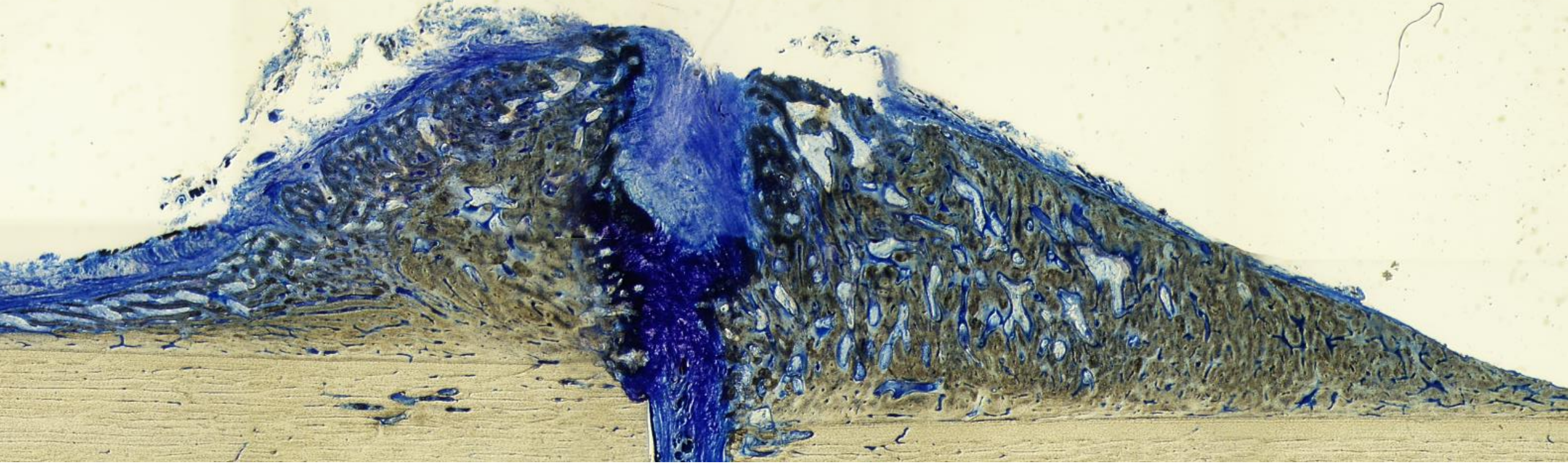


(Bone) Fracture Healing

Part 2/2

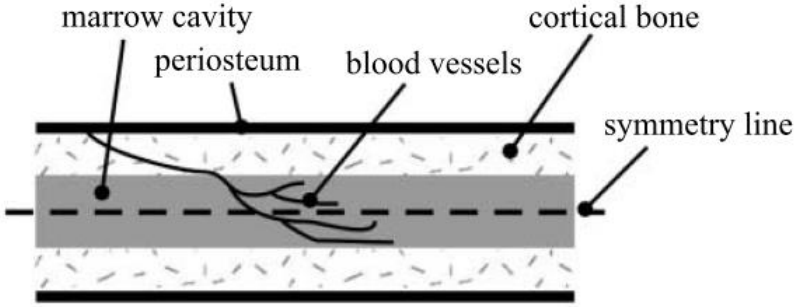
Computational Biomechanics

Summer Term 2017

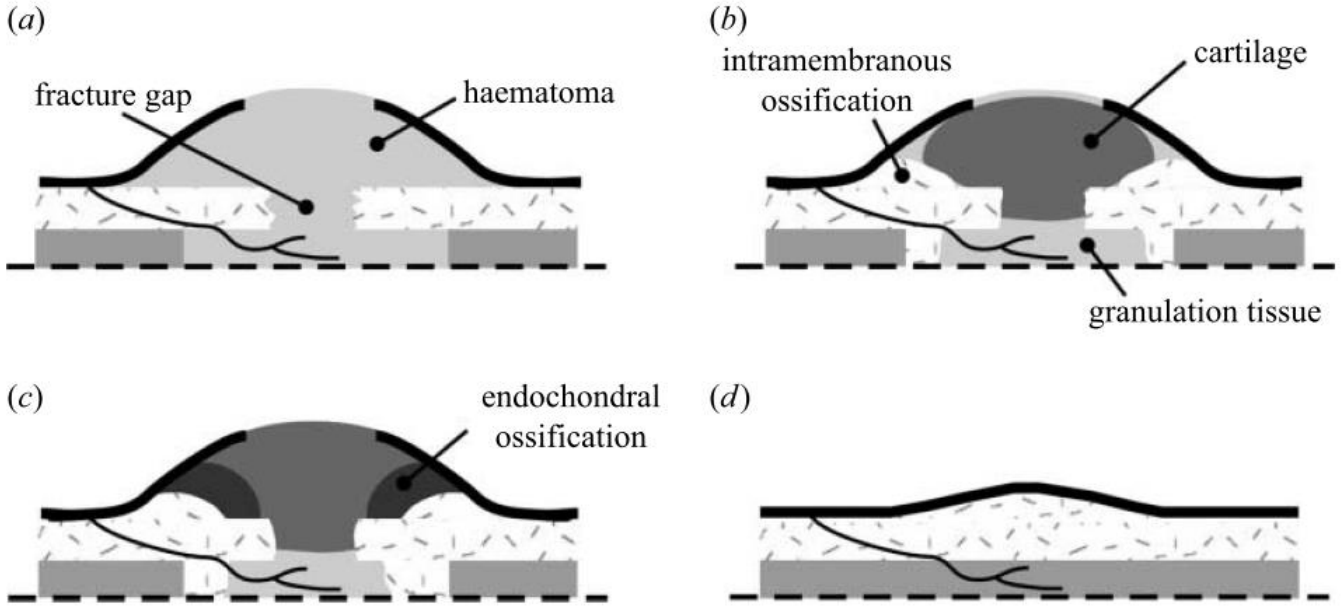
Martin Pietsch

Healing Phases:

- Inflammation
  - Blood coagulates → blood clot
  - Peak within 24 h, completed after ~ 7 days (rats)



- Repair
  - Intramembranous ossification (~2 weeks)
  - Revascularizaion of the hematoma commences
  - Endochondral ossification (chondrocytes)

