(Bone) Fracture Healing

Part 1/2

Computational Biomechanics
Summer Term 2016
Lecture 9/12
Frank Niemeyer
Clinical View

Fracture Sites
Fracture Types

- Displaced vs. non-displaced
- Open vs. closed
- Transverse, spiral, oblique, ...

OpenStax [http://cnx.org/contents/FPtK1zmh@8.25:no74XEM7@3/Fractures-Bone-Repair](http://cnx.org/contents/FPtK1zmh@8.25:no74XEM7@3/Fractures-Bone-Repair)
Treatment & Challenges

- Fracture fixation
  - Align fragments & stabilize
  - Braces, casts, plates, IM nails, external fixator, …
- Complication rate ~ 10 % (Einhorn et al. 2014)
- Delayed union
- Non-union
  - Hypertrophic pseudarthrosis
  - Atrophic pseudarthrosis
  - Synovial pseudarthrosis
- Causes
  - Excessive motion
  - Large gap
  - Loss of blood supply
  - Severe periosteal and/or soft tissue trauma
  - Systemic (age, malnutrition, …)

Clinical View

Healing Phases: Inflammation

- Fracture damaged bone, soft tissue & vasculature
- Blood coagulates → blood clot
- Hypoxic, low pH → cells die
- Ruptured blood vessels → osteocytes in cortical ends near fracture die
- Release of proinflammatory cytokines, growth factors, angiogenic factors
  - Sources: platelets, necrotic cells, damaged bone ends, muscles, periosteum, marrow
- Neutrophils, macrophages, lymphocytes invade; clear site from debris tissue
- Peak within 24 h, completed after ~ 7 days (rats)

Healing Phases: Repair

- **Primary callus response**
  - At some distance to the gap, beneath periosteum
  - Intramembranous ossification
  - Lasts ~ 2 weeks

- Revascularization of the hematoma commences
- MSCs & fibroblasts (blood vessels & soft tissues) invade
- Fibroblasts replace hematoma gradually by granulation tissue → soft callus
- Near/inside the gap: MSCs differentiate into chondrocytes → endochondral ossification
- Result: hard callus, stabilized fracture
- Bony bridging, given the right conditions

Healing Phases: Remodeling

- Maturation
  - Resorption of woven bone
  - Lamellar bone deposition
- Osteoclastic resorption of superfluous bone tissue
- 5 – 8 weeks (rats; humans: years)
- Result
  - Restored bone architecture, anatomy
  - Restored stability
  - Blood supply normalized to pre-fracture levels

Direct Fracture Healing

- Requires very stable fixation
- Tiny gaps, no inflammation, no callus formation
- Contact healing
  - Gap < 0.01 mm
  - BMUs directly remodel lamellar bone cross-fracture
  - Bony union and restoration of Haversian system
- Gap healing
  - Gap < 0.8 mm
  - Gap filled with woven bone
  - Gradually replaced by oriented revascularized osteons

Claes et al. 2012
Roux & Krompecher

- Roux (1881): specific stimulus → specific tissue type
  - Proposed that “cells within tissues engage in a competition for the functional stimulus” (Weinans & Prendergast 1996)
    - „Differenzirende u. gestaltende Wirkungen der function. Reize.“
    - → „Selbstgestaltung“ (self-organization)
  - Compressive → bone
  - Tensile → fibrous connective tissue
  - Compressive/tensile + high shear stress → cartilage

- Krompecher (1937)
  - Agrees with Roux, but
  - ... Hydrostatic pressure → cartilage
Mechanoregulatory Tissue Differentiation Hypotheses

Pauwels

- „Eine neue Theorie über den Einfluss mechanischer Reize auf die Differenzierung der Stützgewebe“ (1960)
- Challenges Roux’s hypothesis
  - Tensile stimuli also stimulate bone formation
  - Long bones: bending loads
  - Refutes Roux’s specific stimulus for cartilage formation
- New hypothesis
  - Bone deposit on an existing framework protecting it from non-physiological deformations
  - Cell-level combinations of pure distortional strain & pure volumetric strain determine differentiation

Niemeyer 2013 (after Pauwels 1973)
Carter et al.

