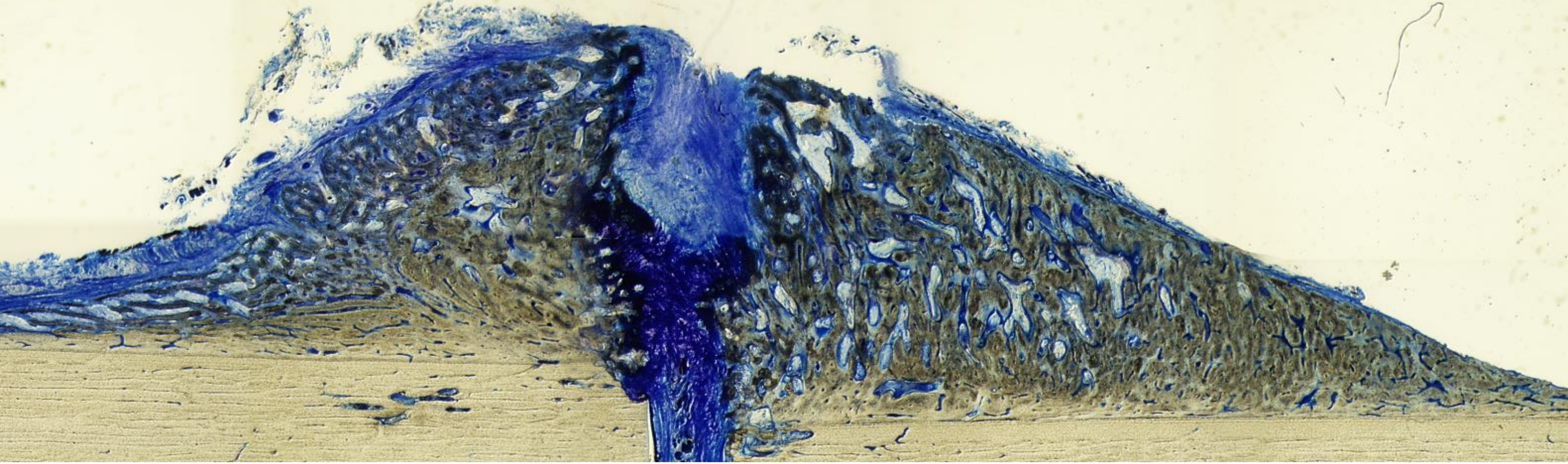


(Bone) Fracture Healing

Part 1/2

Computational Biomechanics

Summer Term 2016

Lecture 9/12

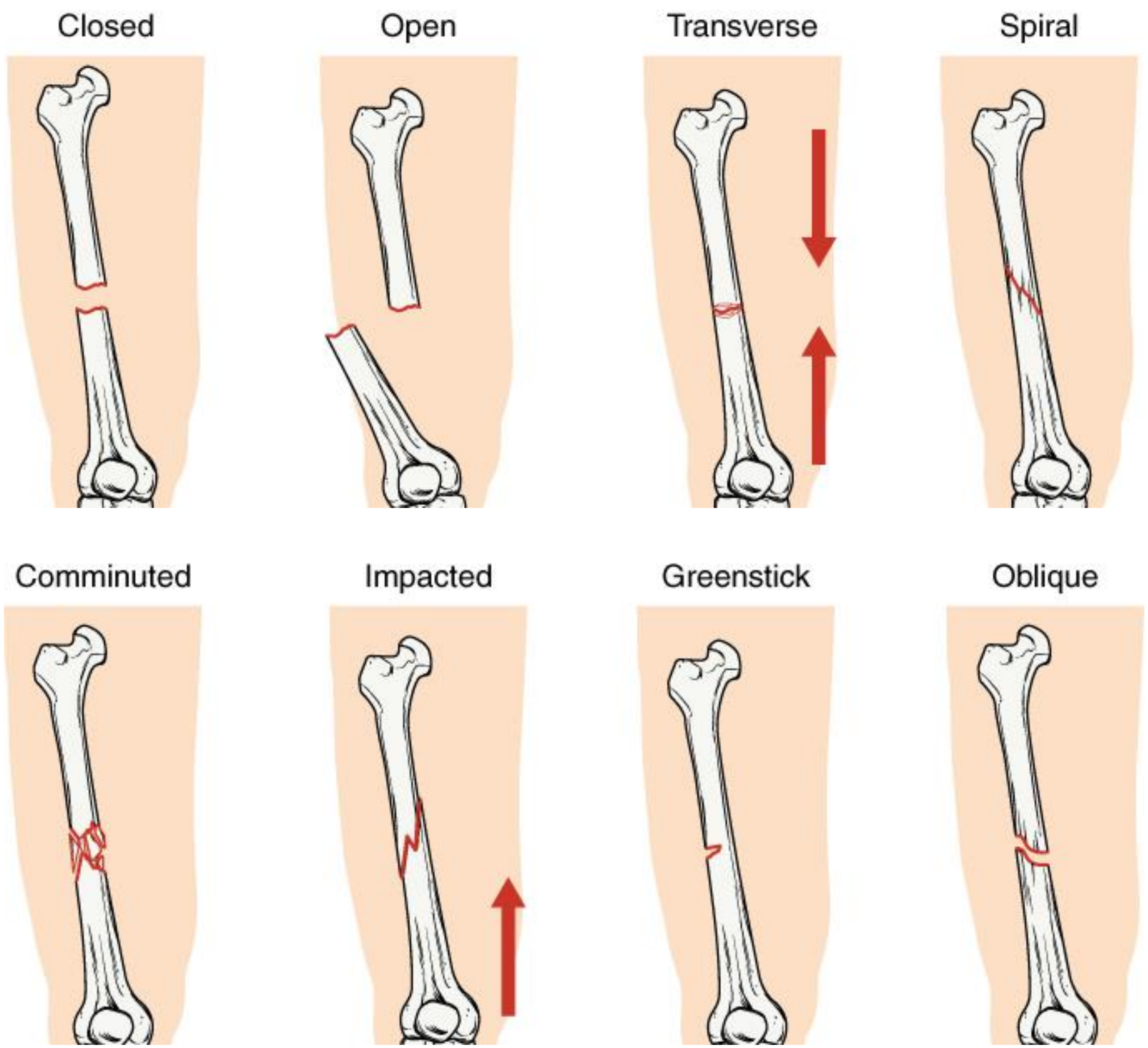
Frank Niemeyer

Clinical View

Fracture Sites

Fracture Types

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

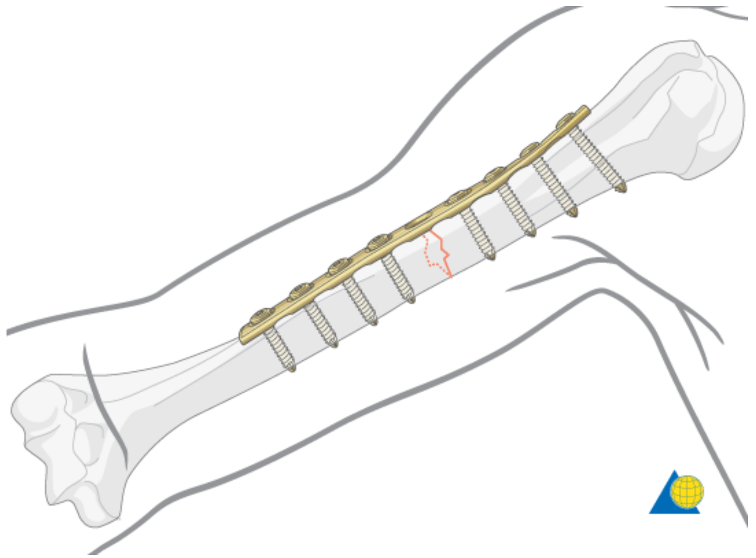


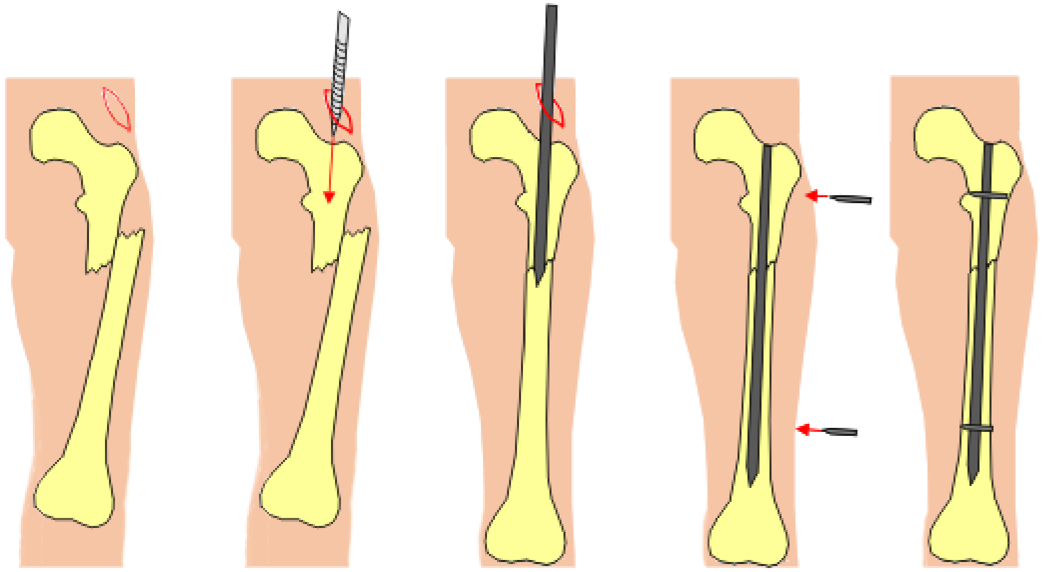
OpenStax http://cnx.org/contents/FPtK1zmh@8.25:no74XEM7@3/Fractures-Bone-Repair

Clinical View

Treatment & Challenges

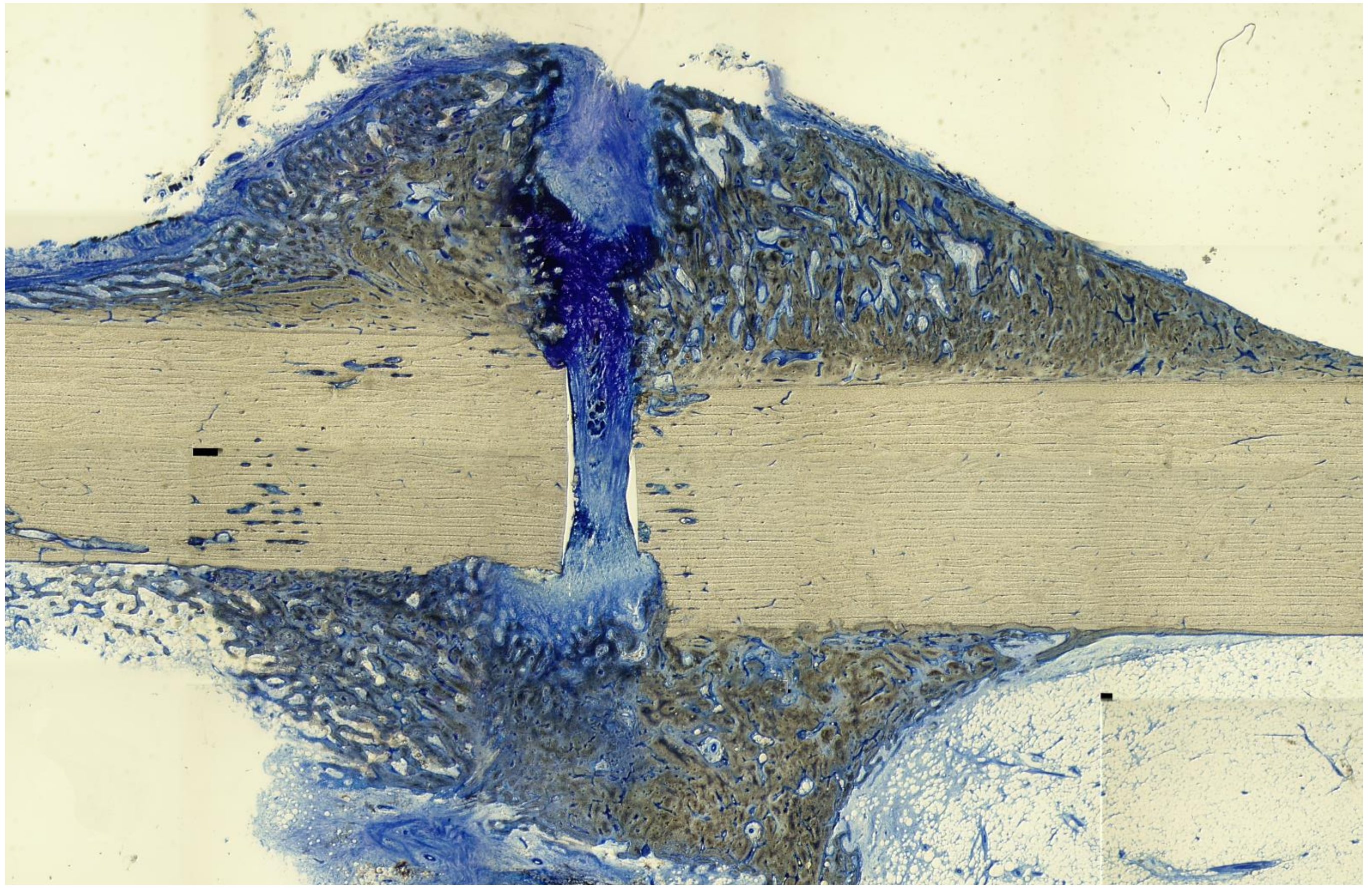
- Fracture fixation
  - Align fragments & stabilize
  - Braces, casts, plates, IM nails, external fixator, ...
- Complication rate ~ 10 % (Einhorn et al. 2014)
- Delayed union
- Non-union
  - Hypertrophic pseudarthrosis
  - Atrophic pseudarthrosis
  - Synovial pseudarthrosis
- Causes
  - Excessive motion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





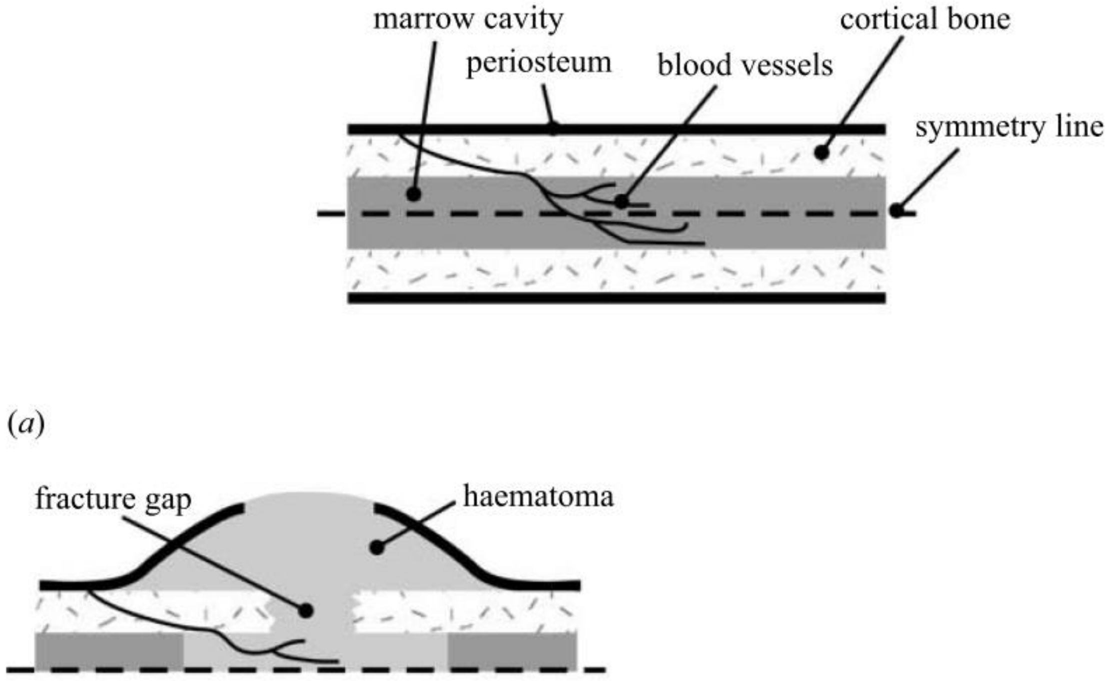
http://www.rob.cs.tu-bs.de/en/research/projects/femur/