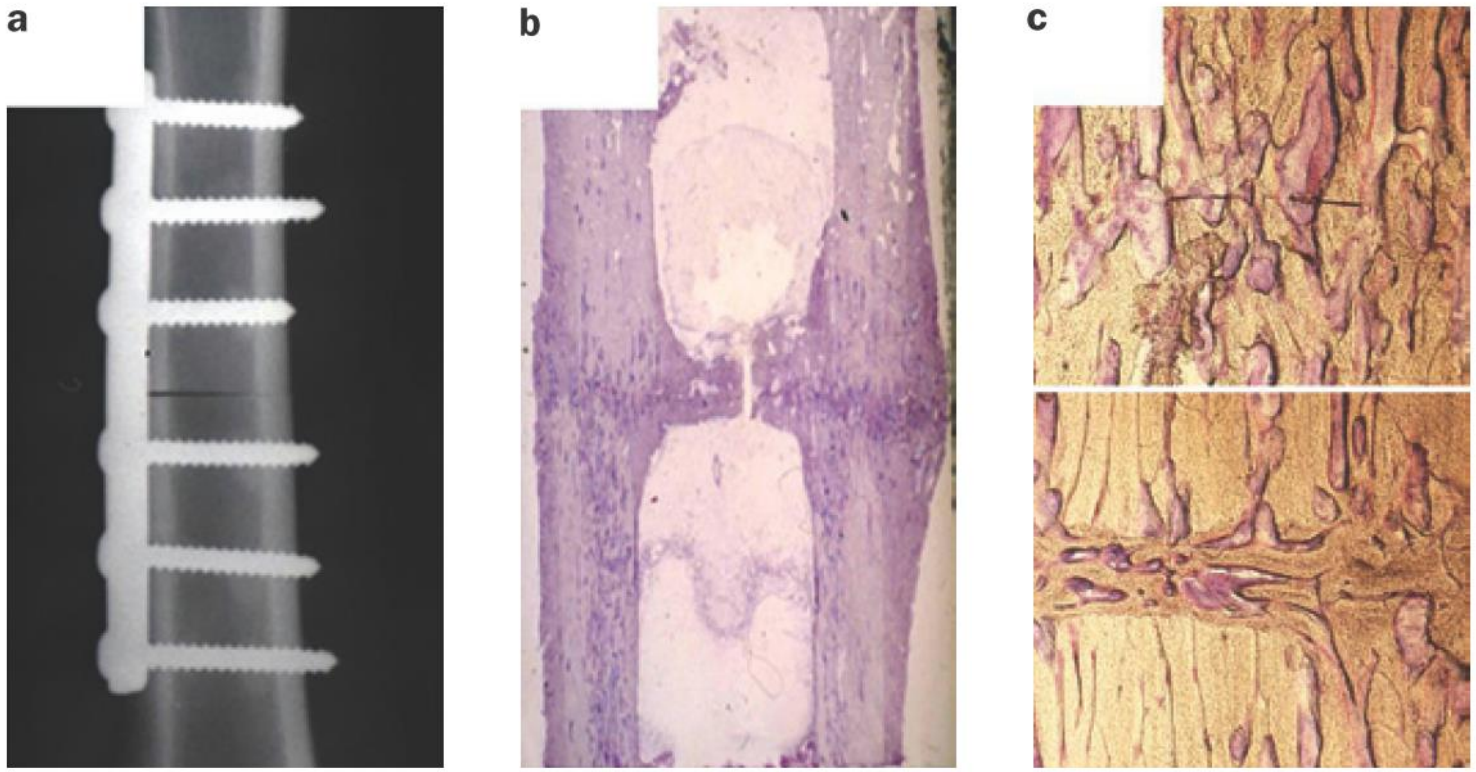


- Remodeling
  - 5 –8 weeks (rats; humans: years)
  - Woven bone -> Lamellar bone

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

When do we use mathematical models?

P. Pivonka and Colin R Dunstan, 2012, Role of mathematical modeling in bone fracture healing

- When simultaneous multiple events make it dicult to predict intuitively the behaviour of the system
- When the time/length scales of various events under investigation are signicantly dierent
- When the system exhibits clearly nonlinear (nonobvious) behavior

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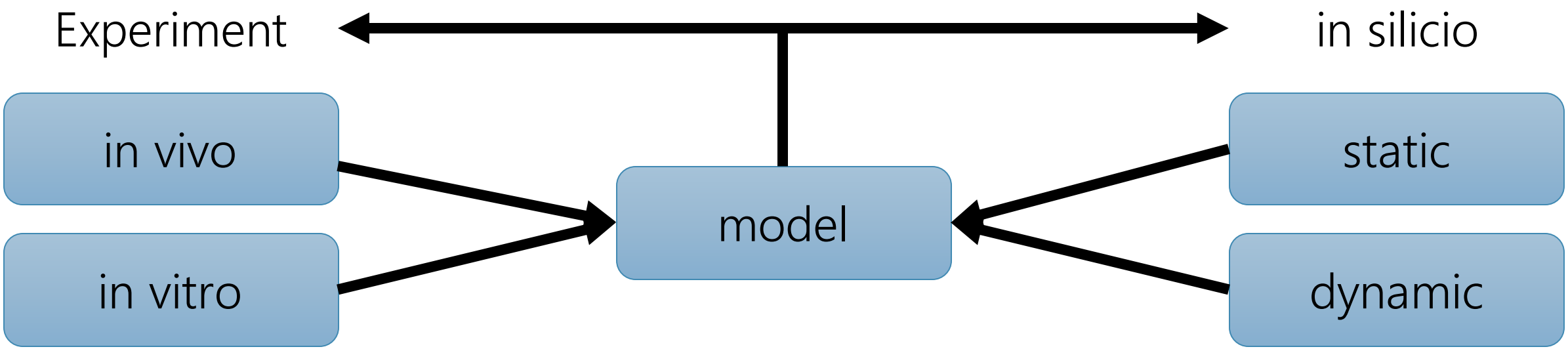


Modelling types of bone fracture healing

P. Pivonka and Colin R Dunstan, 2012, Role of mathematical modeling in bone fracture healing

1. Cellular-scale models
   - Cell population and temporal evolution
   - Concentration of regulatory factors
2. Tissue-scale models
   - Mostly continuous spatio-temporal models
   - Based on partial dierential equations
3. Organ-scale models
   - Primary focus on mechanical stimuli
   - Strong coupling to mechanoregulatory models