- Proposes “osteogenic index” as a function of peak cyclic shear and peak cyclic hydrostatic stress

\[ I = \sum_i n_i (S_i + kD_i) \]

- Influence of vascularity
Mechanoregulatory Tissue Differentiation Hypotheses

Claes & Heigele

• “Reinterpretation of Pauwels” (Heigele 1998)
• Assumptions
  • Local hydrostatic stress and local strain state as determining stimuli
  • Bone formation on existing bony surfaces
  • ... if both hydrostatic stress and shape changing strains stay below certain thresholds
• Thresholds determined based on combined in vivo & FE investigation
• Vaguely defined “strains”
  • Probably normal strain of max. absolute value along x/y axes
Prendergast et al.

- Biological tissue as biphasic material (poroelastic)
  - Solid phase (matrix)
  - Fluid phase (interstitial fluid)
- Tissue differentiation guided by
  - Octahedral shear strain $\gamma$
  - Fluid flow (flow velocity) $v$
- Combined stimulus $S = \gamma/a + v/b$

Mechanoregulatory Tissue Differentiation Hypotheses

Niemeyer 2013 (after Lacroix et al. 2002)
Simulating Remodeling vs. Fracture Healing

- Remodeling: Dynamics of a single “species” (typically bone density)
  → Single ODE/PDE
  → Single mechanical stimulus
  → Osteocytes as mechanosensors

- Fracture Healing: Multiple interacting “species” (tissue and/or cell types)
  → System of coupled PDEs (or other equivalent formalization)
  → Multiple mechanical and biological stimuli
  → Tissue differentiation & maturation
  → Growth
  → Additional mechanosensors required (fracture gap?)
The Ulm Bone Healing Model

Biological Processes

- Cartilage
  - Chondrogenesis
  - Cartilage destruction
- Woven Bone
  - Intramembranous ossification
- Connective tissue
  - Bone resorption
- Lamellar Bone
  - Bone maturation
- Avascular tissue
  - Angiogenesis
  - Vessel destruction
  - Optimal perfusion
The Ulm Bone Healing Model

Representing Biological State

FE mesh

Tissue composition

Vascularity

$c$: $\Omega \times [0, +\infty) \rightarrow [0, 1]^5$ with $\Omega \subset \mathbb{R}^3$

$c: (x, t) \mapsto [c_{\text{woven}}, c_{\text{lamellar}}, c_{\text{cartilage}}, c_{\text{soft}}, c_{\text{vascularity}}]$

where $c_{\text{soft}} = 1 - c_{\text{woven}} - c_{\text{lamellar}} - c_{\text{cartilage}}$

$\sum_{i \in T} c_i(x, t) = 1.0$ with $T := \{\text{soft, cartilage, woven, lamellar}\}$
The Ulm Bone Healing Model

Predicting Tissue Concentrations

\[ c(x, t_1) = c_0 + \int_{t_0}^{t_1} \partial_t c(x, t) \, dt \]

\[ \partial_t c(x, t) \approx f(m(x, t), b(x, t)) \]

**Mechanical stimuli**  
\[ m(x, t) = M(x, t, c(\cdot, t_0 \ldots t), u_{BC}, F_{BC}) \]

**Biological stimuli**  
\[ b(x, t) = B(x, t, c(\cdot, t), c_{BC}) \]

*Depends on history*

*Depends on finite neighborhood of $x$*
The Ulm Bone Healing Model

Numerical Implementation

- Initialization (geometry, meshing, tissue distribution)
- Rule of mixture
- Analyze mechanical response (FEA)
- Compute "effective stimuli" from strain history
- Compute average concentrations
- Tissue differentiation (fuzzy logic)
- Remeshing and state mapping

Time integration loop

$t_n \rightarrow t_{n+1}$

Niemeyer 2013
Rule of Mixture & Structural Analysis (FEA)

Composite linear-elastic material properties (Carter & Hayes 1977, Shefelbine et al. 2005):

\[
E(x, t) = \sum_{i \in T} E_i c_i^3(x, t)
\]

\[
\nu(x, t) = \sum_{i \in T} \nu_i c_i(x, t)
\]
Mechanical Stimuli

Dilatational strain

\[ \varepsilon = \frac{1}{3}(\varepsilon_1 + \varepsilon_2 + \varepsilon_3) \]