Indirect Fracture Healing



Healing Phases: Inflammation

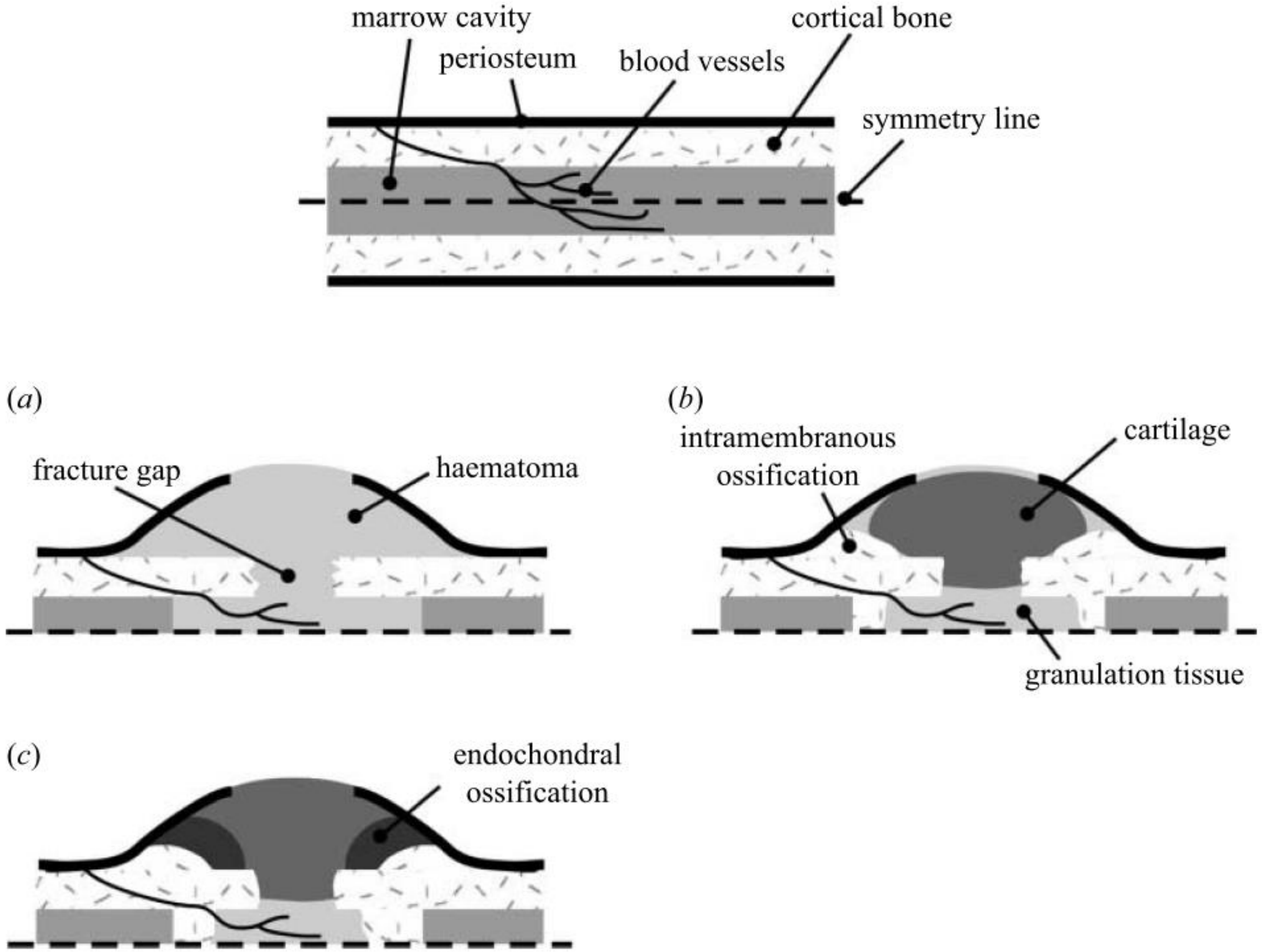
- Fracture damaged bone, soft tissue & vasculature
- Blood coagulates → blood clot
- Hypoxic, low pH → cells die
- Ruptured blood vessels → osteocytes in cortical ends near fracture die
- Release of proinflammatory cytokines, growth factors, angiogenic factors
  - Sources: platelets, necrotic cells,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



Bailón-Plaza & van der Meulen 2001, Geris et al. 2009

Healing Phases: Repair

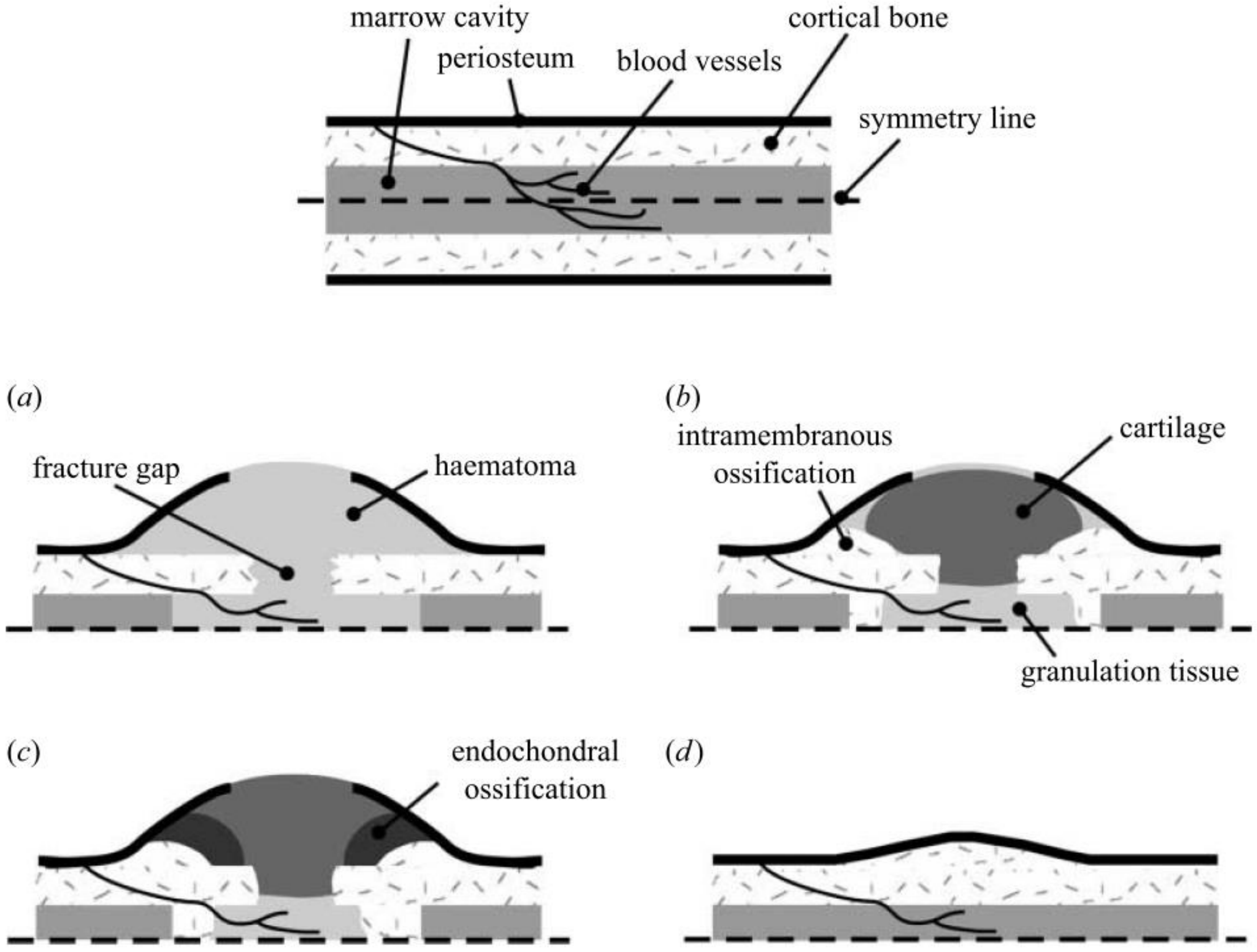
- Primary callus response
  - At some distance to the gap, beneath periosteum
  - Intramembranous ossification
  - Lasts ~ 2 weeks
- Revascularization of the hematoma commences
- MSCs & fibroblasts (blood vessels & soft tissues) invade
- Fibroblasts replace hematoma gradually by granulation tissue → soft callus
- Near/inside the gap: MSCs differentiate into chondrocytes → endochondral ossification
- Result: hard callus, stabilized fracture
- Bony bridging, given the right conditions



Bailón-Plaza & van der Meulen 2001, Geris et al. 2009

Healing Phases: Remodeling

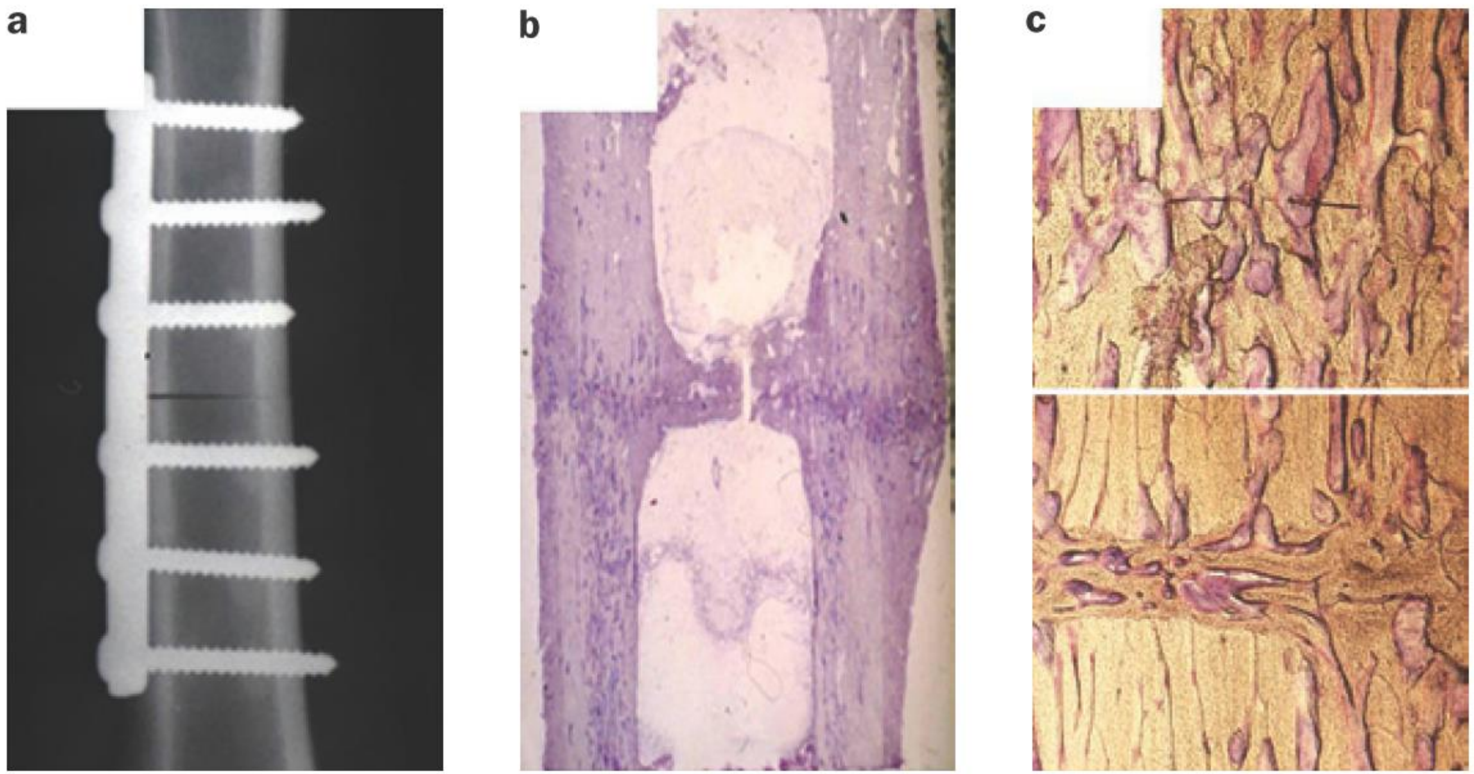
- Maturation
  - Resorption of woven bone
  - Lamellar bone deposition
- Osteoclastic resorption of superfluous bone tissue
- 5 – 8 weeks (rats; humans: years)
- Result
  - Restored bone architecture, anatomy
  - Restored stability
  - Blood supply normalized to pre-fracture levels



Bailón-Plaza & van der Meulen 2001, Geris et al. 2009

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

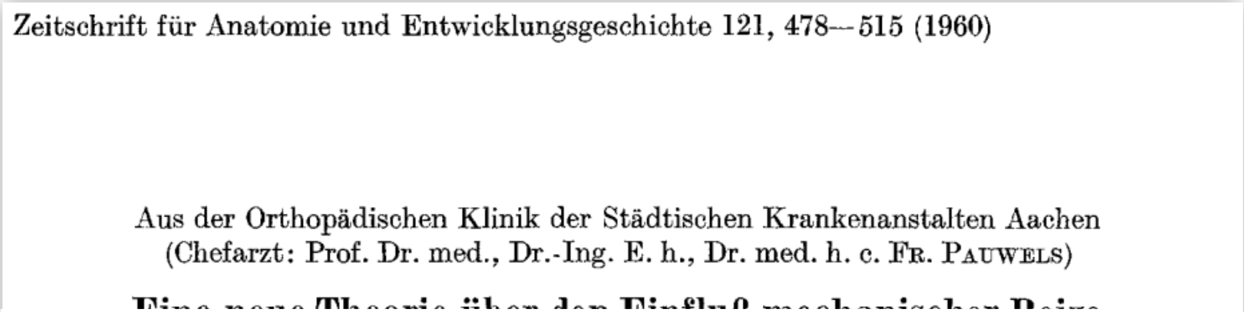
Roux & Krompecher

- 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

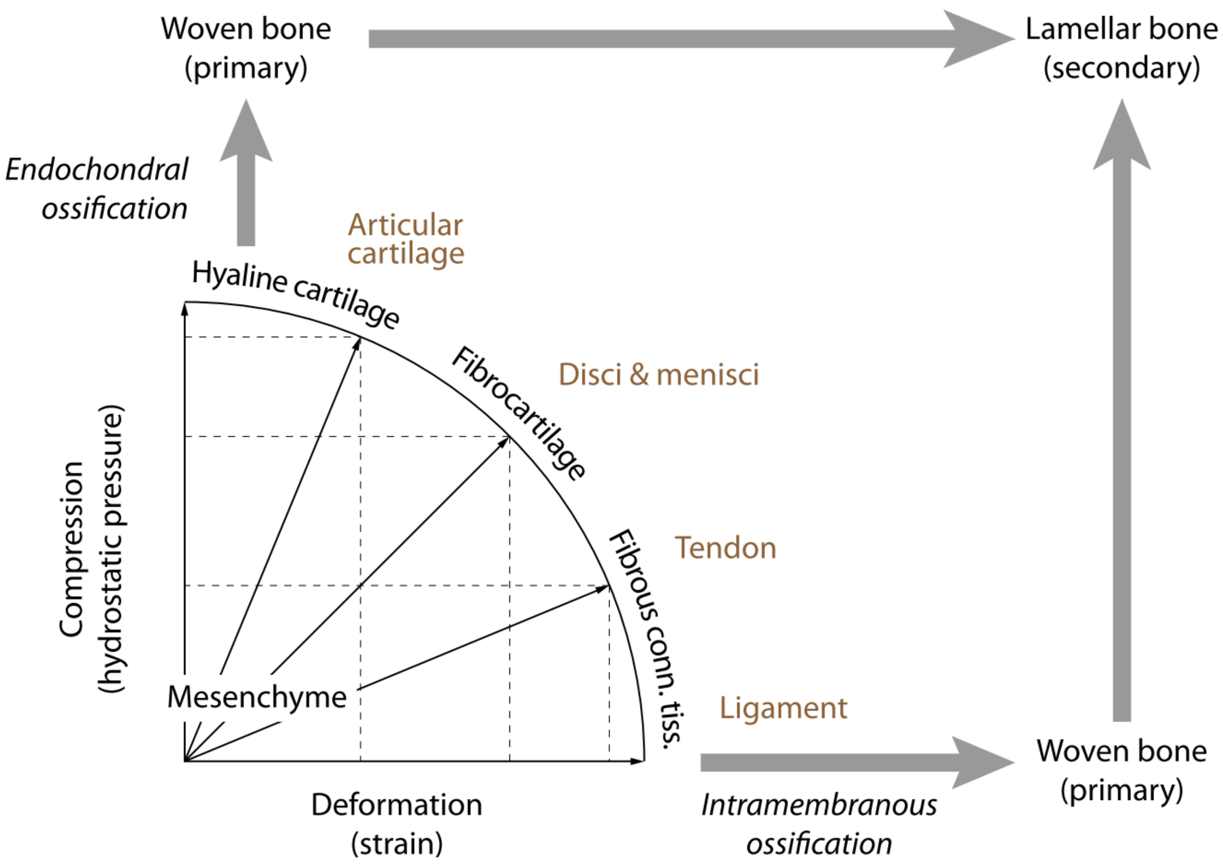
Wilhelm Roux (1850-1924)
© Martin-Luther Universität Halle-Wittenberg

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


Zeitschrift für Anatomie und Entwicklungsgeschichte 121, 478—515 (1960)

Aus der Orthopädischen Klinik der Städtischen Krankenanstalten Aachen
(Chefarzt: Prof. Dr. med., Dr.-Ing. E. h., Dr. med. h. c. FR. PAUWELS)



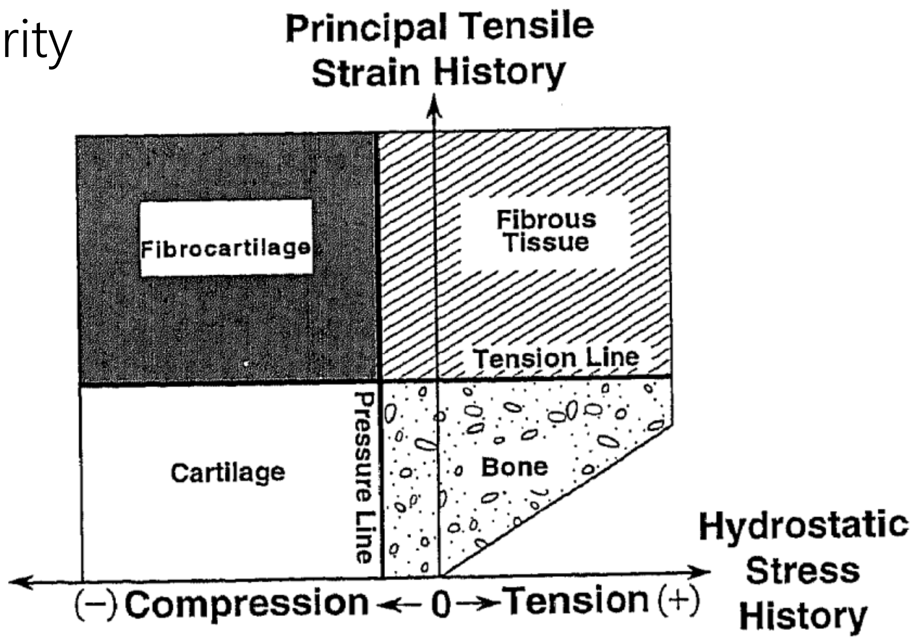
Niemeyer 2013 (after Pauwels 1973)

Carter et al.