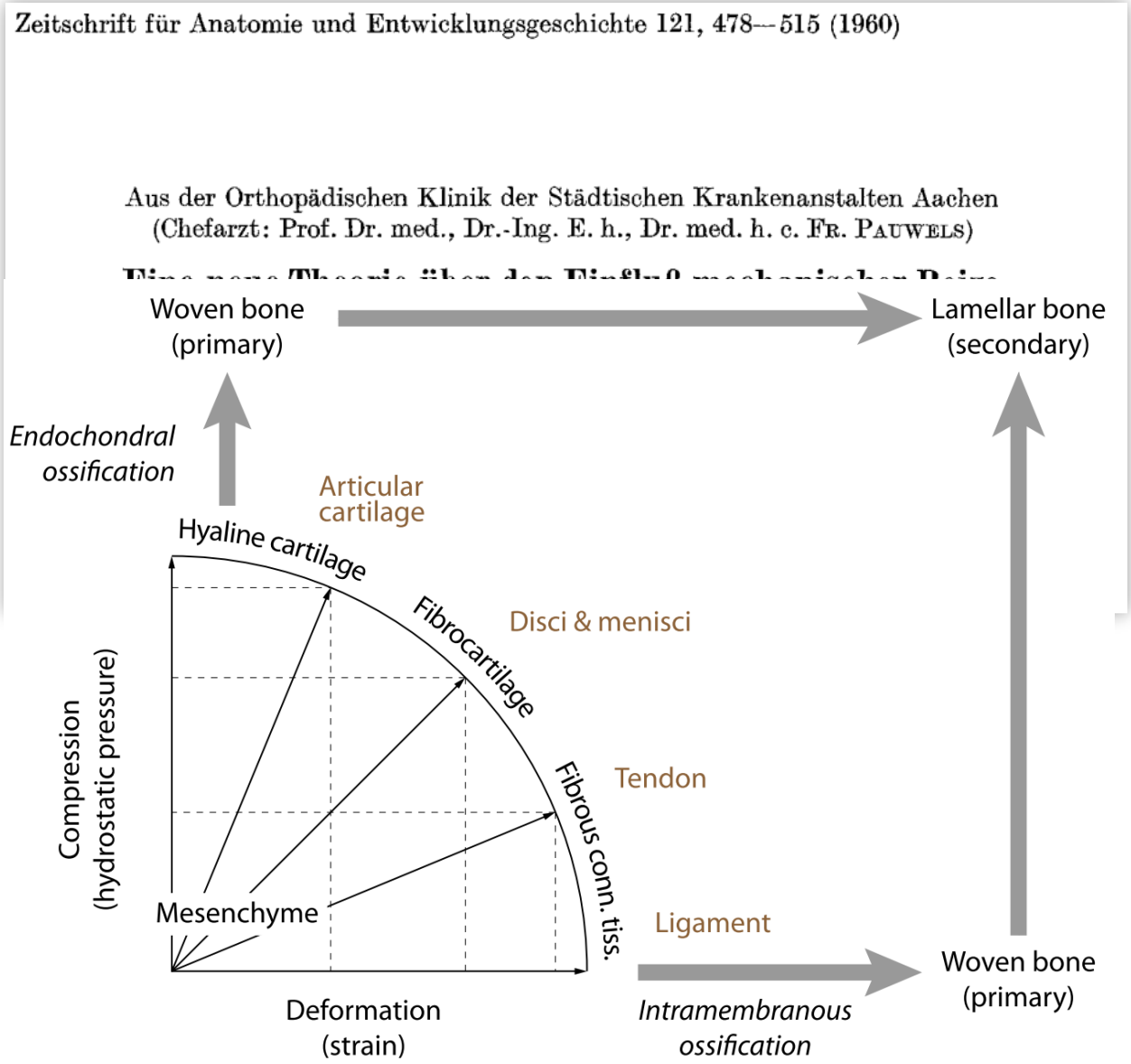
Roux & Krompecher

- 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



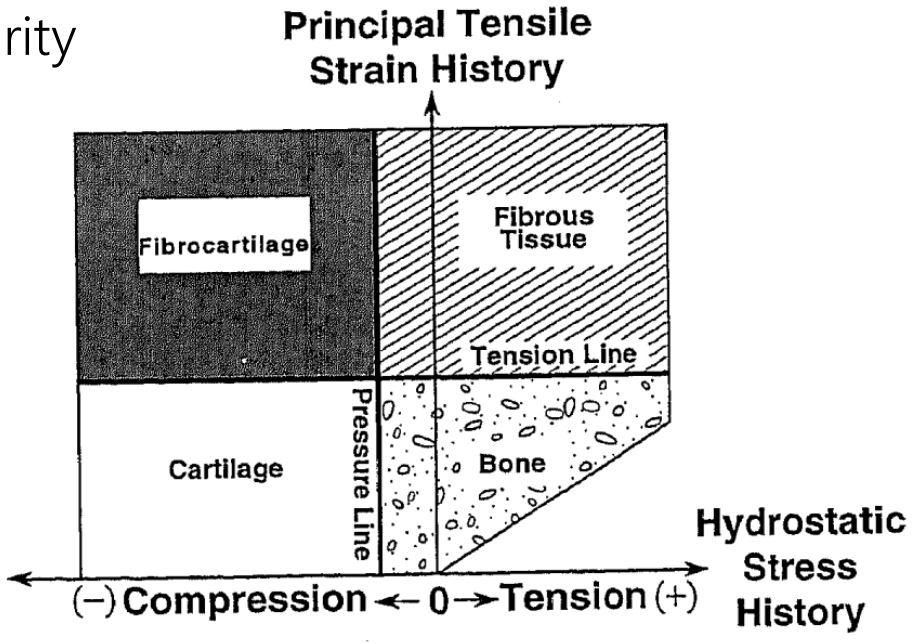
Niemeyer 2013 (after Pauwels 1973)

Carter et al.

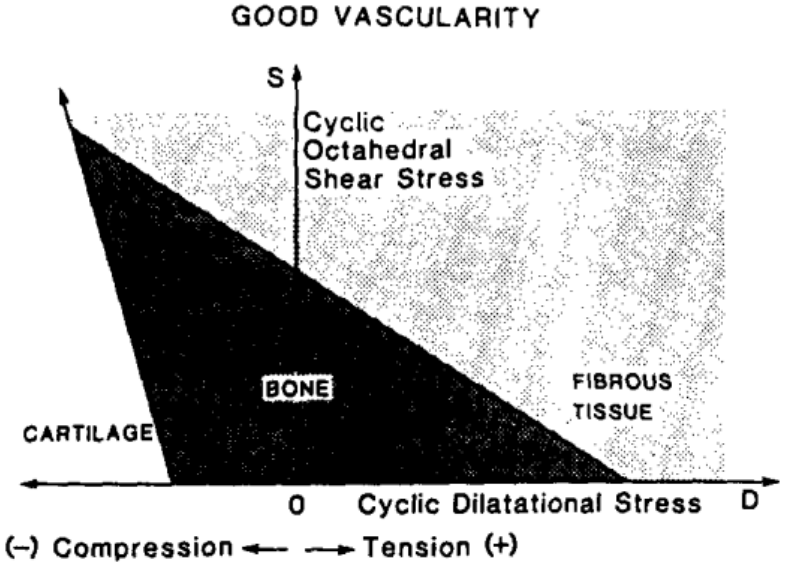
- Proposes "osteogenic index" as a function of peak cyclic shear and peak cyclic hydrostatic stress