Pure volume change

Distortional strain

\[ \gamma = \frac{1}{\sqrt{2}} \sqrt{(\varepsilon_1 - \varepsilon_2)^2 + (\varepsilon_1 - \varepsilon_3)^2 + (\varepsilon_2 - \varepsilon_3)^2} \]

Pure shape change

where \( \varepsilon = \begin{bmatrix} \varepsilon_1 & 0 & 0 \\ 0 & \varepsilon_2 & 0 \\ 0 & 0 & \varepsilon_3 \end{bmatrix} \in \mathbb{R}^3 \rightarrow \mathbb{R}^{3\times3} \)

Mechano-regulated Tissue Differentiation

The Ulm Bone Healing Model | Mechanics

- Cartilage
- Bone
- Connective tissue

Dilatational strain (%)
- 0 - 5.0
- 5.0 - 0.85
- 0.85 - 0.02
- 0.045
- 0.07

Distortional strain (%)
- 16

Bone resorption

Tissue destruction

Effective Mechanical Stimuli

\[ w(t) = \begin{cases} 
    \exp(-\lambda(t - t_{\text{delay}})) & \text{if } t_{\text{delay}} < t \leq t_{\text{mem}} \\
    0 & \text{otherwise}
\end{cases} \]

\[ \tilde{w}(t) = \frac{w(t)}{\int_{-\infty}^{+\infty} w(\tau) d\tau} \]

\[ \varepsilon_{\text{eff}} = \varepsilon \ast \tilde{w} \]

\[ \gamma_{\text{eff}} = \gamma \ast \tilde{w} \]

\[ m = [\varepsilon, \gamma, \varepsilon_{\text{eff}}, \gamma_{\text{eff}}] \]
Calcification Delay & Stimuli Memory

The Ulm Bone Healing Model | Mechanics

-Normalized total strain vs Time
-Weight vs Time passed since event
-Normalized raw stimulus vs Time
-Normalized effective stimulus vs Time
Biological Stimuli

\[ \mathbf{b} = [c_{\text{woven}}, c_{\text{lamellar}}, c_{\text{cartilage}}, c_{\text{soft}}, c_{\text{vascularity}}, s_b, s_v] \]

Non-local influence

Paracrine signaling: Cells release signals that affect nearby target cells.

http://www.snipview.com/q/Paracrine_signaling

Appositional Growth
Biological Stimuli

\[ b = \left[ c_{\text{woven}}, c_{\text{lamellar}}, c_{\text{cartilage}}, c_{\text{soft}}, c_{\text{vascularity}}, s_b, s_v \right] \]

Non-local influence

\[ s_b(x, t) = (c_{\text{bone}}(\cdot, t) * G_\sigma)(x) \]

\[ \equiv \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} c_{\text{bone}}(\xi, \nu; t) G_\sigma(x - \xi, y - \nu) d\xi \, dv \]

\[ s_v(x, t) = (c_{\text{vasc}}(\cdot, t) * G_\sigma)(x) \]

e.g. in two spatial dimensions

\[ G_\sigma(x, y) \propto \frac{1}{2\pi\sigma^2} \exp \frac{-x^2 - y^2}{2\sigma^2} \]
Evaluating \( f \) with Fuzzy Logic

\[
\partial_t c(x,t) \approx f(m(x,t), b(x,t), \text{local vascularity})
\]

- Local bone concentration
- Weighted-average bone tissue concentration
- Cartilage concentration
- Local vascularity
- Weighted-average vascularity
- Distortional strain (immediate and effective)
- Dilatational strain (immediate and effective)

Fuzzy logic controller

- Fuzzification
- Rule evaluation
- Defuzzification

Change in bone concentration
Change in cartilage concentration
Change in vascularity

if vascularity is medium and not bone is low and dist_strain_eff is low then delta_bone is positive
Fuzzy Logic & Fuzzy Inference (Mamdani)

Fuzzification (fuzzy proposition) \( x \text{ is } \mu_A := \mu_A(x) = A \in [0, 1] \)

Logical and \( A \land B := \min(A, B) \)

Logical or \( A \lor B := \max(A, B) \)

Logical not \( \neg A := 1 - A \)

Logical implication \( A \rightarrow B := \mu_{C_i} : y \mapsto A \land \mu_B(y) \)