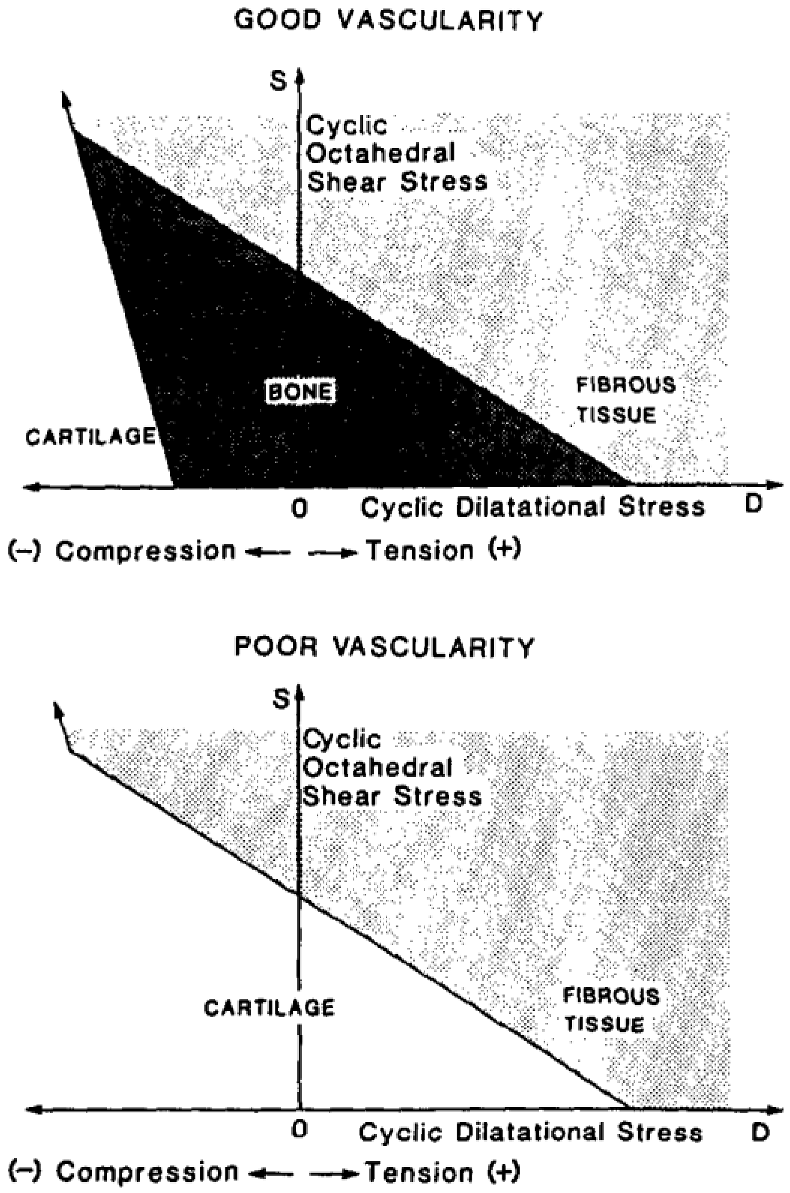
- Proposes "osteogenic index" as a function of peak cyclic shear and peak cyclic hydrostatic stress

$$I = \sum_i n_i(S_i + kD_i)$$

- Influence of vascularity



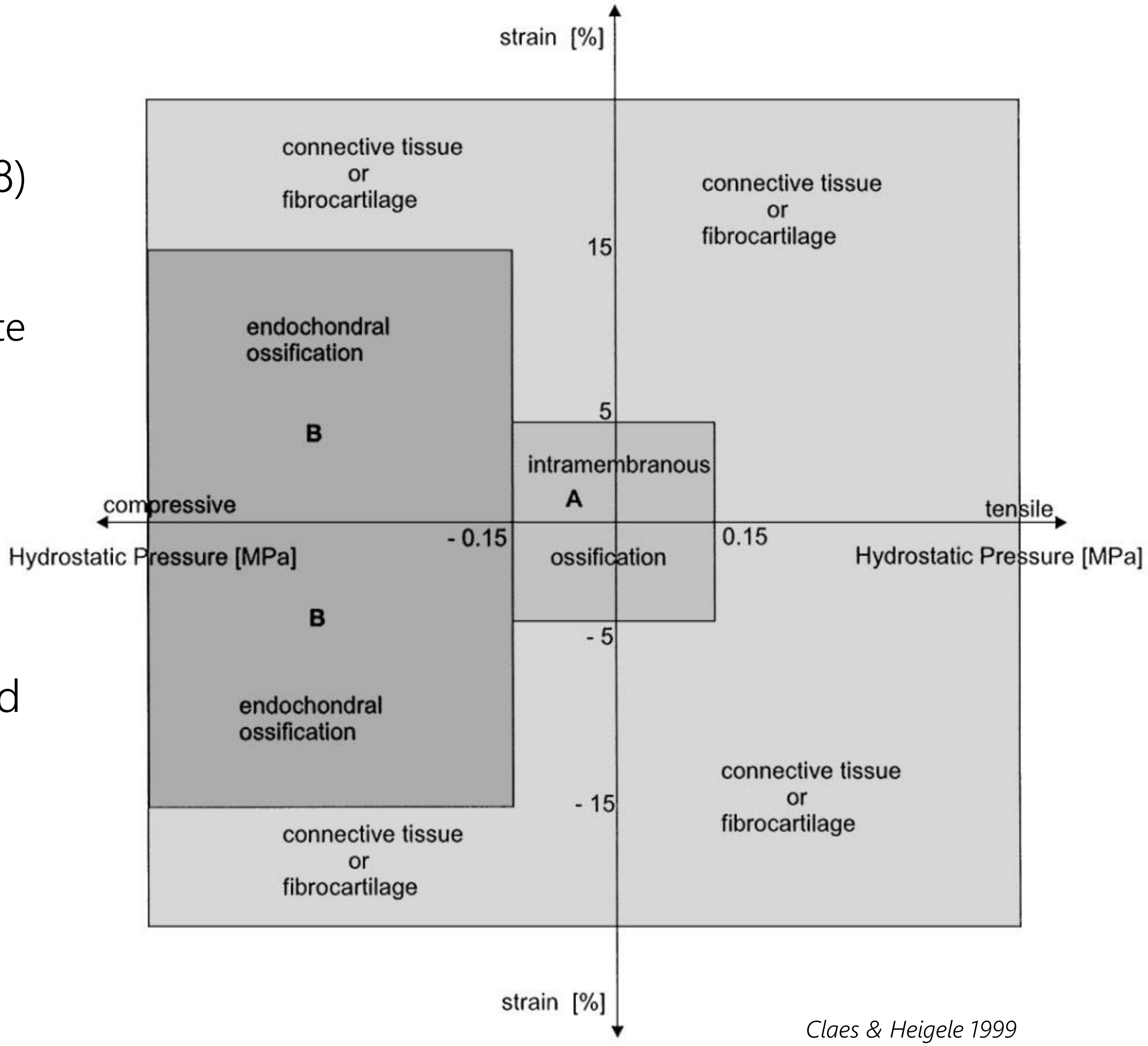
Carter et al. 1998



Carter 1987

Claes & Heigele

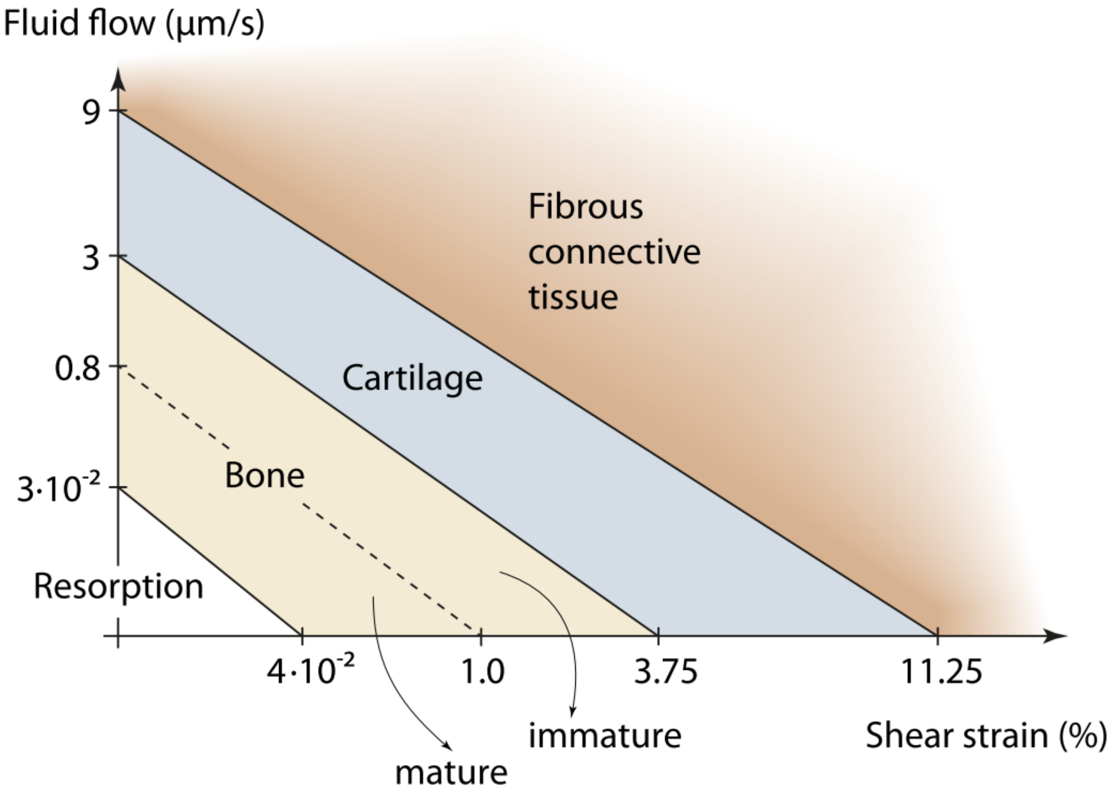
- "Reinterpretation of Pauwels" (Heigele 1998)
- Assumptions
  - Local hydrostatic stress and local strain state as determining stimuli
  - Bone formation on existing bony surfaces
  - … if both hydrostatic stress and shape changing strains stay below certain thresholds
- Thresholds determined based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



Claes & Heigele 1999

Prendergast et al.

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



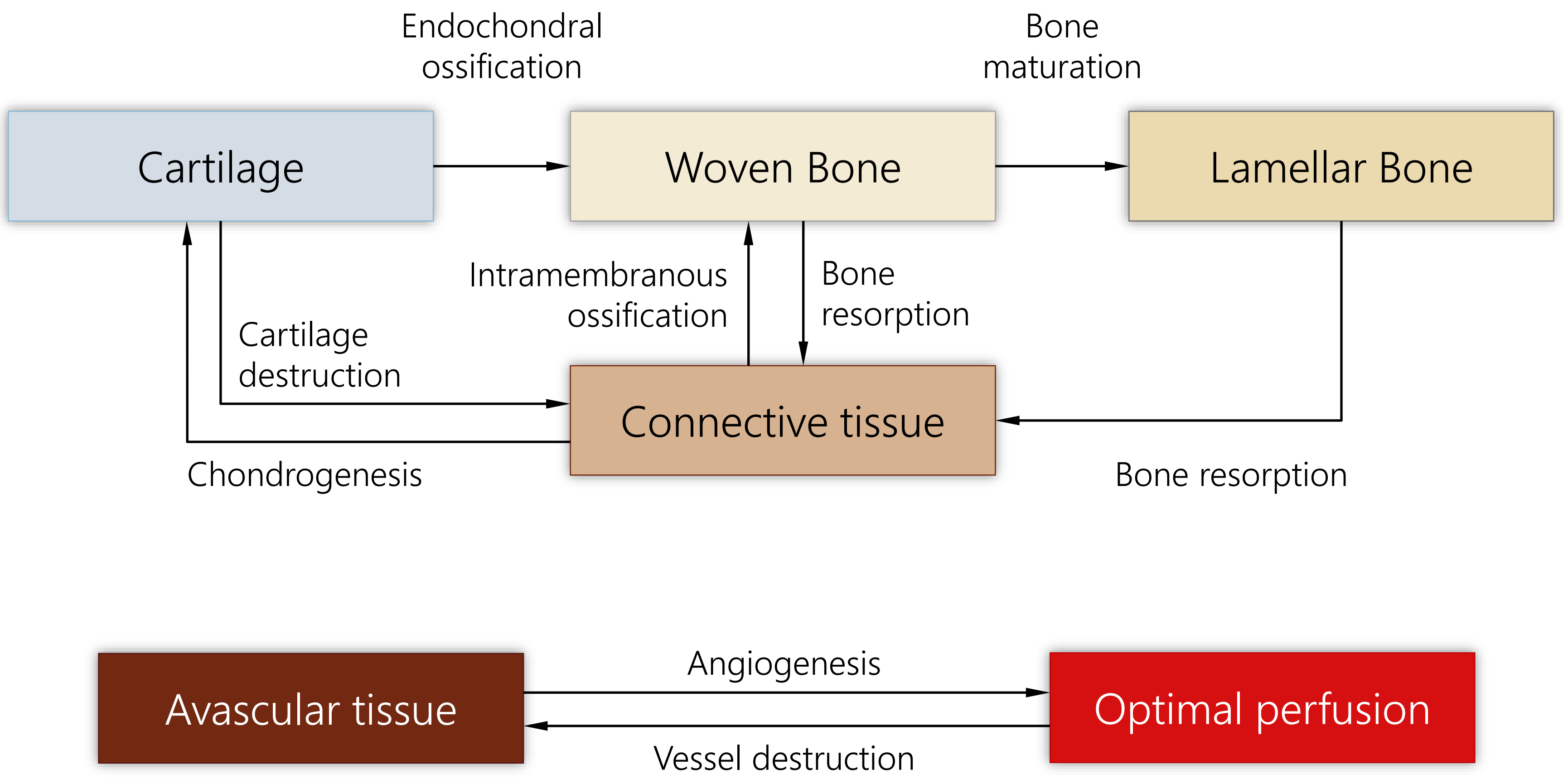
Niemeyer 2013 (after Lacroix et al. 2002)

Simulating Remodeling vs. Fracture Healing

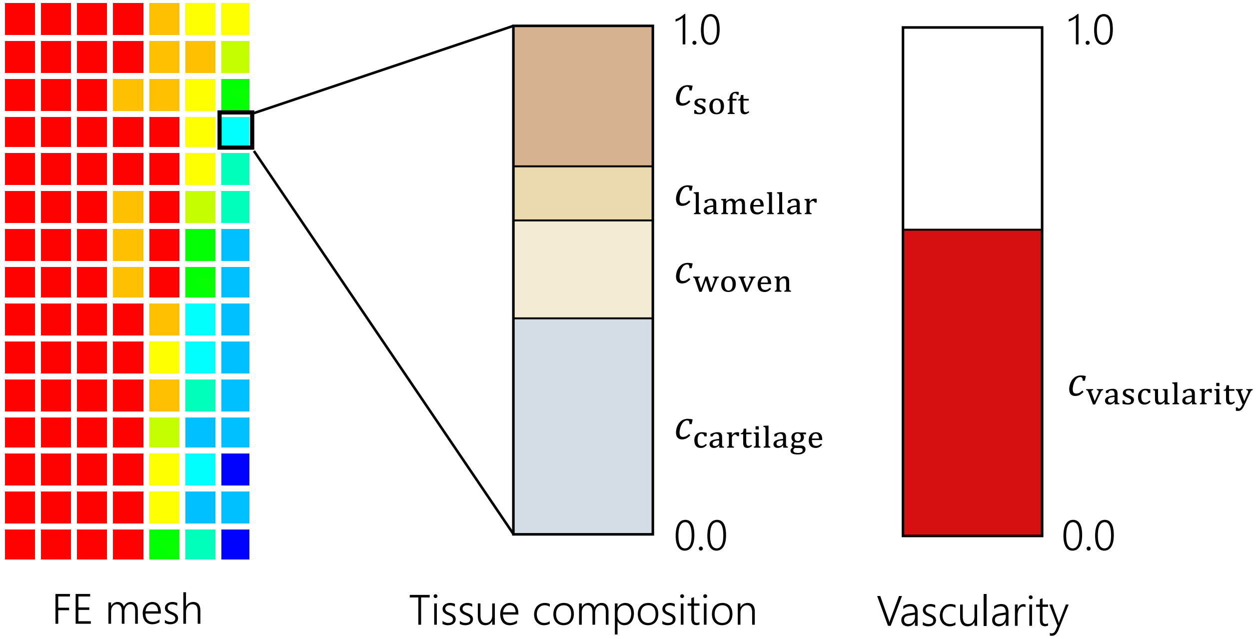
- Remodeling: Dynamics of a single “species” (typically bone density)
  → Single ODE/PDE
  → Single mechanical stimulus
  → Osteocytes as mechanosensors

- 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?)