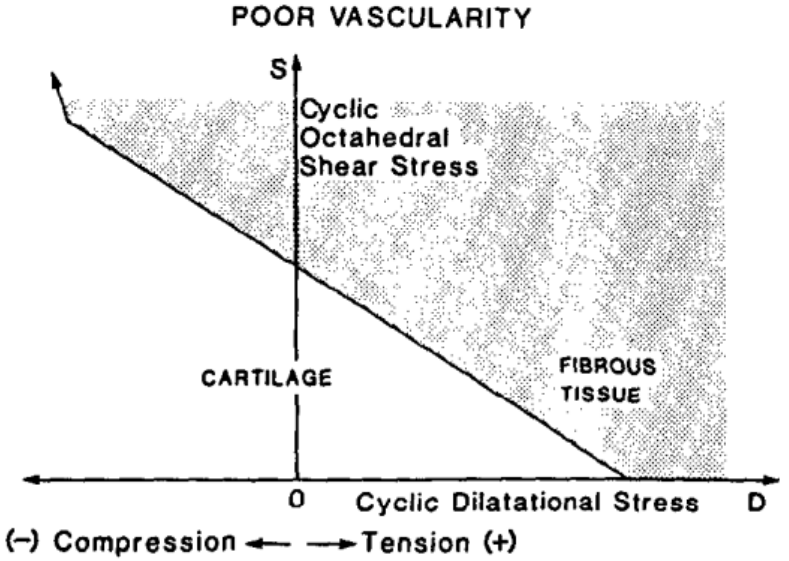
$$I = \sum_i n_i(S_i + kD_i)$$

- Influence of vascularity



Carter et al. 1998

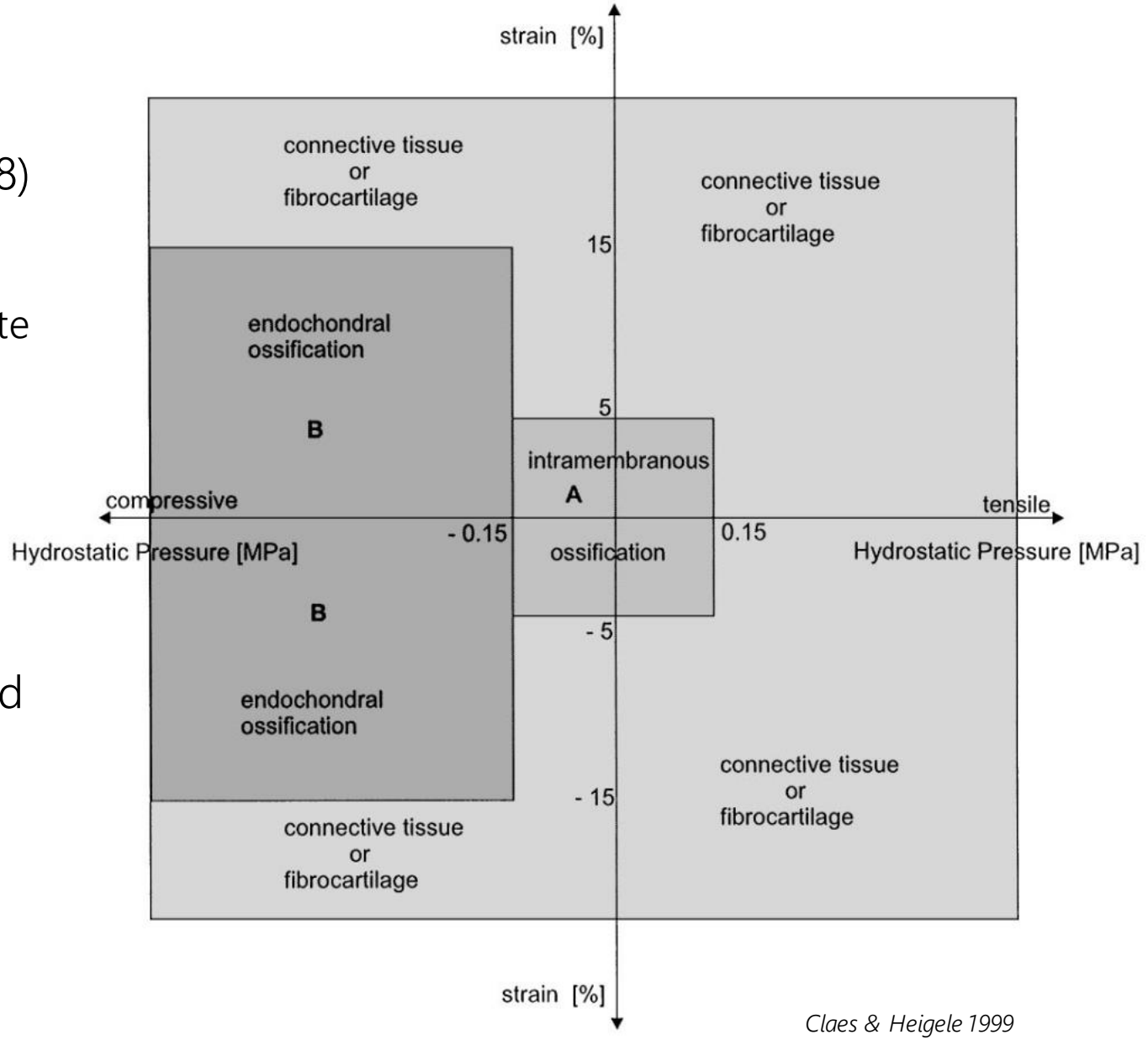




Carter 1987

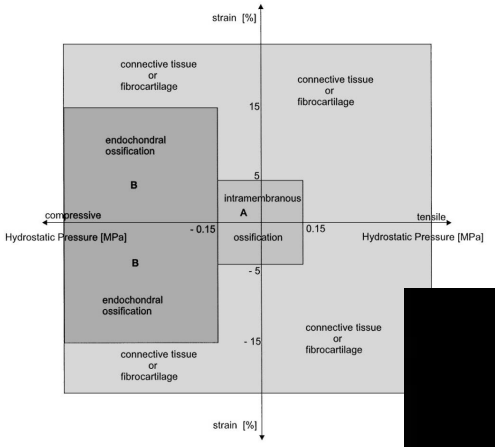
Claes & Heigele

- "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



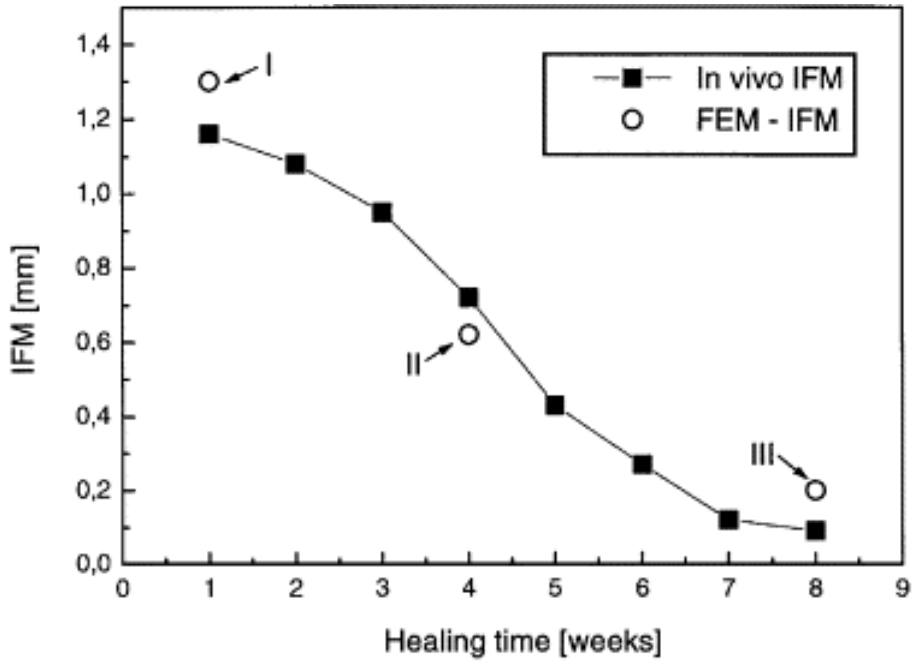
Claes & Heigele 1999

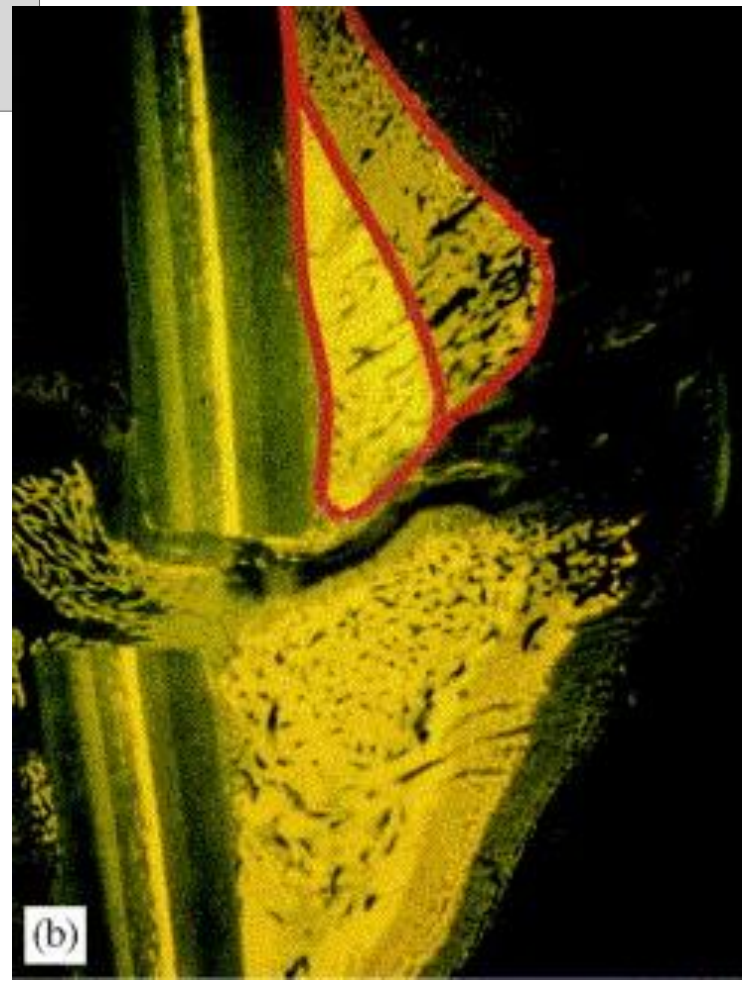
Claes & Heigele, Why ->



Experimental output:

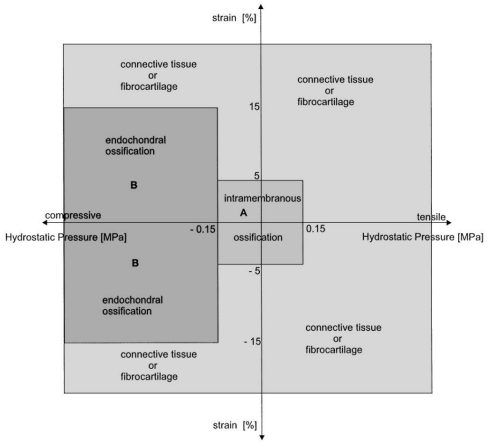
- After week 0; 4; 8
- Visual tissue distribution
- Interfragmentary movement (IFM)

