutine userfld(matId, elemId,
  & ldstep, isubst, time, dtime,
  & kDomIntPt, kLayer, kSectPt,
  & nDirect, nShear, nComp, nStatev,
  & coords,
  & Temp,dTemp)
...
```

*** primary function ***

Edit Field Variables During Solution

Input arguments

matId (int,sc,i) material #
elemId (int,sc,i) element #
ldstep (int,sc,i) load step num
isubst (int,sc,i) substep num
time (int,sc.d) time
ANSYS Classic/APDL

- ANSYS Classic is the old GUI for ANSYS
- Workbench adds convenience, often at the cost of control
- Classic is closely linked with the ANSYS Parametric Design Language (APDL)
- APDL can be used as an input language to talk directly to the ANSYS solver
- To set-up and run subroutines, we will use APDL to talk to ANSYS
Programming workflow

- Programming languages (C variants, Fortran, Java, etc.) require a compiler

  code → compile → execute

- Scripting languages (MATLAB, APDL, Python, etc.) are "interpreted" at runtime

  code → interpret/execute
**USERFLD subroutine**

- Pre-compiled using Intel Fortran compiler
- Called by ANSYS by specifying the location of compiled binaries on the command line

```plaintext
set ANS_USER_PATH = "C:\test"
echo %ANS_USER_PATH%
anys161.exe -b -i input -o output
```

- Make a .bat file for ease of use
- ANSYS command can be generated from the ANSYS Launcher (launcher161.exe)

User-defined field (UF01) across all nodes in the model

UF01 = Young’s modulus (YM)

Solve and update UF01 using the USERFLD subroutine
APDL script

- Generate your own APDL script based on the template
- Get nodes, elements, and components from Workbench (FE Modeler)
- Use a good text editor (Notepad++ is available on PCLAB computers)
- Post-process or use ANSYS Classic GUI

Import geometries into Workbench (Design Modeler)
Mesh as a mechanical model
Use FE Modeler to export mesh and components
Summary

- Bone microstructure and composition
- Bone constitutive models
- Bone remodelling mechanisms
- Bone remodelling calculations
  - External remodelling
  - Internal remodelling

- Assignment 3 handed out today, due week 13
- Group project reports and presentations are due in week 13
- Quiz in week 12