Biological Processes



Representing Biological State



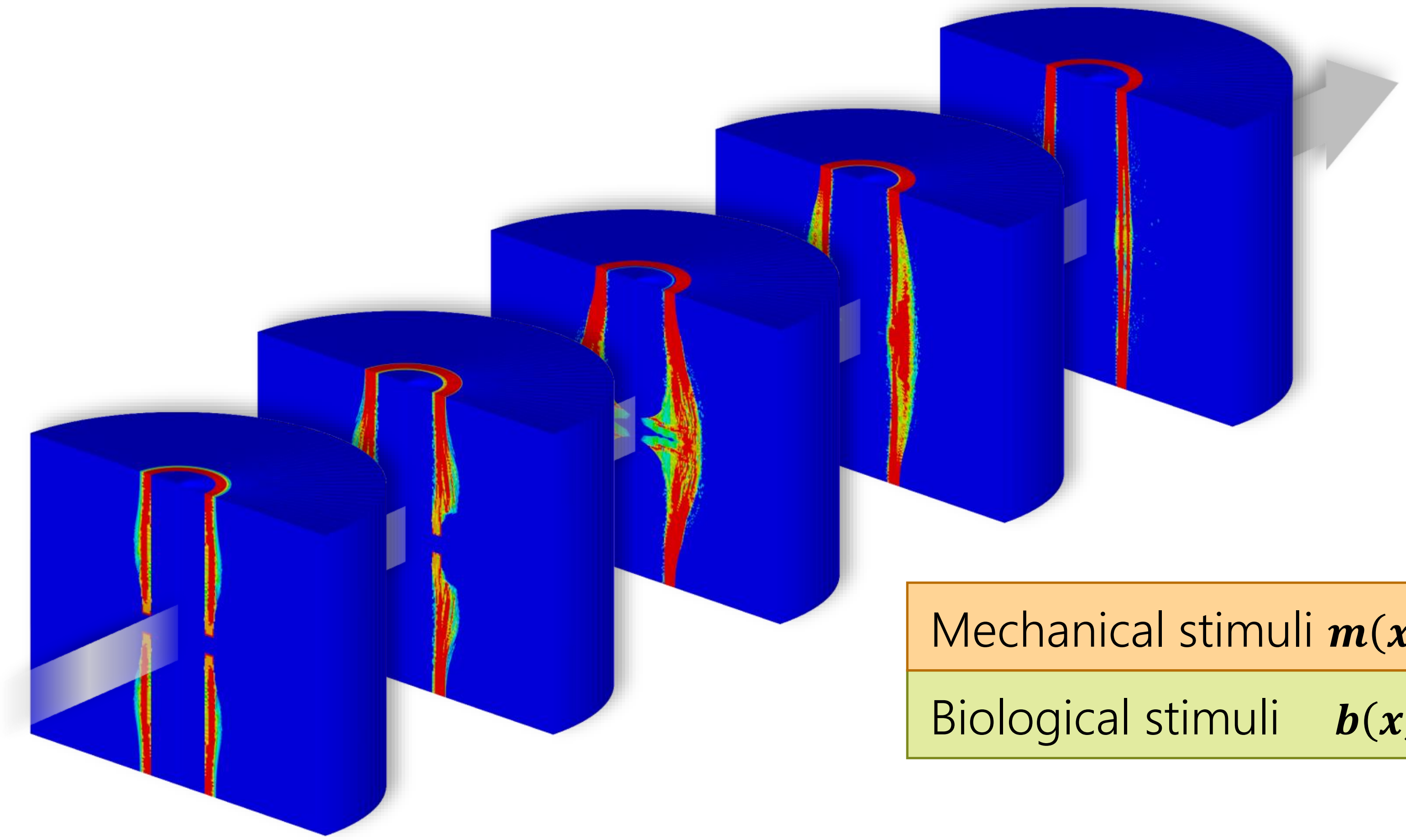
$\boldsymbol{c}\colon \Omega \times [0, +\infty) \to [0,1]^5$ with $\Omega \subset \mathbb{R}^3$

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

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

$\sum_{i \in T} c_i(\boldsymbol{x}, t) = 1.0$ with $T \coloneqq \{\text{soft}, \text{cartilage}, \text{woven}, \text{lamellar}\}$

Predicting Tissue Concentrations



$$\boldsymbol{c}(\boldsymbol{x}, t_1) = \boldsymbol{c}_0 + \int_{t_0}^{t_1} \underbrace{\partial_t \boldsymbol{c}(\boldsymbol{x}, t)}_{\text{unknown}} \, dt$$

$$\partial_t \boldsymbol{c}(\boldsymbol{x}, t) \approx \boldsymbol{f}\big(\boldsymbol{m}(\boldsymbol{x}, t), \boldsymbol{b}(\boldsymbol{x}, t)\big)$$

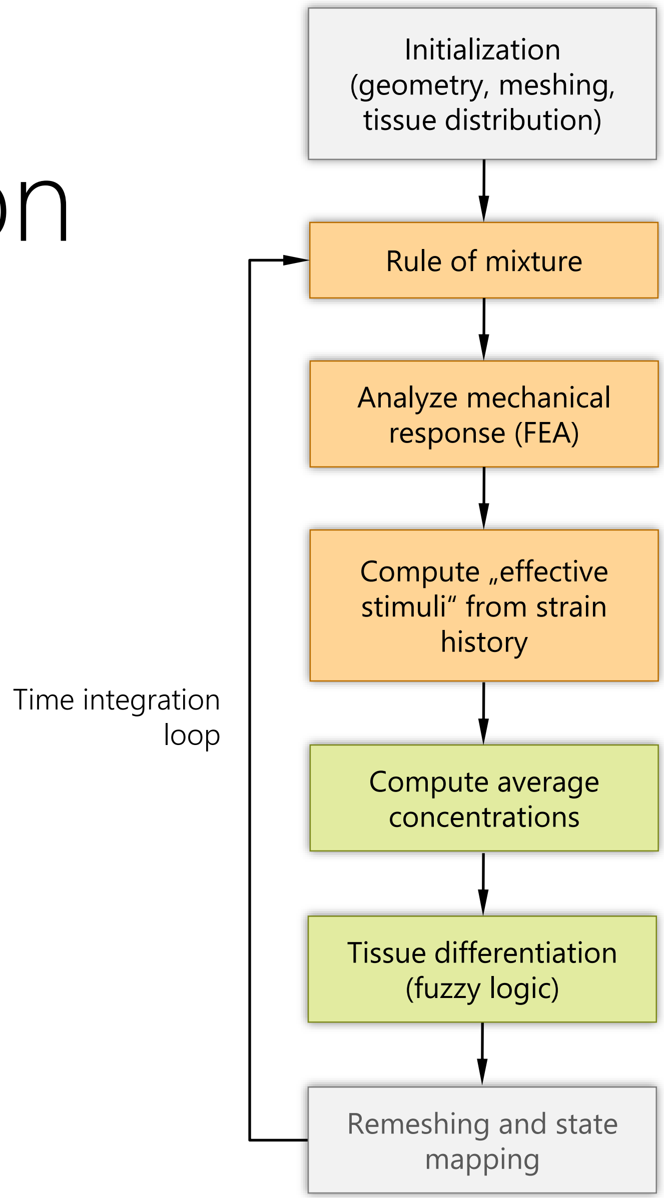
Depends on history

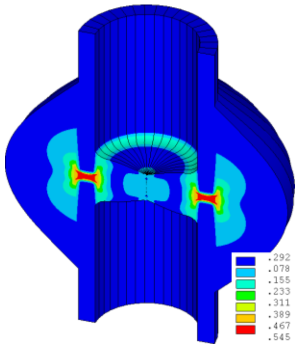
Mechanical stimuli	$\boldsymbol{m}(\boldsymbol{x}, t) = \boldsymbol{\mathcal{M}}(\boldsymbol{x}, t, \boldsymbol{c}(\cdot, t_0 \ldots t), \boldsymbol{u}_{\mathrm{BC}}, \boldsymbol{F}_{\mathrm{BC}})$
Biological stimuli	$\boldsymbol{b}(\boldsymbol{x}, t) = \boldsymbol{\mathcal{B}}(\boldsymbol{x}, t, \boldsymbol{c}(\cdot, t), \boldsymbol{c}_{\mathrm{BC}})$

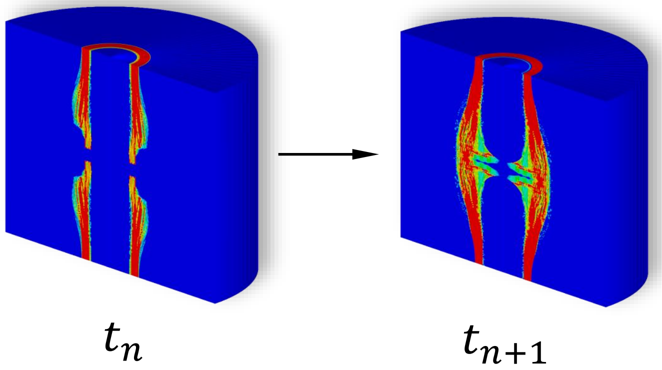
Depends on finite neighborhood of $\boldsymbol{x}$

The Ulm Bone Healing Model

Numerical Implementation







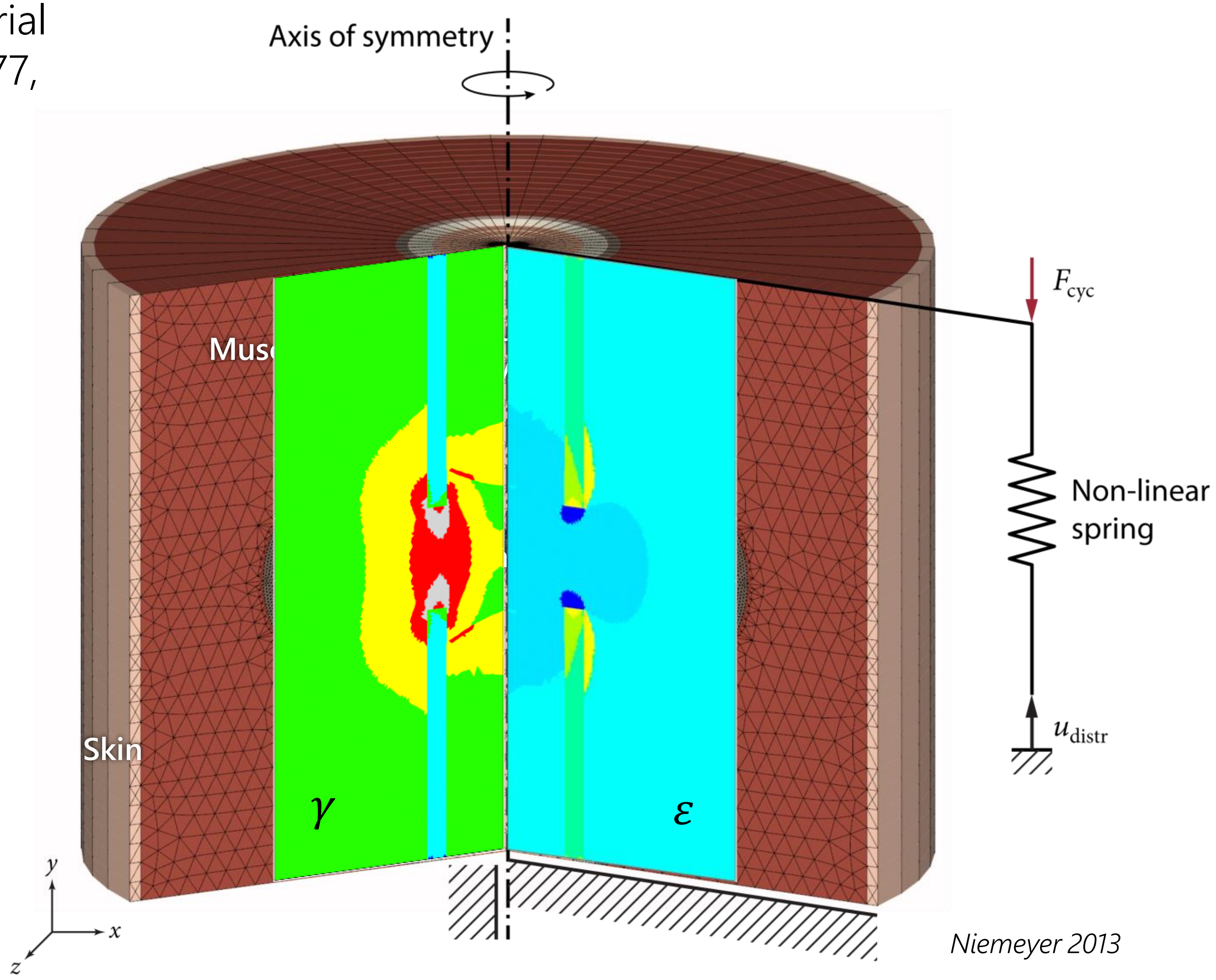
Niemeyer 2013

Rule of Mixture & Structural Analysis (FEA)

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

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

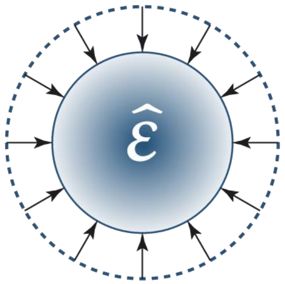
$$\nu(\boldsymbol{x},t) = \sum_{i \in T} \nu_i c_i(\boldsymbol{x},t)$$



Niemeyer 2013

Mechanical Stimuli

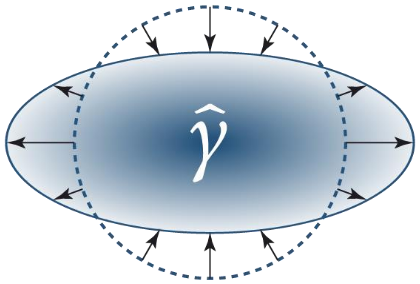
Dilatational strain



Pure volume change

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

Distortional strain



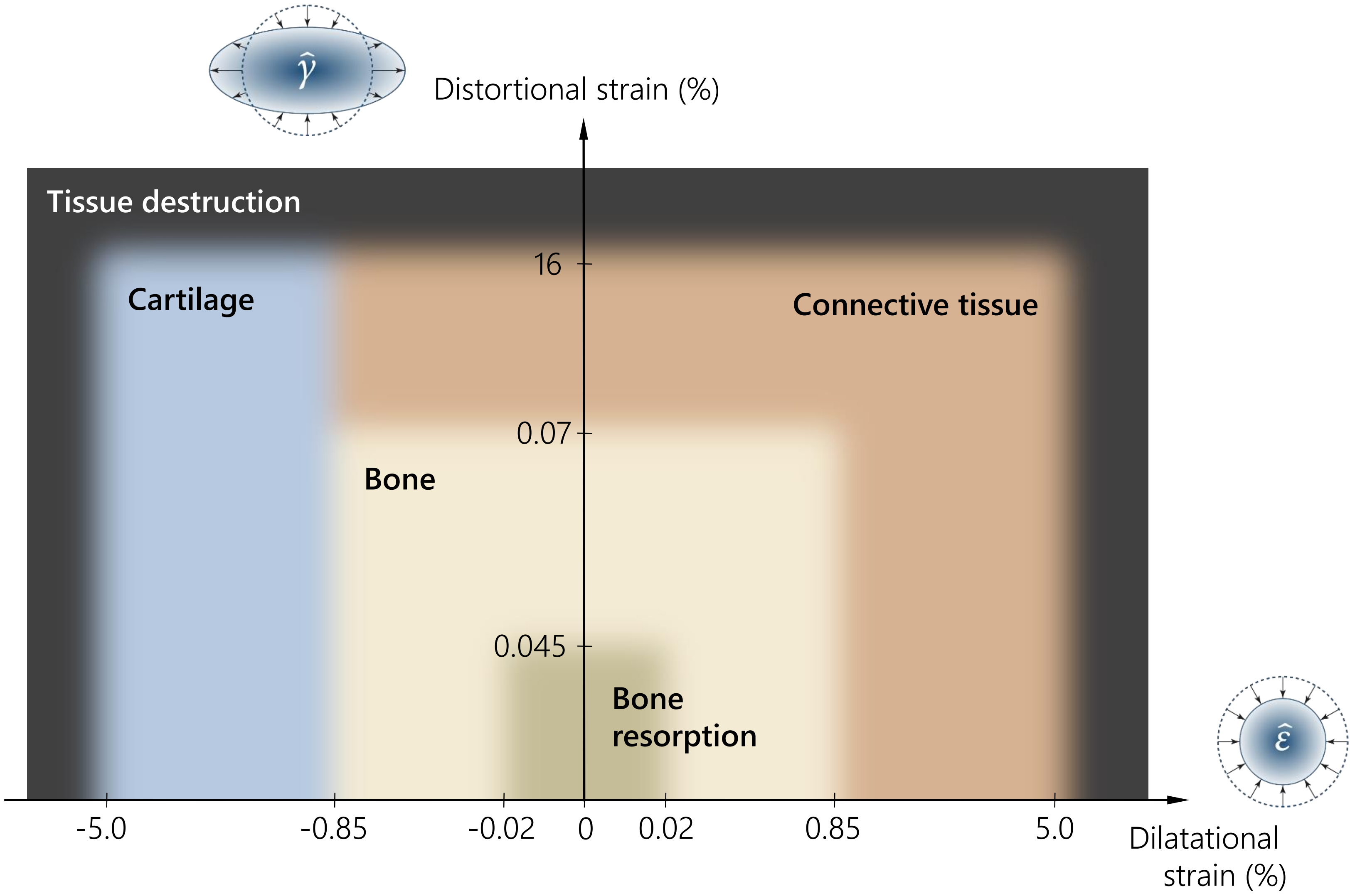
Pure shape change

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

where $\boldsymbol{\varepsilon} = \begin{bmatrix} \varepsilon_1 & 0 & 0 \\ 0 & \varepsilon_2 & 0 \\ 0 & 0 & \varepsilon_3 \end{bmatrix} \in \mathbb{R}^3 \to \mathbb{R}^{3\times3}$