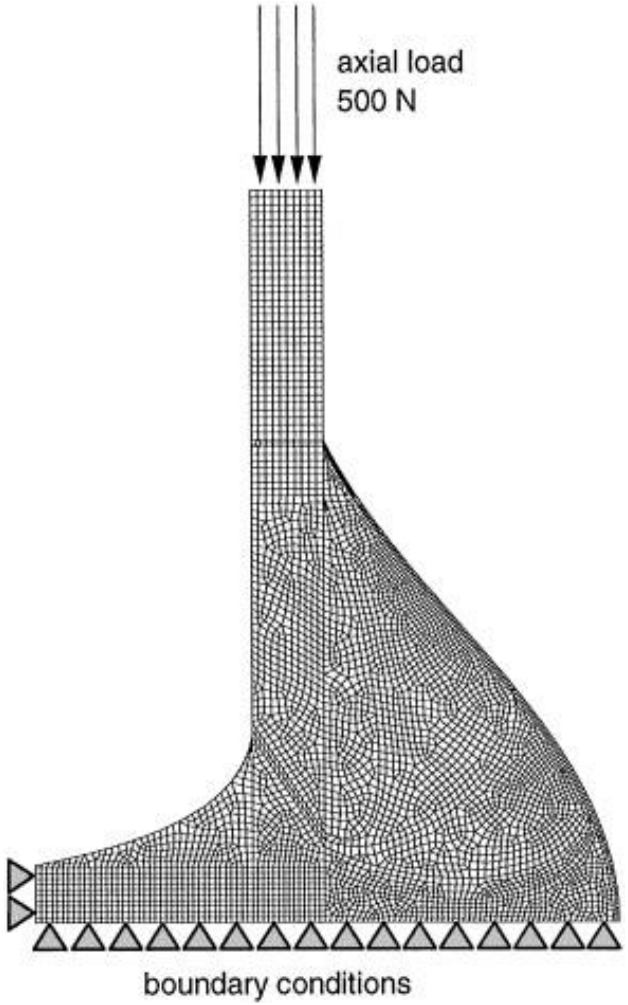


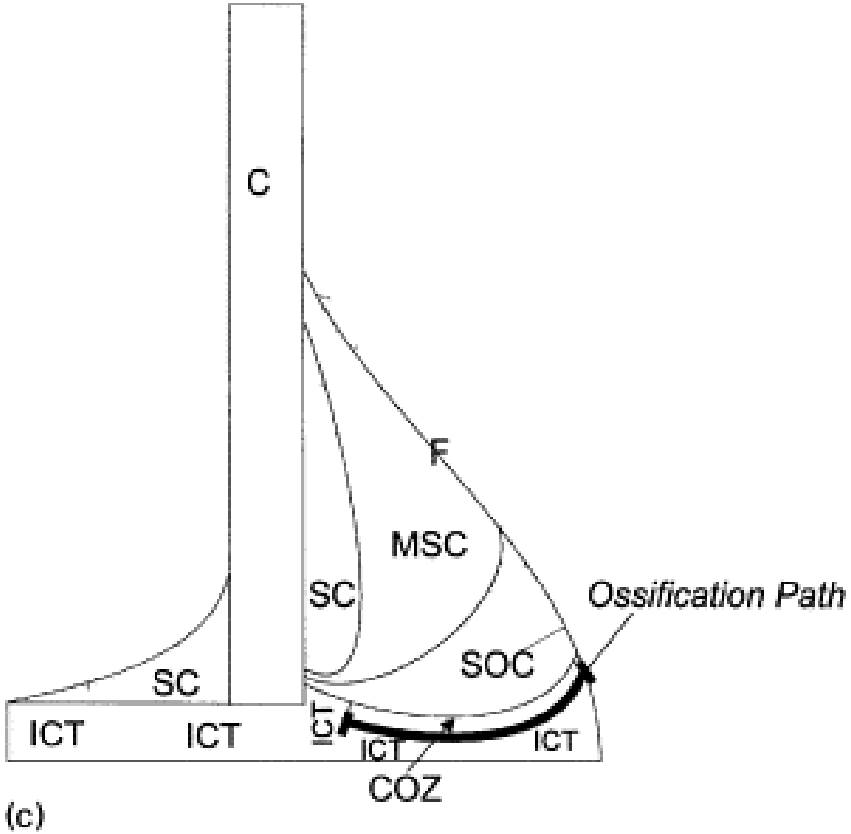


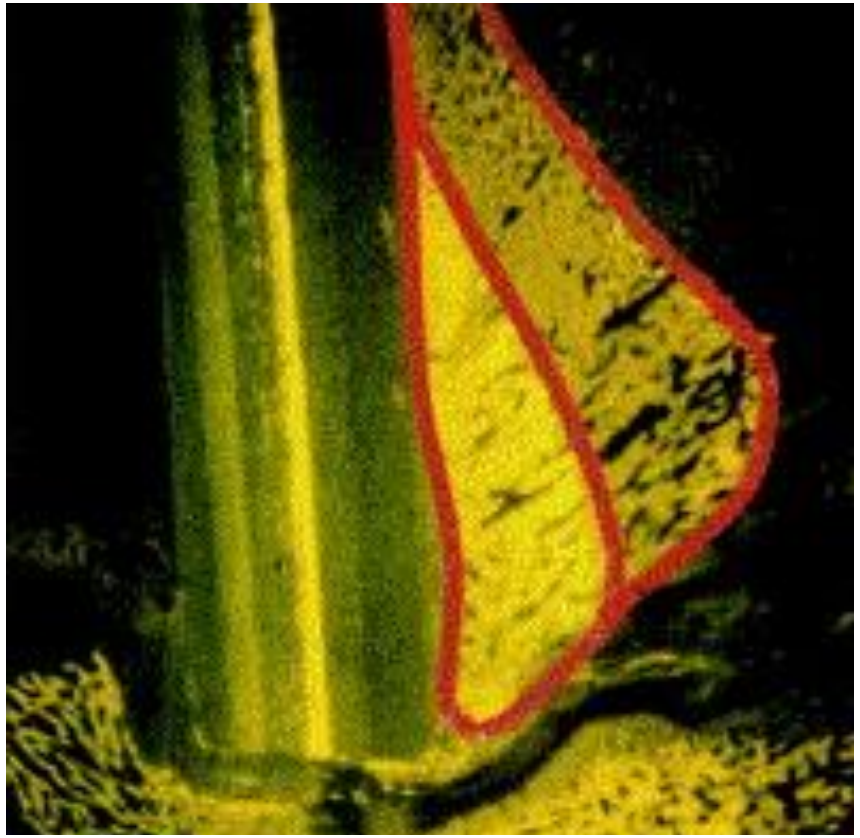
Claes & Heigele 1999

Claes & Heigele, Why ->



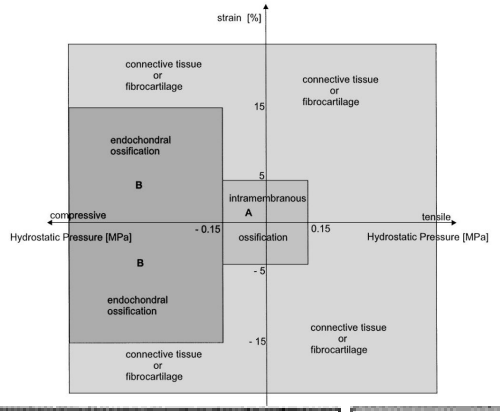