„Or“ aggregation \( \mu_C : x \mapsto \max \{\mu_{C_0}(x), ..., \mu_{C_n}(x)\} \)

Defuzzification \( y_C := \text{CoA}(\mu_C) = \frac{\int x\mu_C(x) \, dx}{\int \mu_C(x) \, dx} \)
Example (1/3): Fuzzification & Premise Eval.

\[
\text{if } c_{\text{vasc}} \text{ is sufficient and not } c_{\text{bone}} \text{ is low then } \delta c_{\text{bone}} \text{ is positive}
\]

\[
c_{\text{vasc}} \text{ is sufficient and not } c_{\text{bone}} \text{ is low}
\]
\[
= 0.45 \quad \text{and not} \quad 0.25
\]
\[
= 0.45 \quad \text{and} \quad 1 - 0.25
\]
\[
= \min(0.45, 0.75)
\]
\[
= 0.45
\]
Example (2/3): Implication

\[
\text{c_vasc is sufficient and not c_bone is low}
\]

\[
= 0.45 \quad \text{and not} \quad 0.25
\]

\[
= 0.45 \quad \text{and} \quad 1 - 0.25
\]

\[
= \min(0.45, 0.75) = 0.45
\]

If 0.45
then \( \text{delta_c_bone is positive} \)
Example (3/3)
The Ulm Bone Healing Model

Time Integration

\[ c(x, t_1) = c_0 + \int_{t_0}^{t_1} \partial_t c(x, t) \, dt \]

Initial value problem

\[ \partial_t c(x, t) \approx f(m(x, t), b(x, t)) = \Delta c \]

Boundary value problem (depends on structural FEA)

Forward Euler:

\[ c(x, t + \Delta t) \approx c(x, t) + \Delta t \Delta c \]

Heun’s method (explicit trapezoidal):

\[ \tilde{c}(x, t + \Delta t) = c(x, t) + \Delta t \Delta c \]

\[ \tilde{m}(x, t + \Delta t) = \mathcal{M}(x, t + \Delta t, \tilde{c}, u_{BC}, F_{BC}) \]

\[ \tilde{b}(x, t + \Delta t) = \mathcal{B}(x, t + \Delta t, \tilde{c}, c_{BC}) \]

\[ \Delta \tilde{c} = f(\tilde{m}, \tilde{b}) \]

\[ c(x, t + \Delta t) \approx c(x, t) + \frac{1}{2} \Delta t (\Delta c + \Delta \tilde{c}) \]

Needs to keep track of mechanical stimuli history (or even multiple histories for predictor-corrector schemes)
The Ulm Bone Healing Model

Numerical Implementation

Initialization (geometry, meshing, tissue distribution)

Rule of mixture

Analyze mechanical response (FEA)

Compute "effective stimuli" from strain history

Compute average concentrations

Tissue differentiation (fuzzy logic)

Remeshing and state mapping

Time integration loop

$t_n$ → $t_{n+1}$

Niemeyer 2013
Callus Healing (Sheep, External Fixator)

The Ulm Bone Healing Model | Applications

Simon & Niemeyer, 2015
Simulation Results

The Ulm Bone Healing Model | Applications

Simulation Results

7% initial IFS

30% initial IFS

Time (days) 7 14 21 28 35 42 49 56 ...

Relative bone concentration (%)
Simulation Results

The Ulm Bone Healing Model | Applications

Simon & Niemeyer, 2015
Remodeling

The Ulm Bone Healing Model | Applications | Callus Healing

Maturation and Remodeling

Allowed IFM: $x_{\text{leave}} = 3.00 \text{ mm}$
Location: Fracture gap, centrally
Spinal Fusion

Conventional

"Amplifix"

©ACES Ing.-GmbH.
Simulation Results

The Ulm Bone Healing Model | Applications | Spinal Fusion

Niemeyer et al. 2015
Distraction Osteogenesis

Callus distraction  
Segment transport

(from Rüter & Brutscher 1989)
Viscoplasticity

Forced displacement

Tissue slowly follows (creep flow)

Remaining elastic strain = signal sensed by cells

Niemeyer 2013
Remeshing & Solution Mapping

The Ulm Bone Healing Model | Applications | Distraction Osteogenesis

Niemeyer 2013
Simulation Results

Callus distraction
+ 3.00 mm dynamization