Simon et al. 2002, 2010, Shefelbine et al. 2005

Mechano-regulated Tissue Differentiation



Simon et al. 2002, 2010, Shefelbine et al. 2005, Niemeyer 2013

Effective Mechanical Stimuli

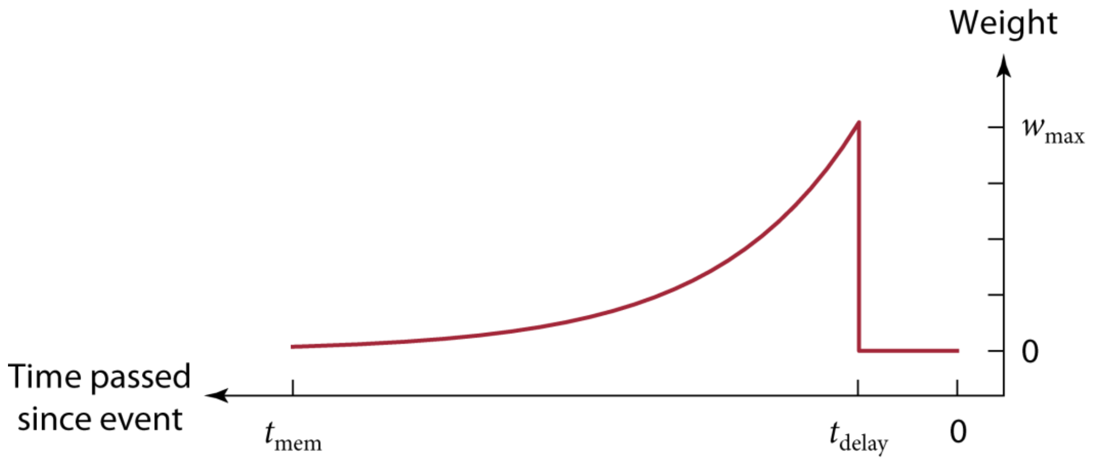
$$w(t) = \begin{cases} \exp\left(-\lambda(t - t_{\text{delay}})\right) & \text{if } t_{\text{delay}} < t \leq t_{\text{mem}} \\ 0 & \text{otherwise} \end{cases}$$

$$\widetilde{w}(t) = \frac{w(t)}{\int_{-\infty}^{+\infty} w(\tau)\, d\tau}$$

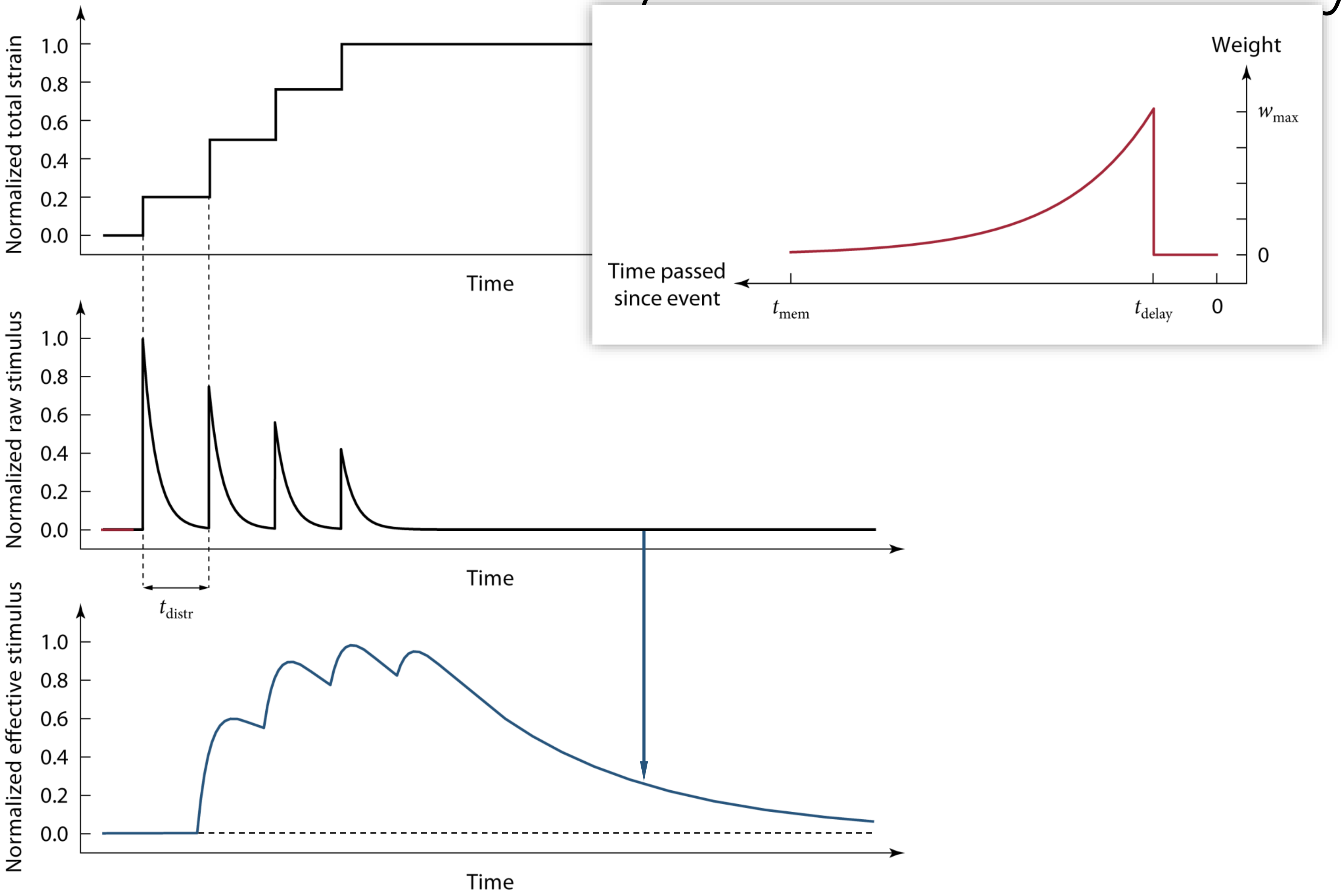
$$\varepsilon_{\text{eff}} = \varepsilon * \widetilde{w}$$

$$\gamma_{\text{eff}} = \gamma * \widetilde{w}$$

$$\boldsymbol{m} = [\varepsilon, \gamma, \varepsilon_{\text{eff}}, \gamma_{\text{eff}}]$$

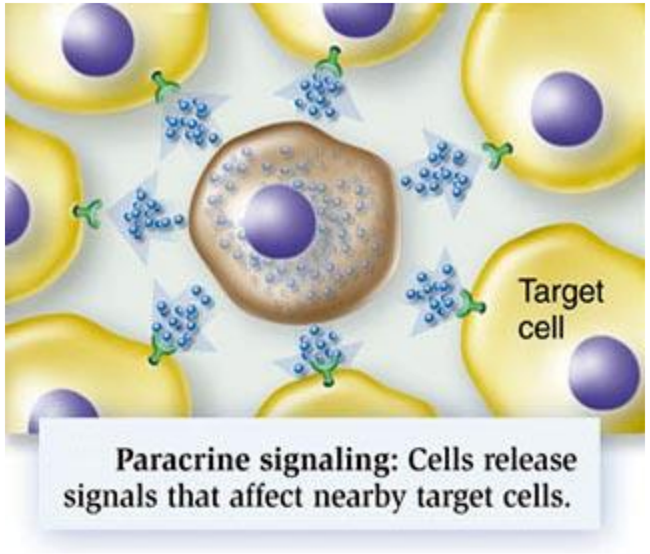


Calcification Delay & Stimuli Memory

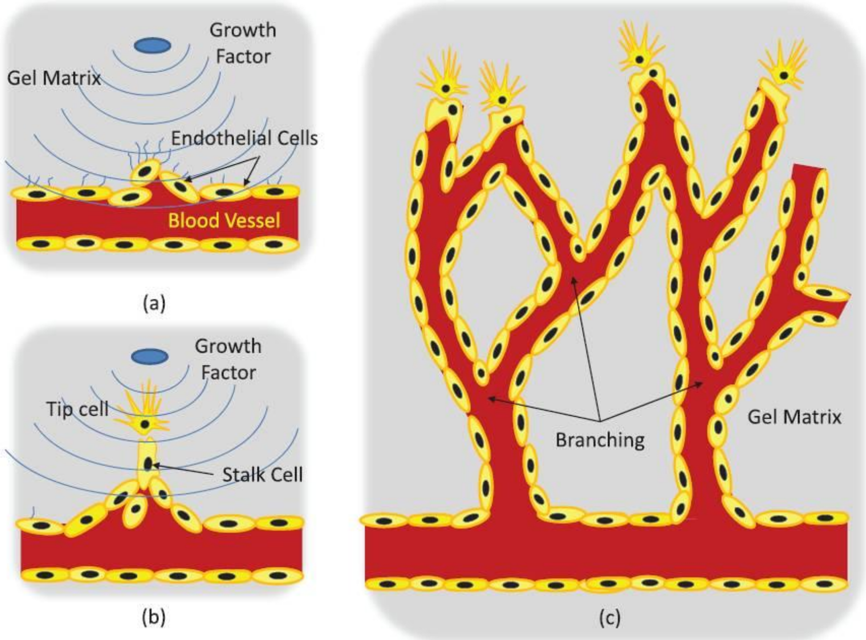


Biological Stimuli

$$\boldsymbol{b} = [c_{\text{woven}}, c_{\text{lamellar}}, c_{\text{cartilage}}, c_{\text{soft}}, c_{\text{vascularity}}, \underbrace{s_{\text{b}}, s_{\text{v}}}_{\text{Non-local influence}}]$$

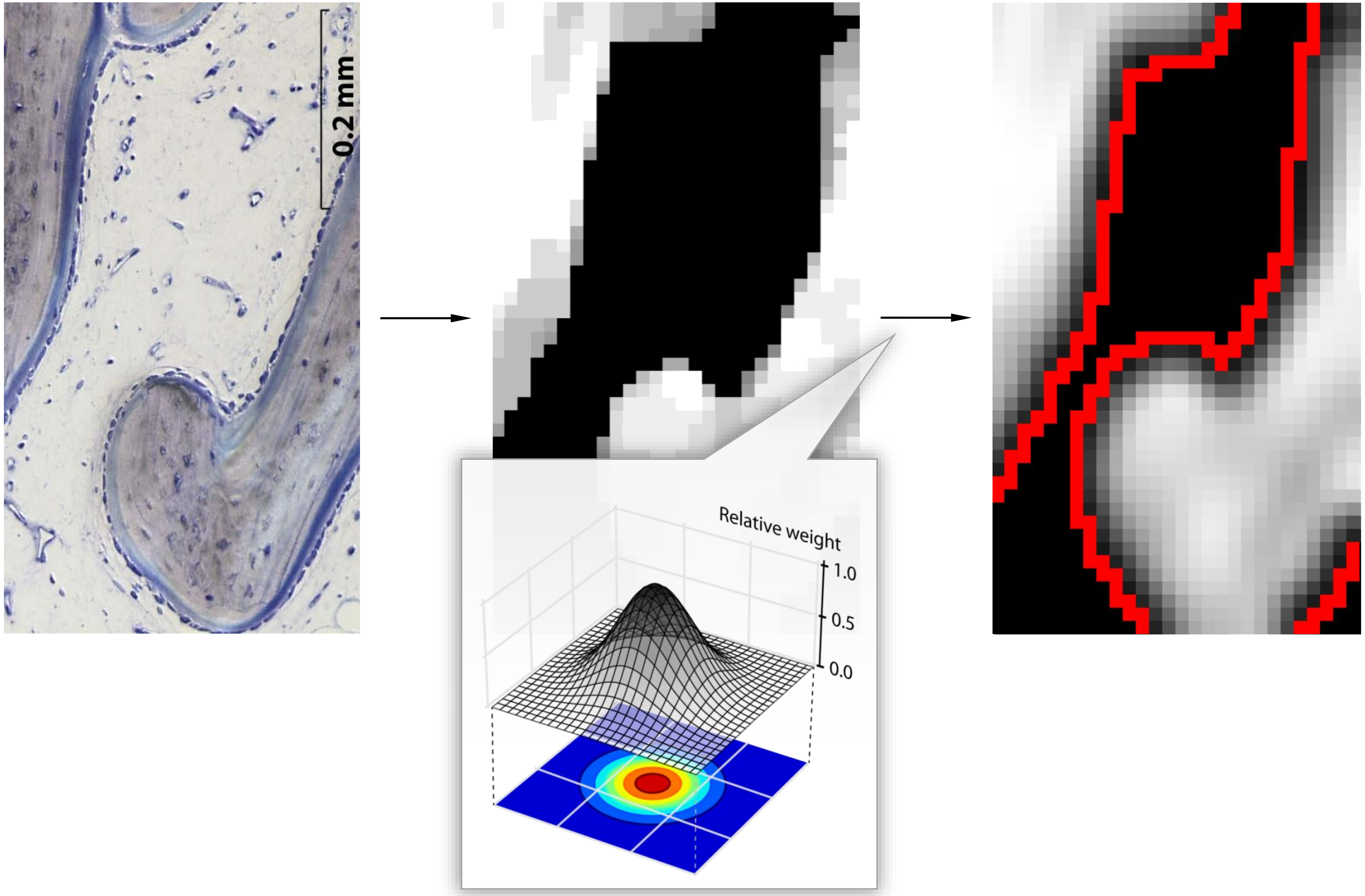


http://www.snipview.com/q/Paracrine_signaling



http://web.mit.edu/smart/research/biosym/BioSym-Sub-projects-Thrust%203.html

Appositional Growth



Biological Stimuli

$$\boldsymbol{b} = [c_{\text{woven}}, c_{\text{lamellar}}, c_{\text{cartilage}}, c_{\text{soft}}, c_{\text{vascularity}}, \underbrace{s_{\text{b}}, s_{\text{v}}}_{\text{Non-local influence}}]$$

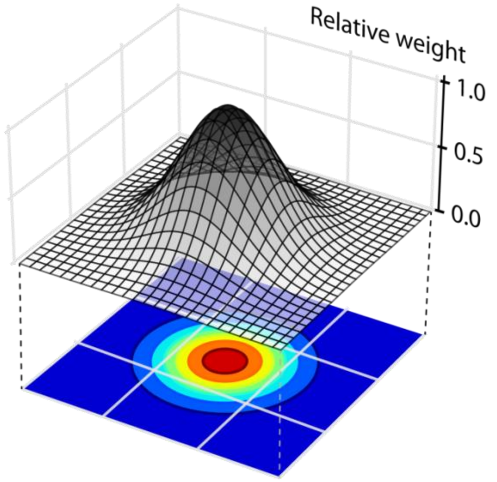
$$s_{\text{b}}(\boldsymbol{x}, t) = (c_{\text{bone}}(\cdot, t) * G_\sigma)(\boldsymbol{x})$$

$$\stackrel{\text{in 2D}}{=} \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} c_{\text{bone}}(\xi, \upsilon; t)\, G_\sigma(x - \xi, y - \upsilon)\, d\xi\, d\upsilon$$