Claes & Heigele 1999

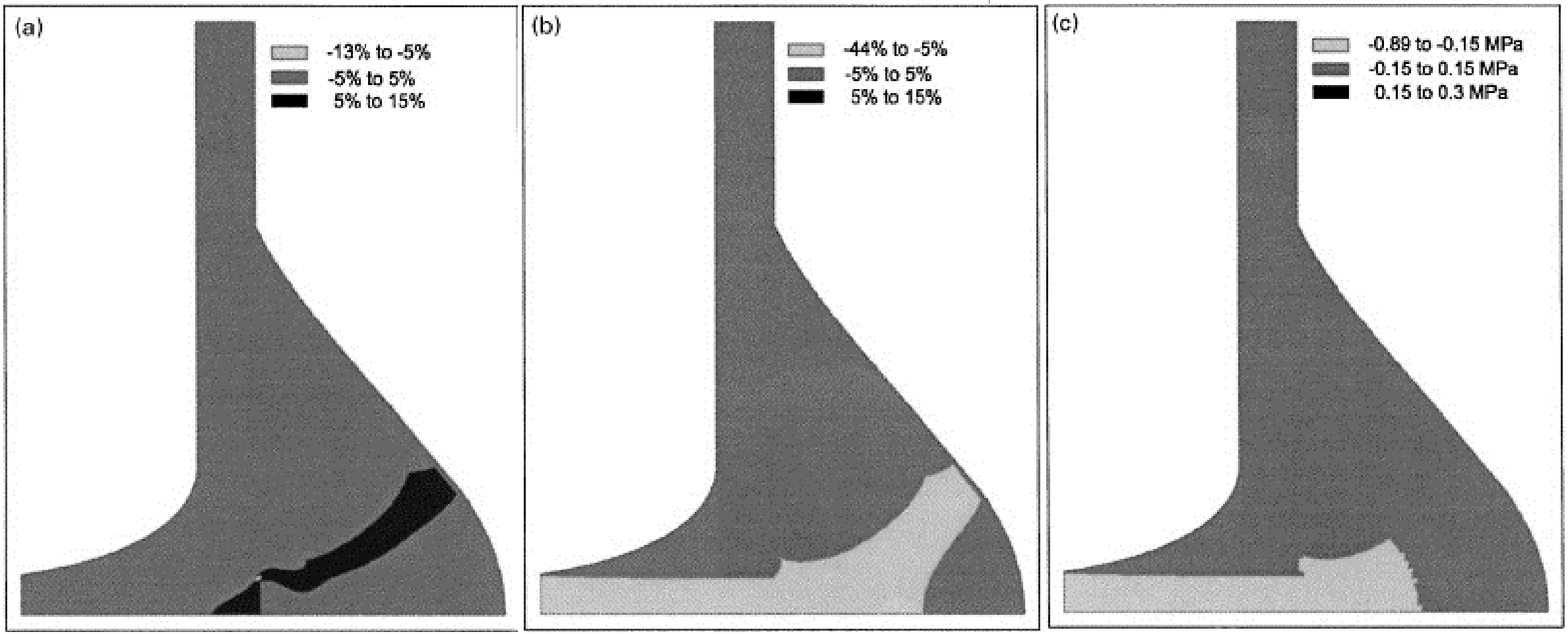
Claes & Heigele, Why ->



Strain x-direction

Strain y-direction

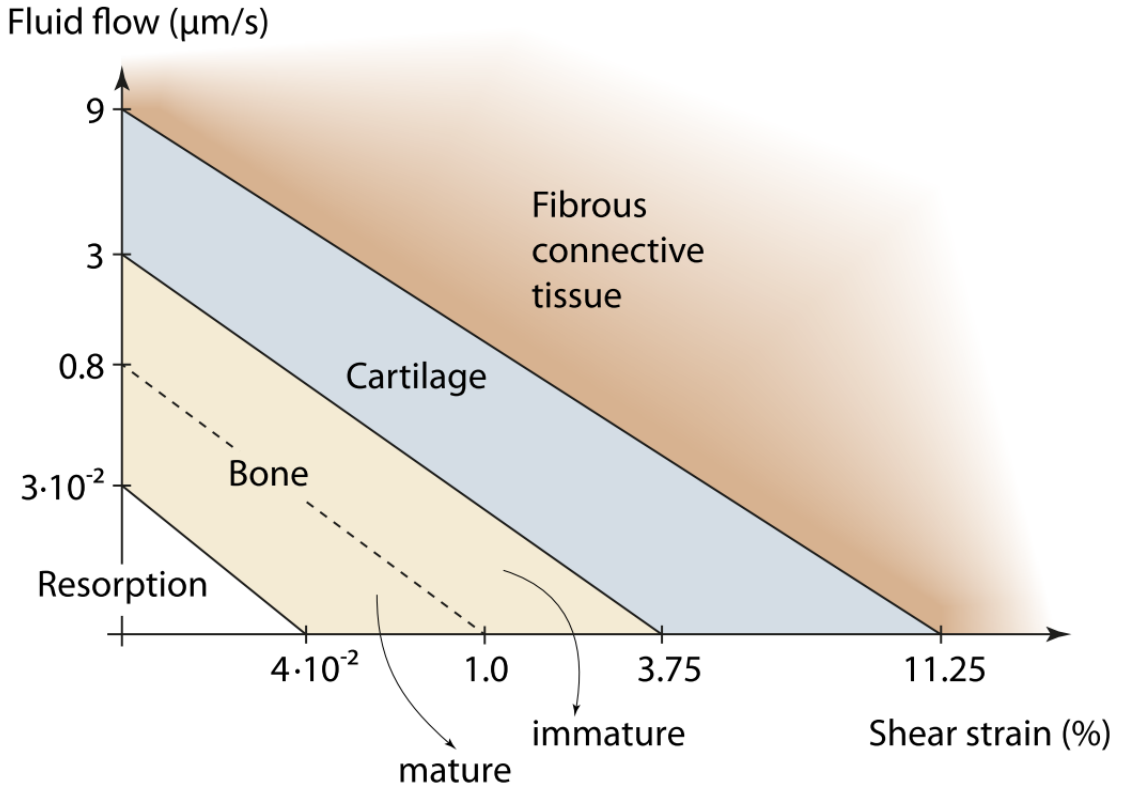
Hydrostatic pressure



Claes & Heigele 1999

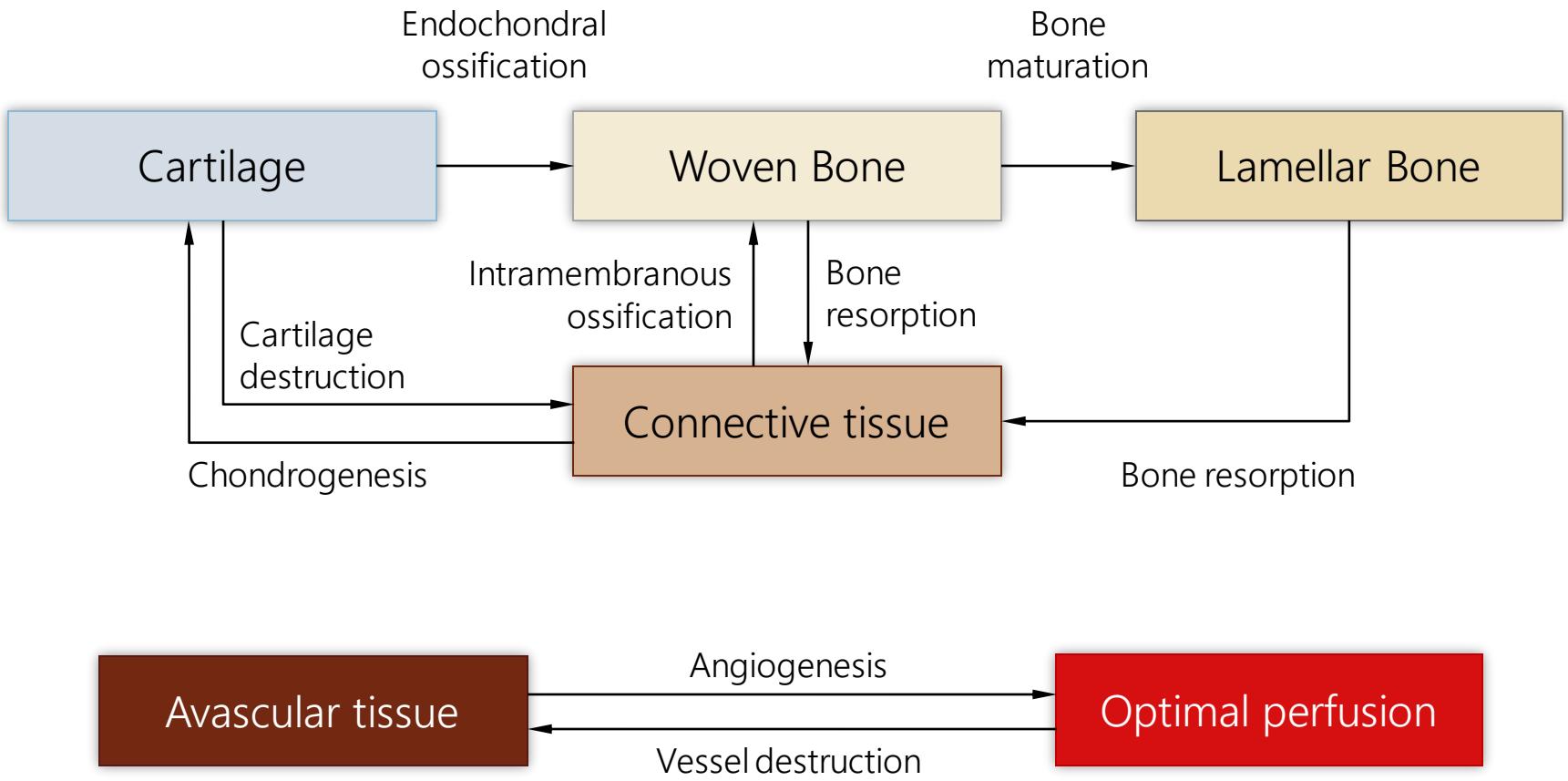
Prendergast et al.

- 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 $S = \gamma/a + v/b$

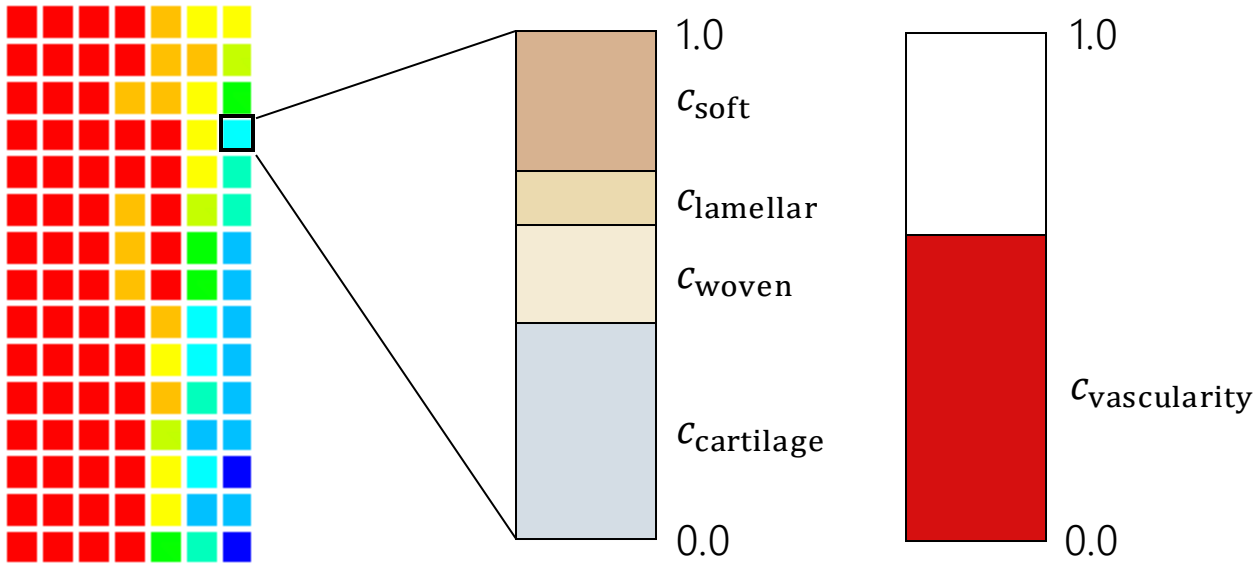


Niemeyer 2013 (after Lacroix et al. 2002)