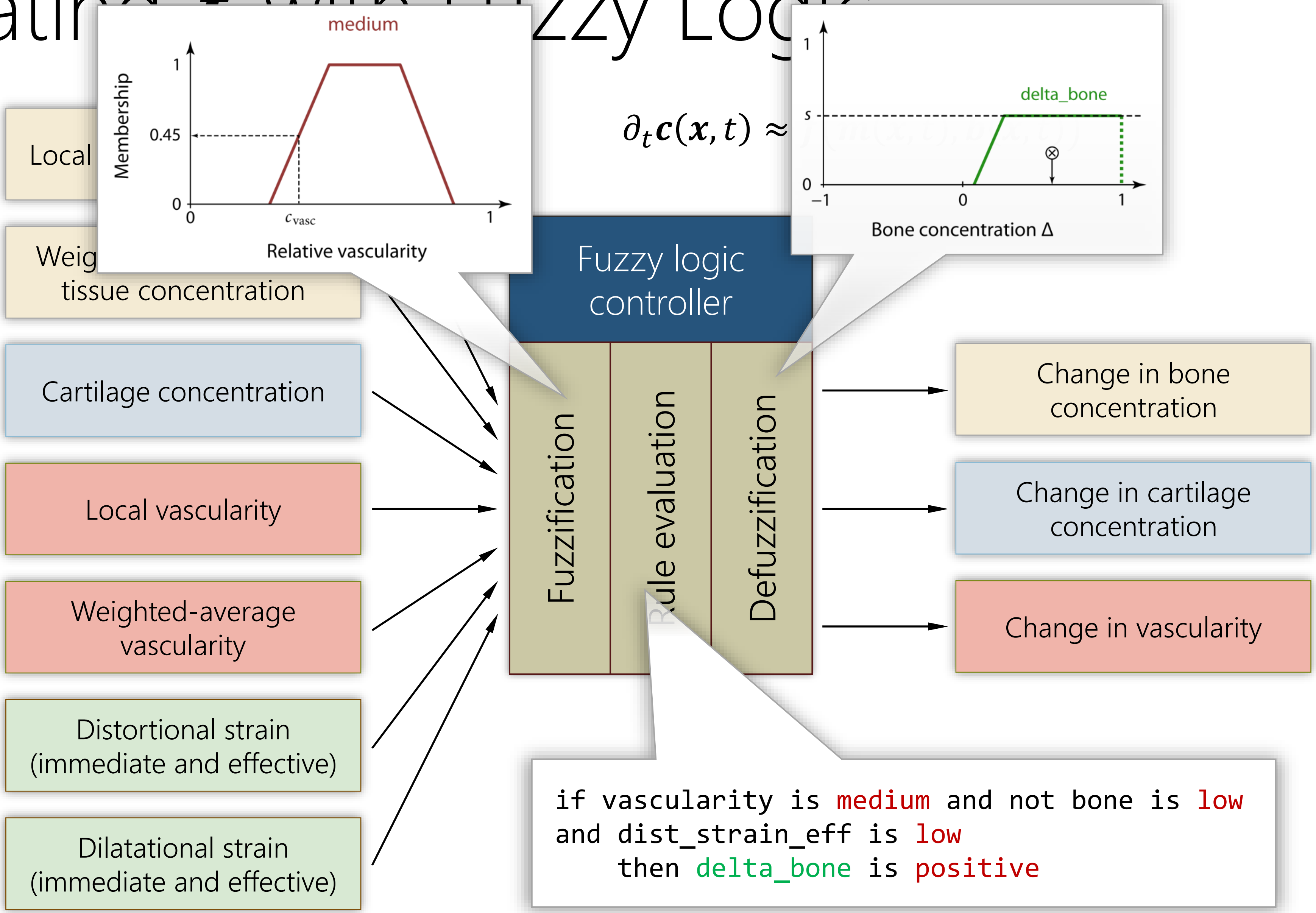
$$s_{\text{v}}(\boldsymbol{x}, t) = (c_{\text{vasc}}(\cdot, t) * G_\sigma)(\boldsymbol{x})$$

e.g. in two spatial dimensions

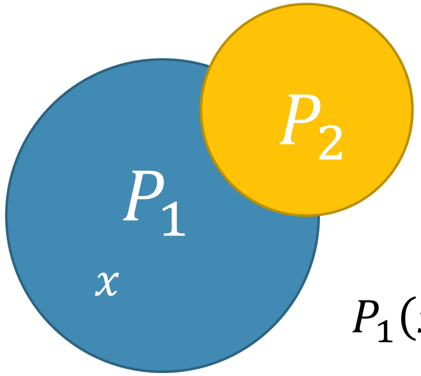
$$G_\sigma(x, y) \propto \frac{1}{2\pi\sigma^2} \exp \frac{-x^2 - y^2}{2\sigma^2}$$



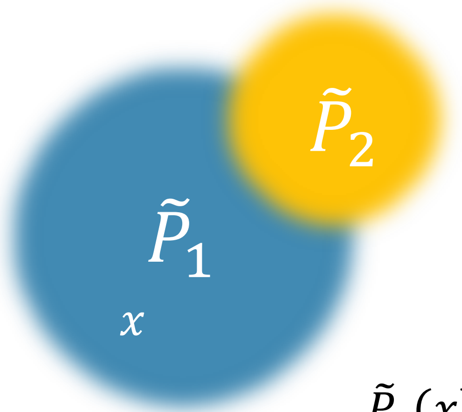
Evaluating f with Fuzzy Logic



Fuzzy Logic & Fuzzy Inference (Mamdani)



$P_1(x) \in \{\text{true}, \text{false}\}$

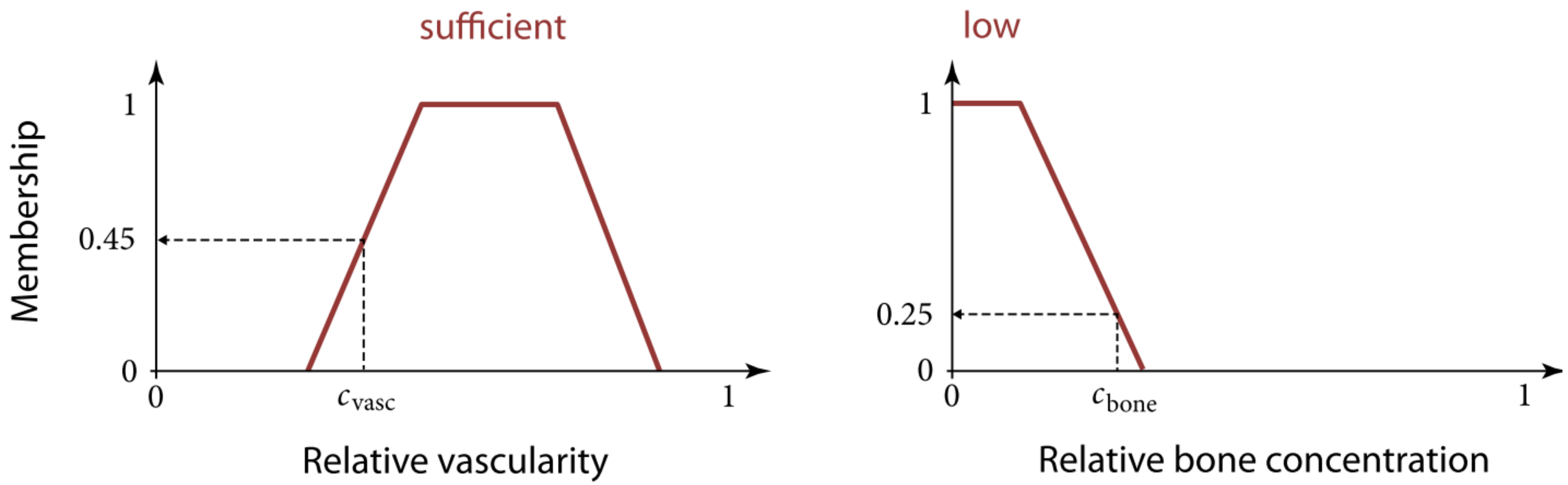


$\tilde{P}_1(x) = \mu_1(x) \in [0, 1]$

Fuzzification (fuzzy proposition)	$x \text{ is } \mu_A \coloneqq \mu_A(x) = A \in [0, 1]$
Logical and	$A \wedge B \coloneqq \min(A, B)$
Logical or	$A \vee B \coloneqq \max(A, B)$
Logical not	$\neg A \coloneqq 1 - A$
Logical implication	$A \rightarrow B \coloneqq \mu_{C_i} : y \mapsto A \wedge \mu_B(y)$
„Or" aggregation	$\mu_C : x \mapsto \max\left\{\mu_{C_0}(x), \dots, \mu_{C_n}(x)\right\}$
Defuzzification	$y_C \coloneqq \text{CoA}(\mu_C) = \dfrac{\int x\mu_C(x)\, dx}{\int \mu_C(x)\ dx}$

Example (1/3): Fuzzification & Premise Eval.

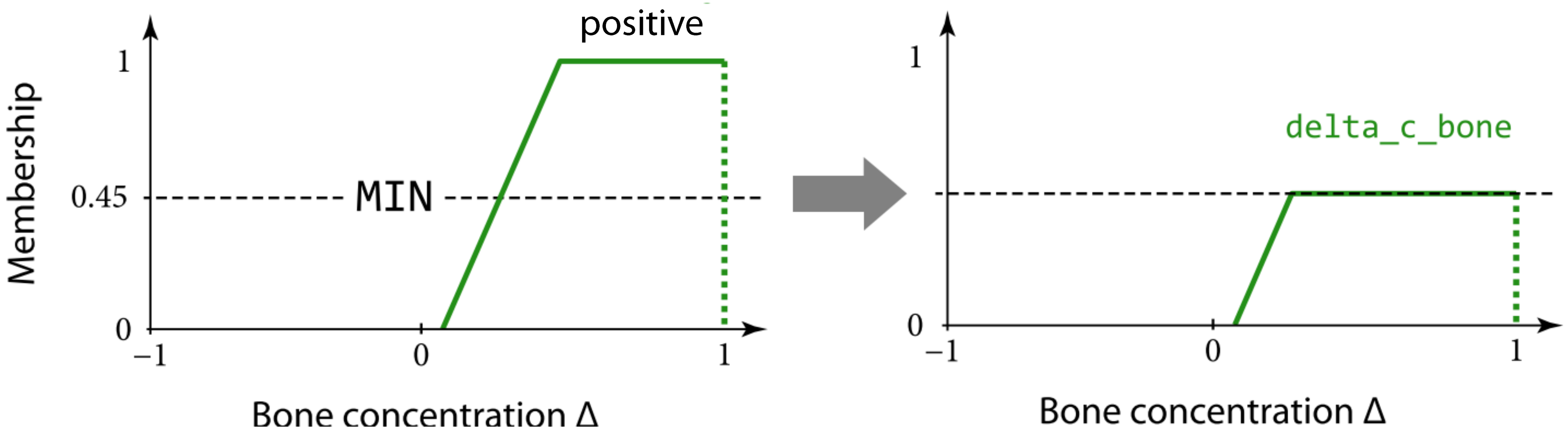
```
if c_vasc is sufficient and not c_bone is low
    then delta_c_bone is positive
```



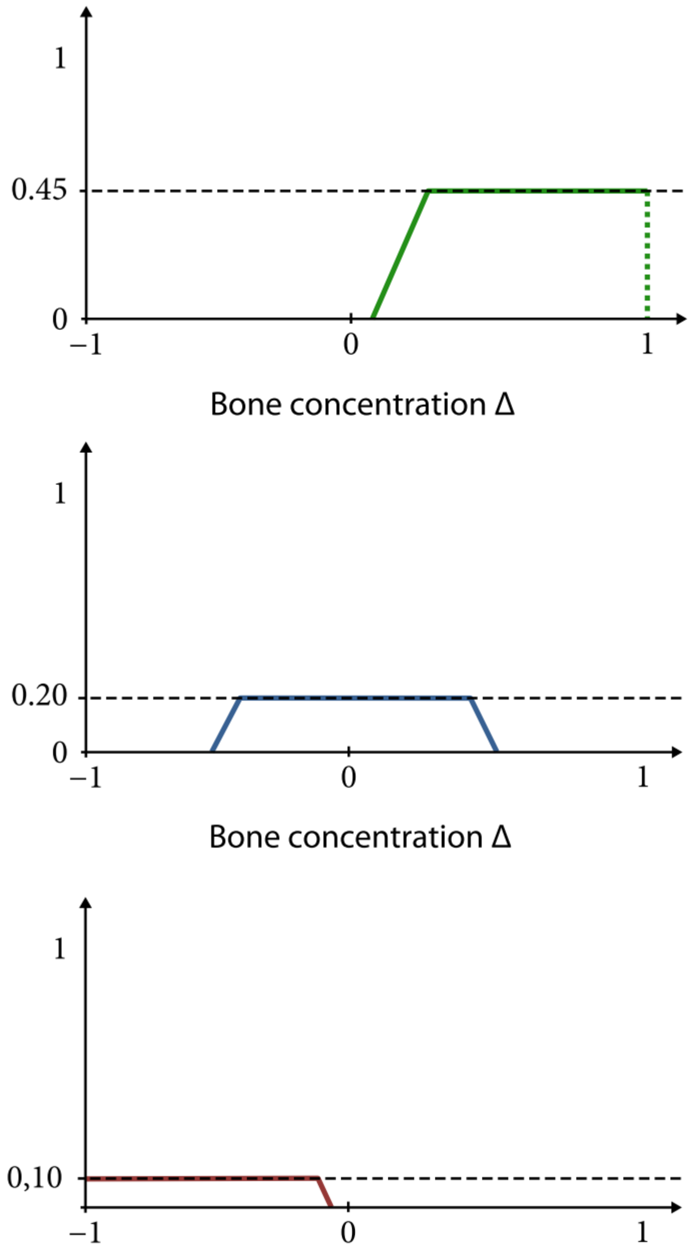

```
c_vasc is sufficient and not c_bone is low

       = 0.45         and not      0.25
       = 0.45         and      1 - 0.25
       = min(0.45, 0.75)
       = 0.45
```

Example (2/3): Implication

```
c_vasc is sufficient and not c_bone is low

          = 0.45          and not       0.25
          = 0.45          and       1 - 0.25
          = min(0.45, 0.75)
          = 0.45

if 0.45
    then delta_c_bone is positive
```



Example (3/3)


1
0.45
0
−1
0
1
Bone concentration Δ
1
0.20
0
−1
0
1
Bone concentration Δ
1
0,10
−1
0
1

Time Integration

Initial value problem

$$\boldsymbol{c}(\boldsymbol{x}, t_1) = \boldsymbol{c}_0 + \int_{t_0}^{t_1} \partial_t \boldsymbol{c}(\boldsymbol{x}, t)\, dt$$

Boundary value problem
(depends on structural FEA)

$$\partial_t \boldsymbol{c}(\boldsymbol{x}, t) \approx \boldsymbol{f}\big(\boldsymbol{m}(\boldsymbol{x}, t), \boldsymbol{b}(\boldsymbol{x}, t)\big) = \Delta \boldsymbol{c}$$

Forward Euler:

$$\boldsymbol{c}(\boldsymbol{x}, t + \Delta t) \approx \boldsymbol{c}(\boldsymbol{x}, t) + \Delta t \Delta \boldsymbol{c}$$

Heun's method (explicit trapezoidal):

$$\tilde{\boldsymbol{c}}(\boldsymbol{x}, t + \Delta t) = \boldsymbol{c}(\boldsymbol{x}, t) + \Delta t \Delta \boldsymbol{c}$$

$$\widetilde{\boldsymbol{m}}(\boldsymbol{x}, t + \Delta t) = \boldsymbol{\mathcal{M}}(\boldsymbol{x}, t + \Delta t, \tilde{\boldsymbol{c}}, \boldsymbol{u}_{\mathrm{BC}}, \boldsymbol{F}_{\mathrm{BC}})$$

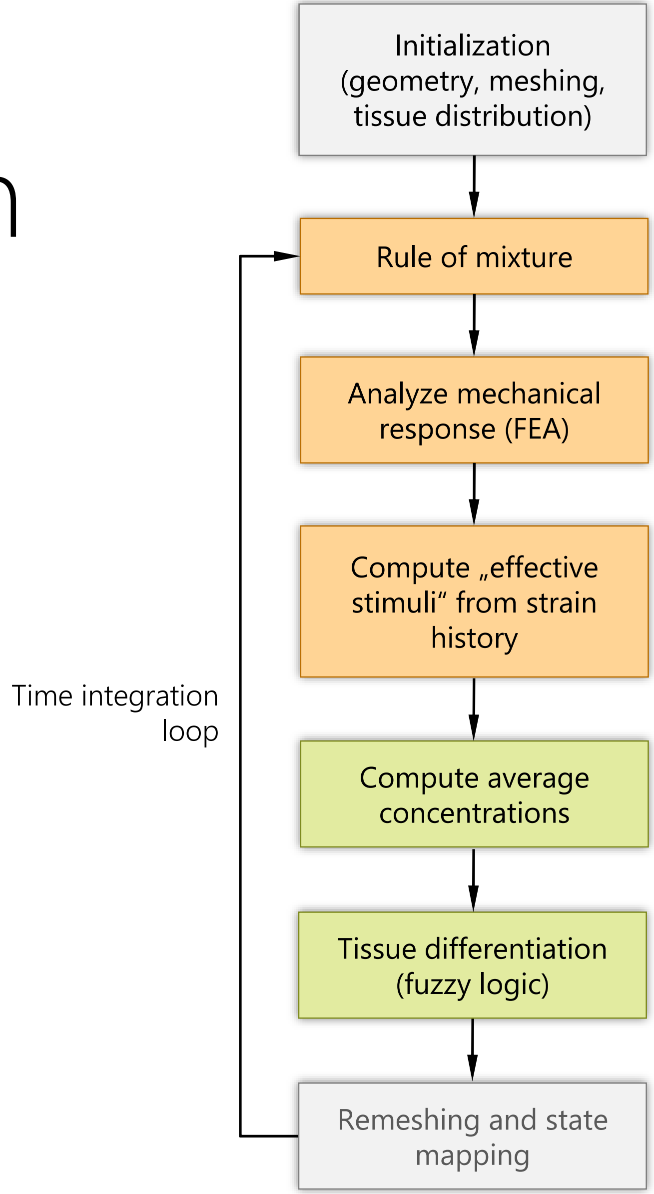
$$\widetilde{\boldsymbol{b}}(\boldsymbol{x}, t + \Delta t) = \boldsymbol{\mathcal{B}}(\boldsymbol{x}, t + \Delta t, \tilde{\boldsymbol{c}}, \boldsymbol{c}_{\mathrm{BC}})$$

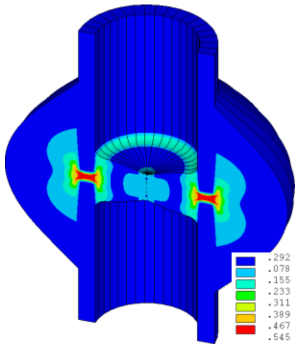
$$\Delta \tilde{\boldsymbol{c}} = \boldsymbol{f}\big(\widetilde{\boldsymbol{m}}, \widetilde{\boldsymbol{b}}\big)$$

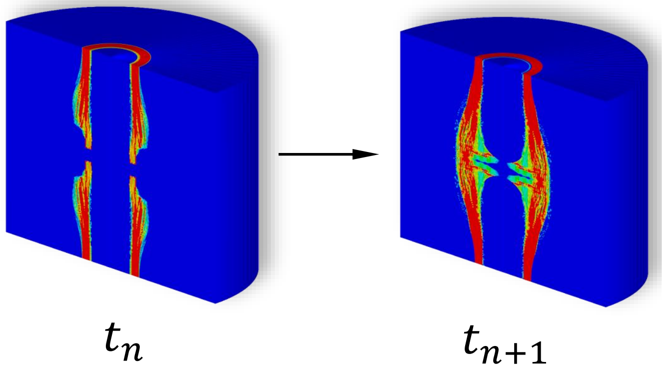
$$\boldsymbol{c}(\boldsymbol{x}, t + \Delta t) \approx \boldsymbol{c}(\boldsymbol{x}, t) + \frac{1}{2} \Delta t (\Delta \boldsymbol{c} + \Delta \tilde{\boldsymbol{c}})$$

Needs to keep track of mechanical stimuli history (or even multiple histories for predictor-corrector schemes)

Numerical Implementation

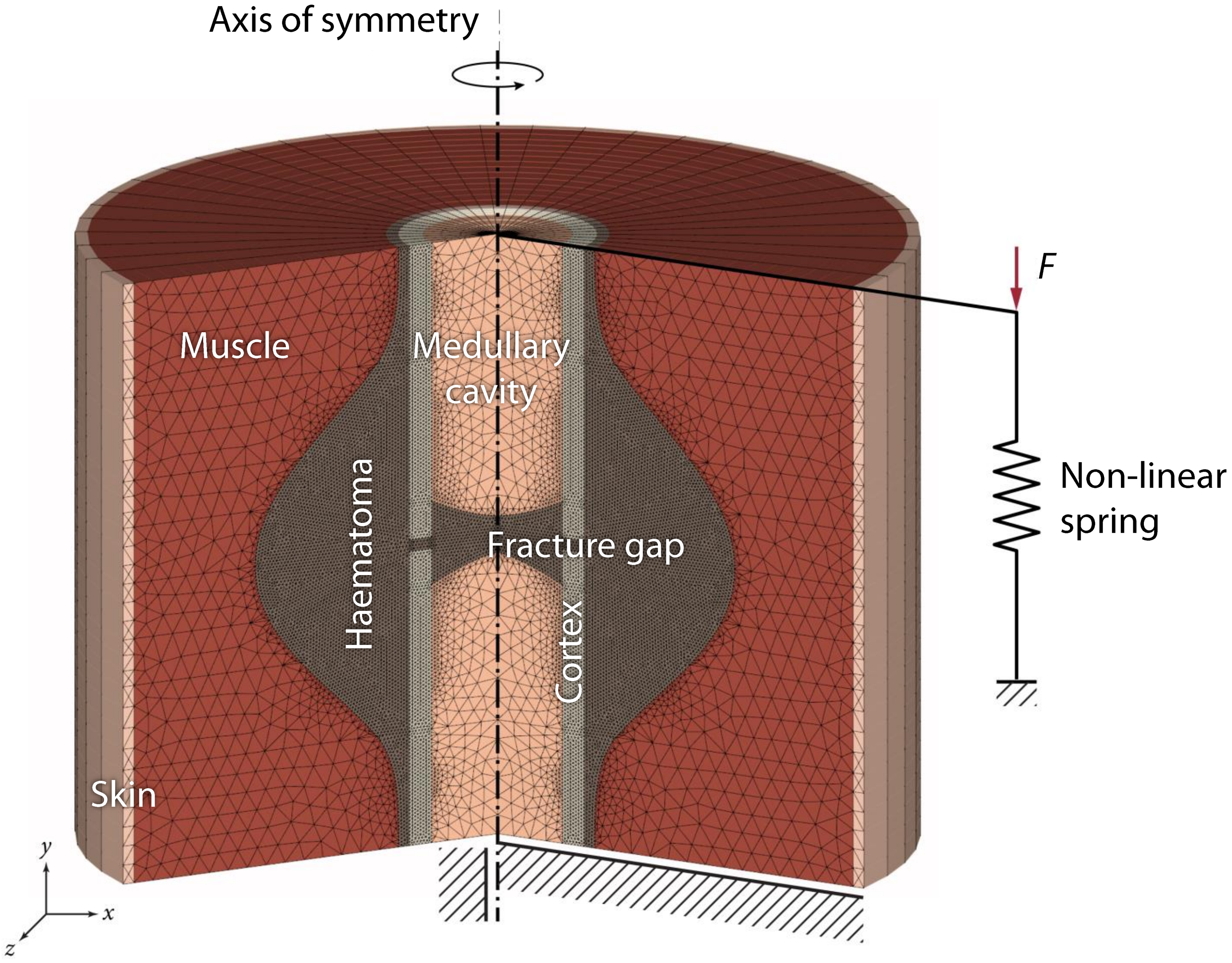






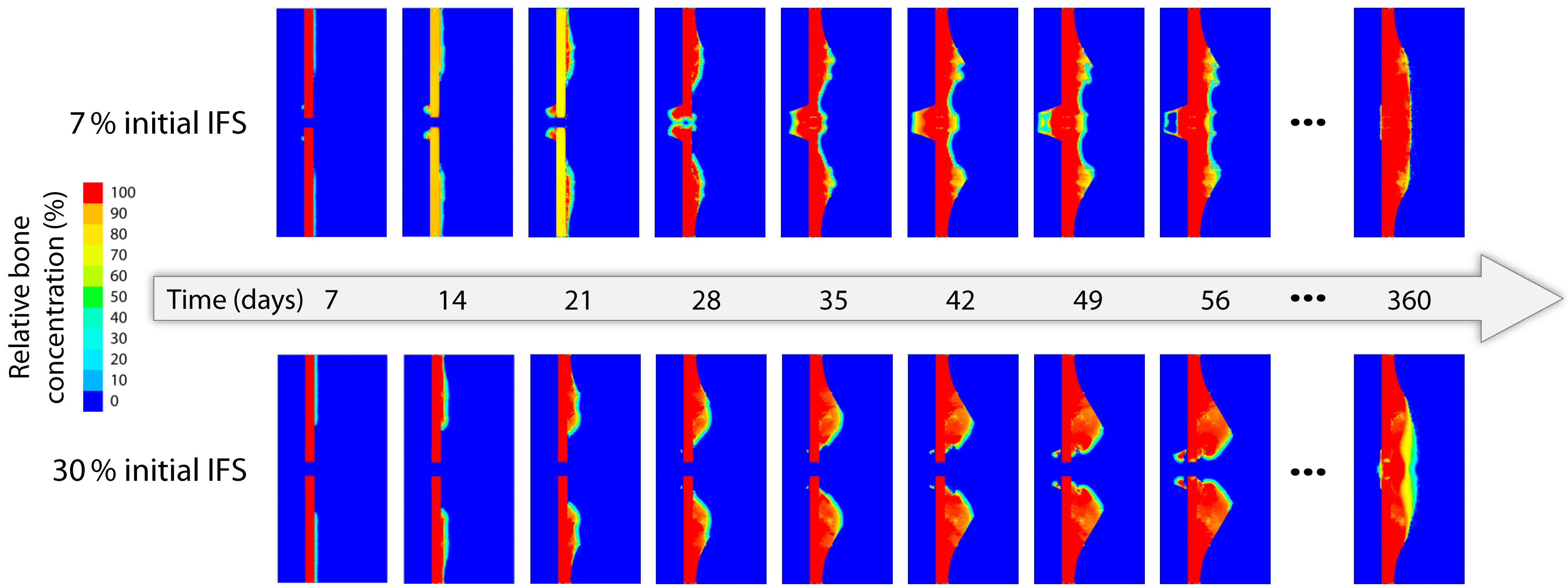
Niemeyer 2013

Callus Healing (Sheep, External Fixator)



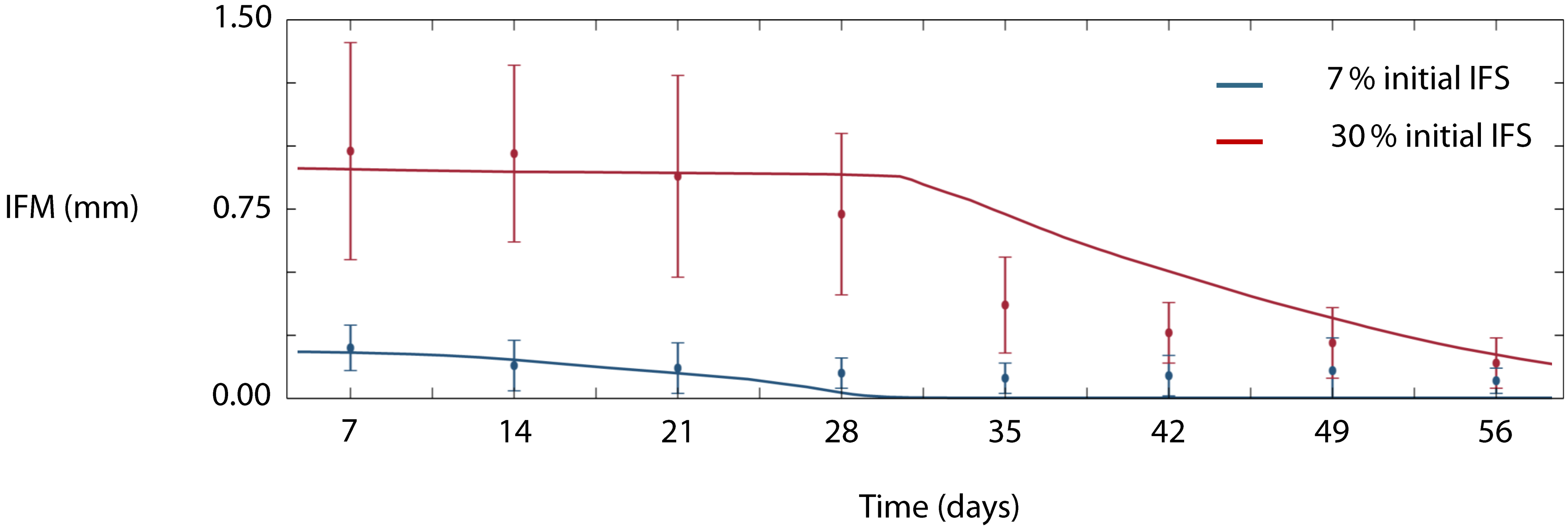
Simon & Niemeyer, 2015

Simulation Results



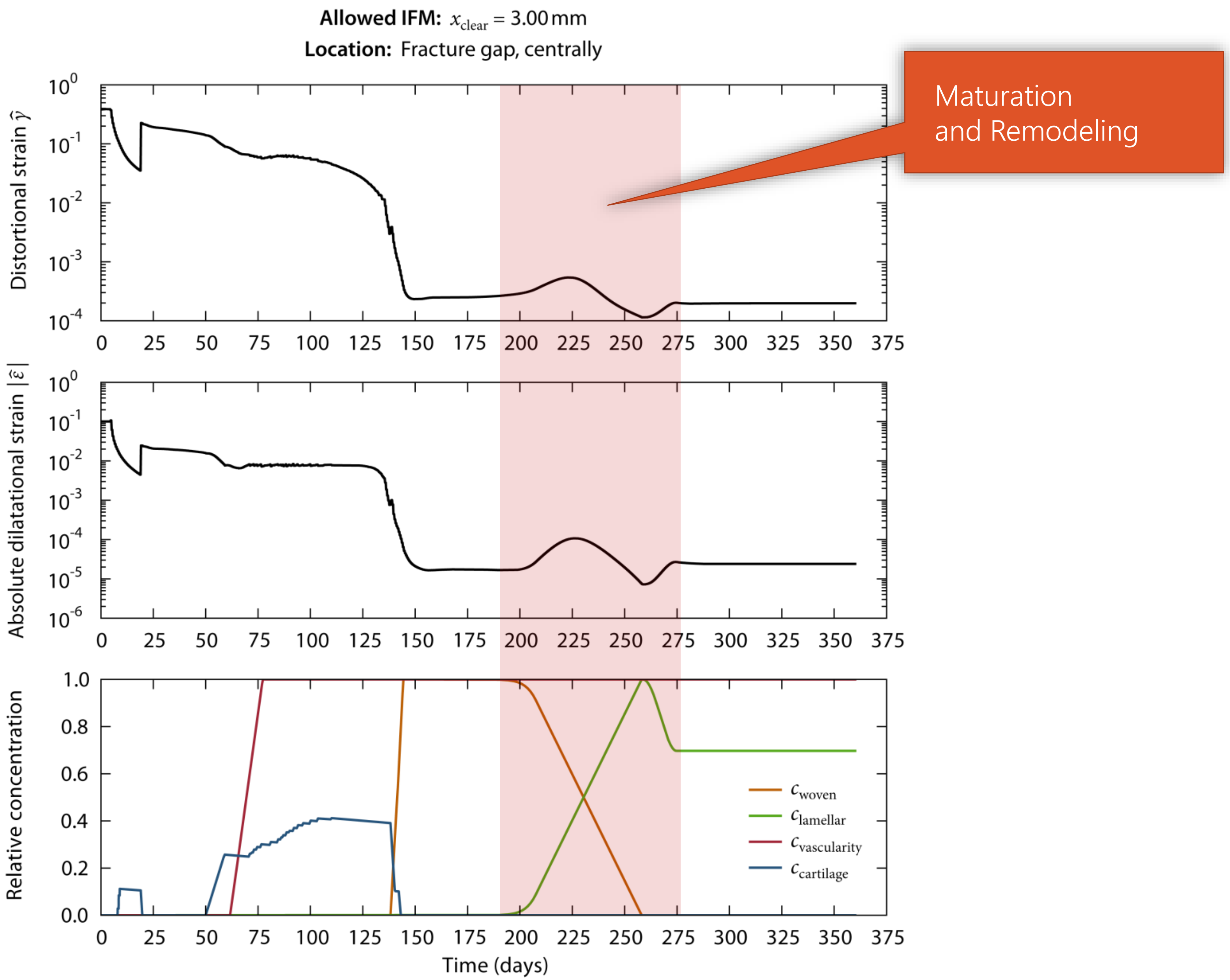
Simon & Niemeyer, 2015

Simulation Results



Simon & Niemeyer, 2015

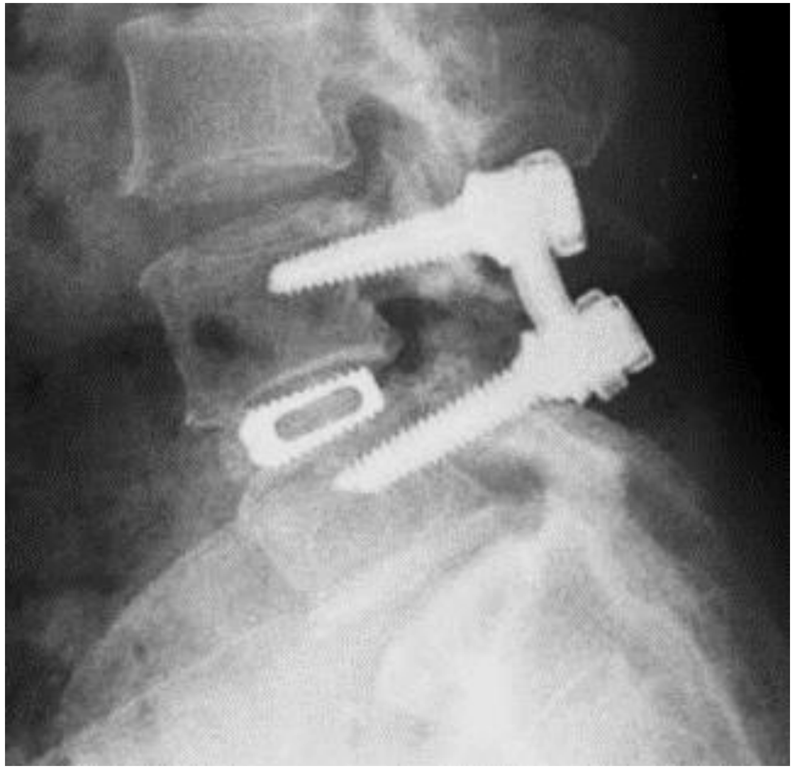
Remodeling



Allowed IFM: x_{clear} = 3.00 mm
Location: Fracture gap, centrally
Maturation and Remodeling
Distortional strain $\hat{\gamma}$
Absolute dilatational strain $|\hat{\varepsilon}|$
Relative concentration
Time (days)
c_{woven}
$c_{lamellar}$
$c_{vascularity}$
$c_{cartilage}$

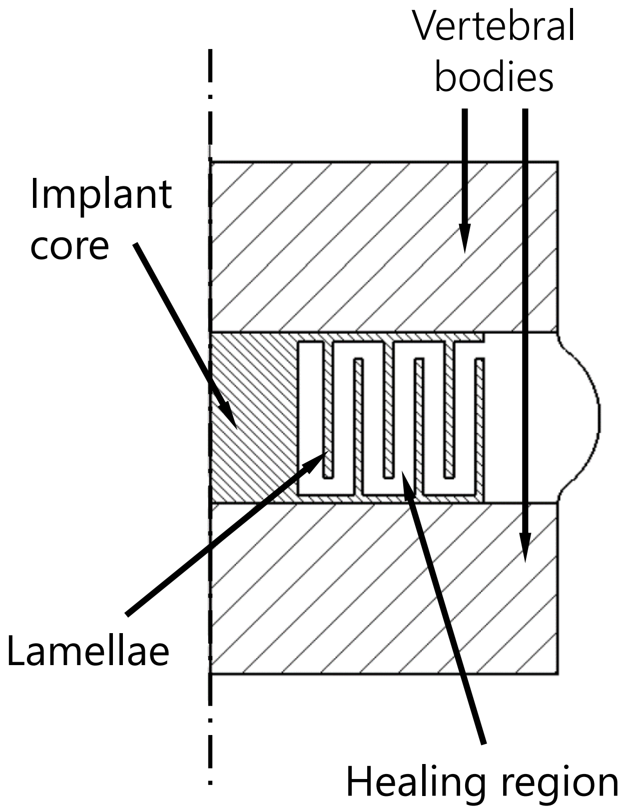
Spinal Fusion

Conventional

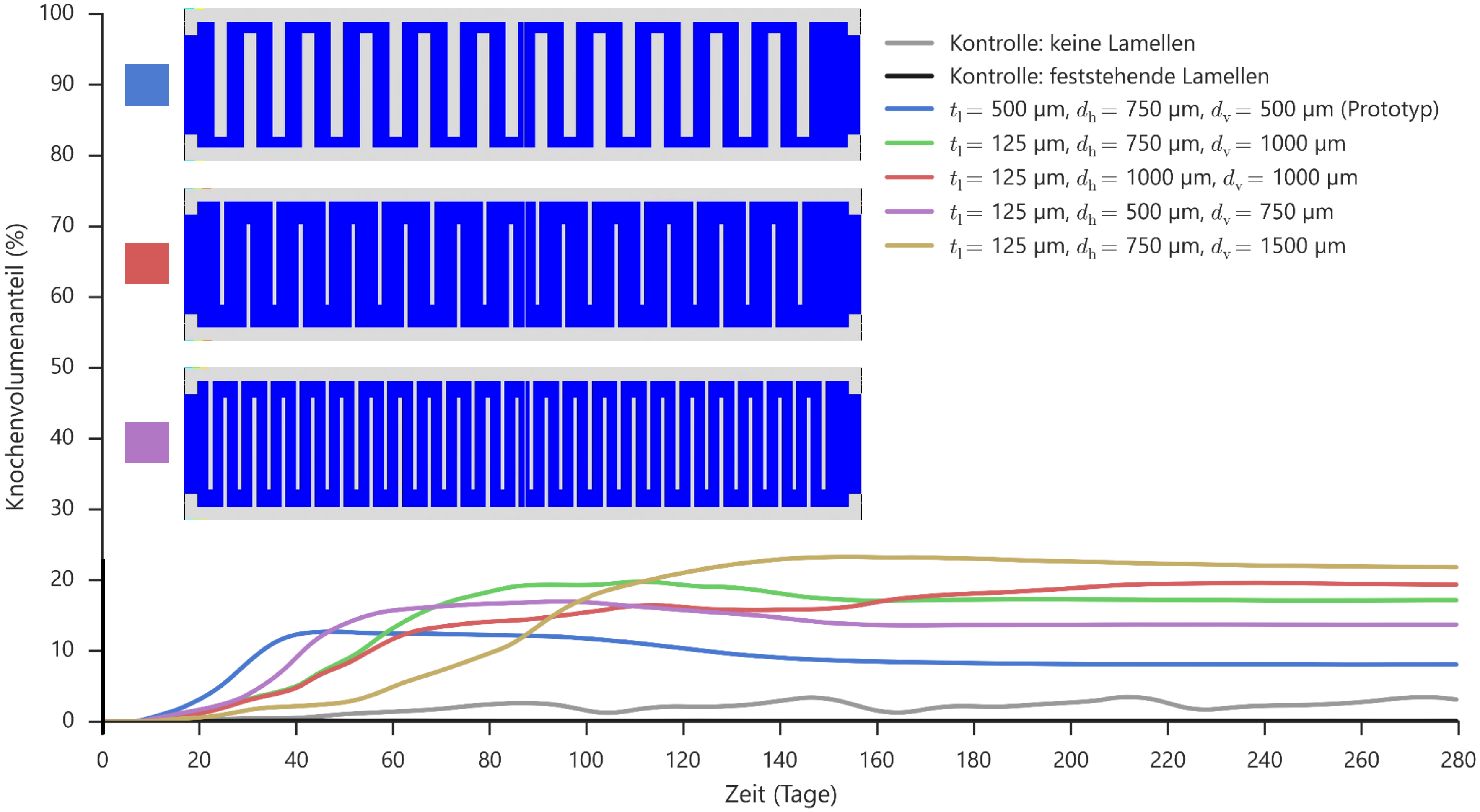


Kim et al., 2009

„Amplifix"

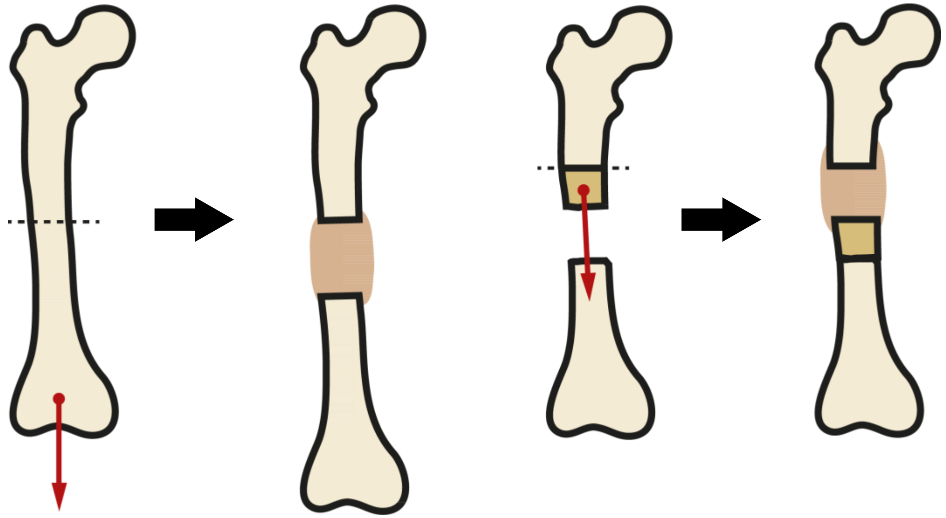


Simulation Results

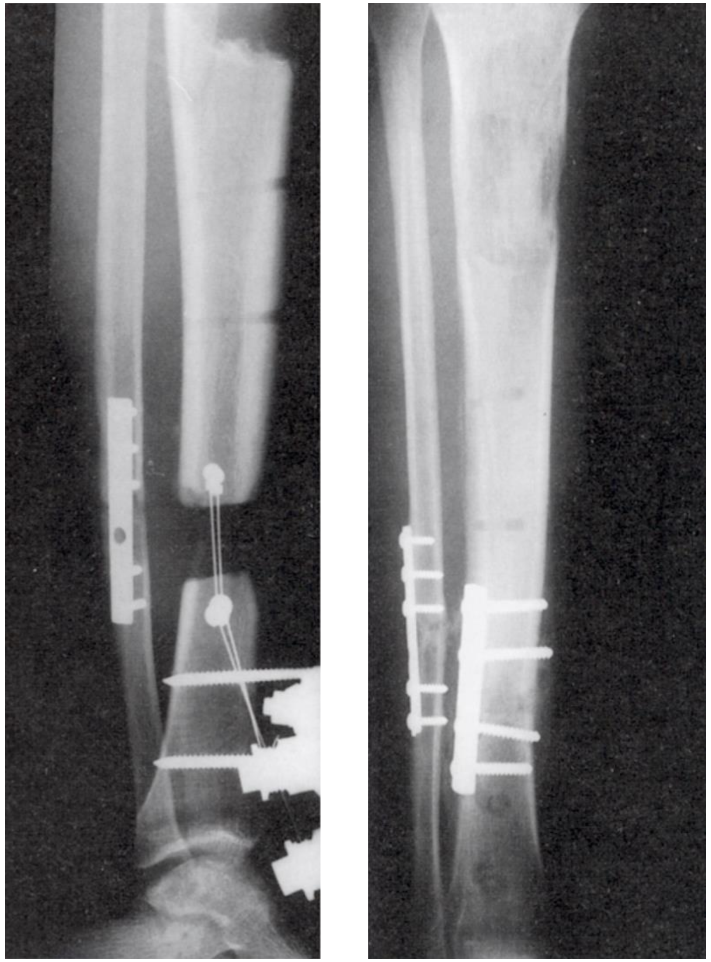


Niemeyer et al. 2015

Distraction Osteogenesis

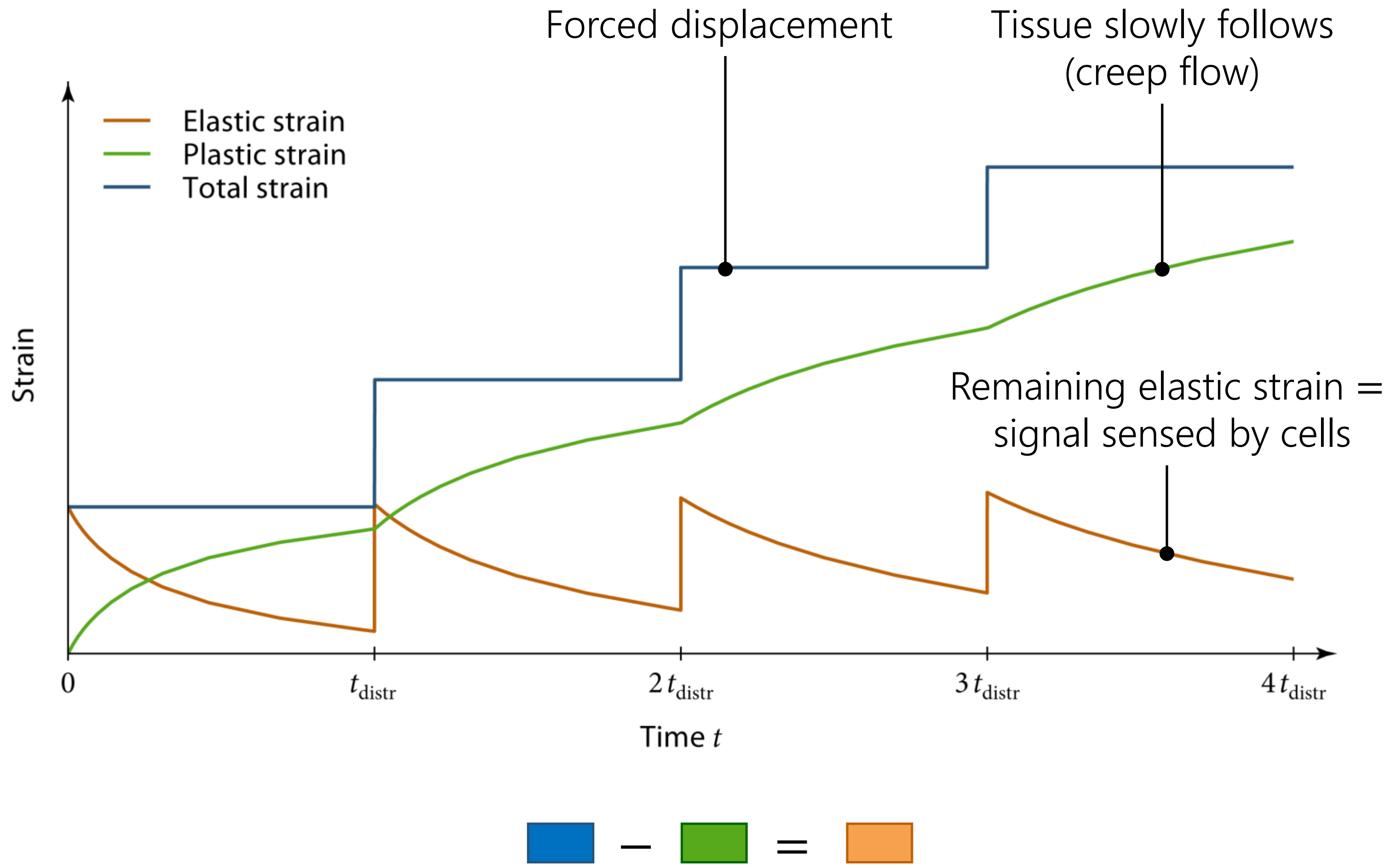


Callus distraction Segment transport



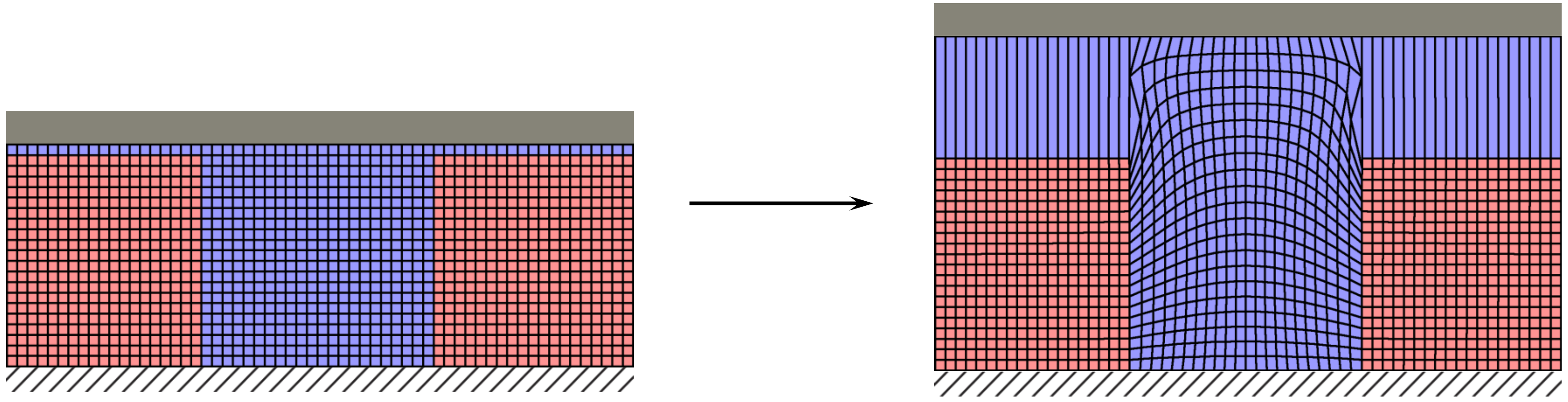
(from Rüter & Brutscher 1989)

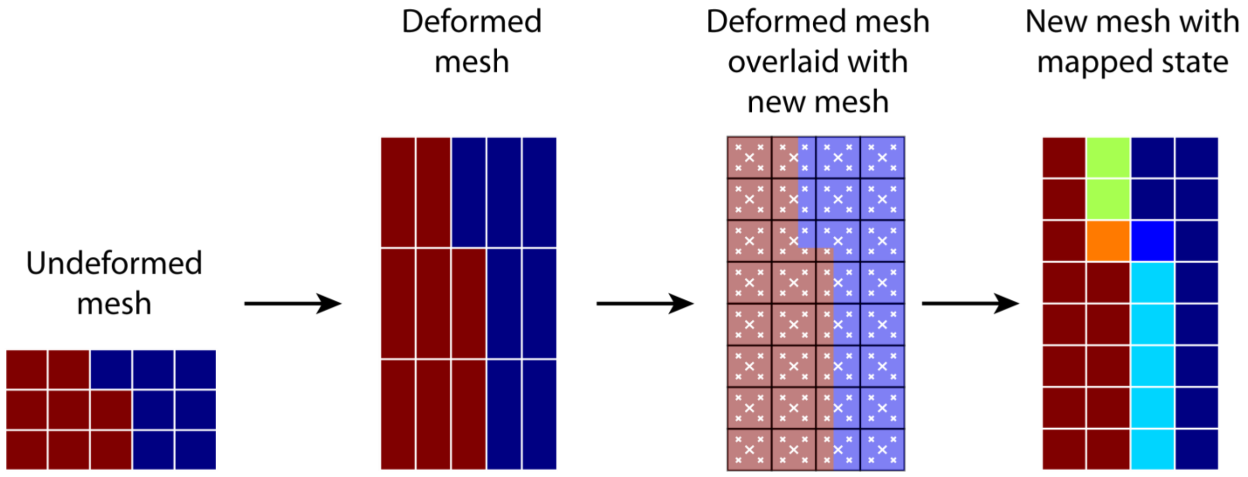
Viscoplasticity



Niemeyer 2013

Remeshing & Solution Mapping





Niemeyer 2013

Simulation Results

Callus distraction
+ 3.00 mm dynamization