Biological Processes



Representing Biological State



FE mesh Tissue composition Vascularity

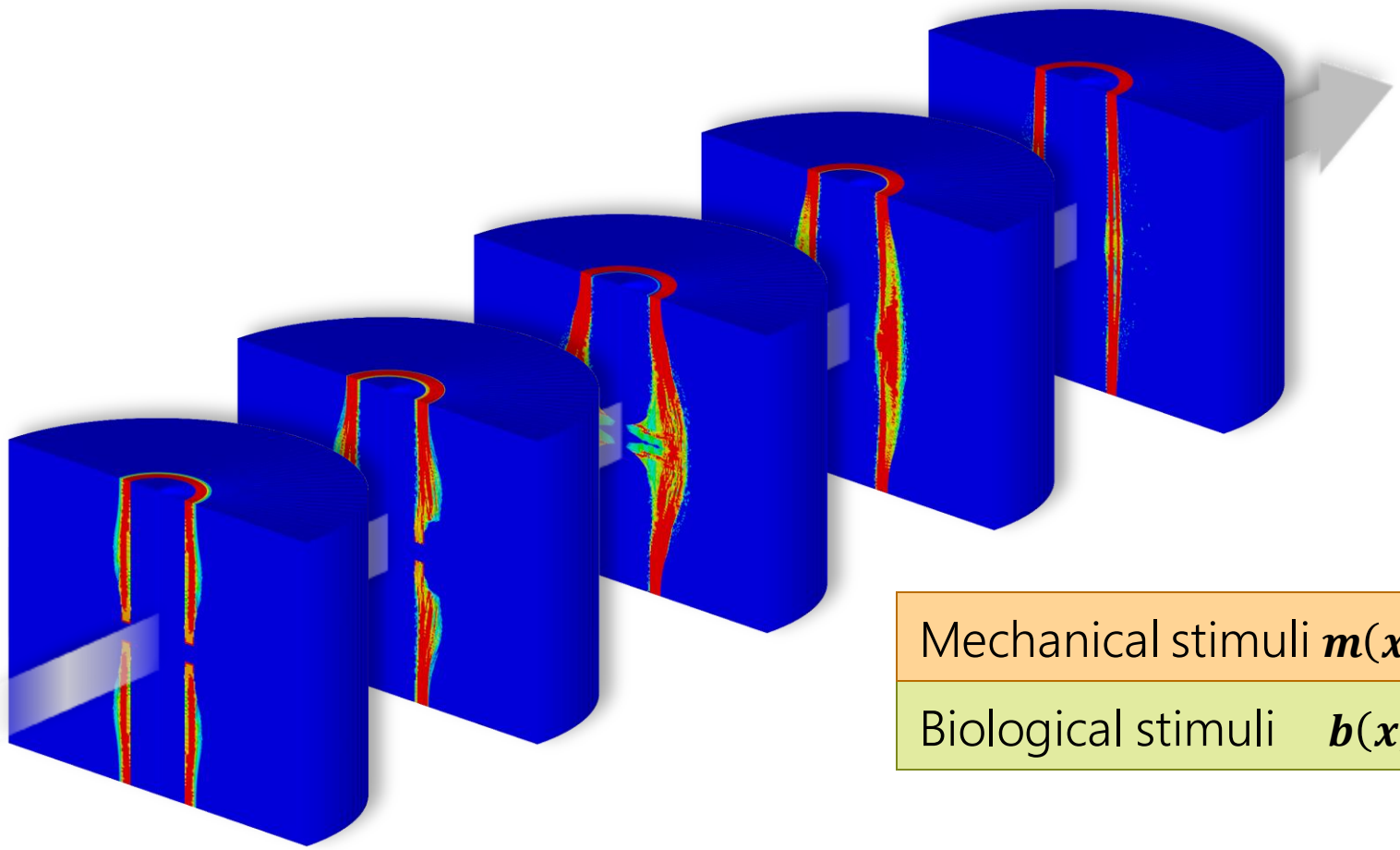
$$\boldsymbol{c}\colon \Omega \times [0,+\infty) \to [0,1]^5 \text{ with } \Omega \subset \mathbb{R}^3$$

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

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

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

Predicting Tissue Concentrations



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

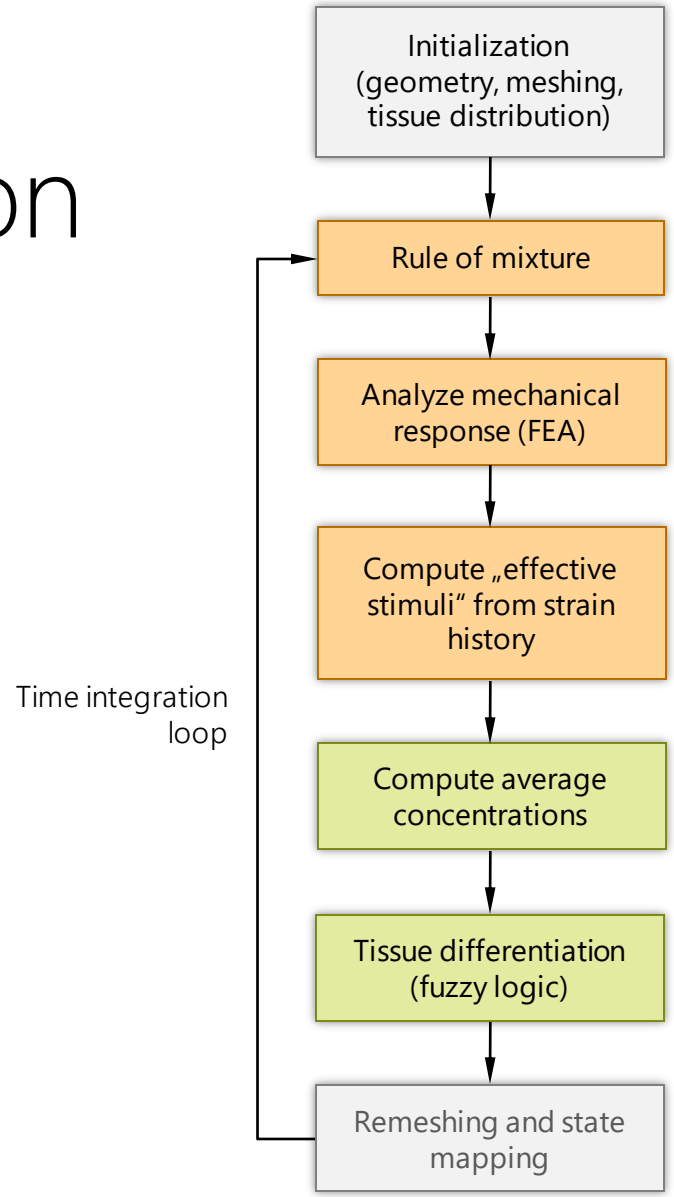
$$\partial_t \boldsymbol{c}(\boldsymbol{x}, t) \approx \boldsymbol{f}\big(\boldsymbol{m}(\boldsymbol{x}, t), \boldsymbol{b}(\boldsymbol{x}, t)\big)$$

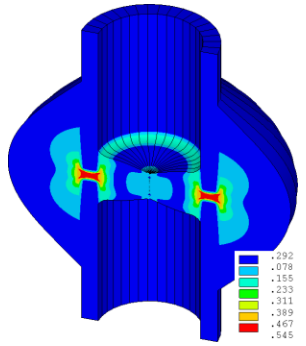
Depends on history

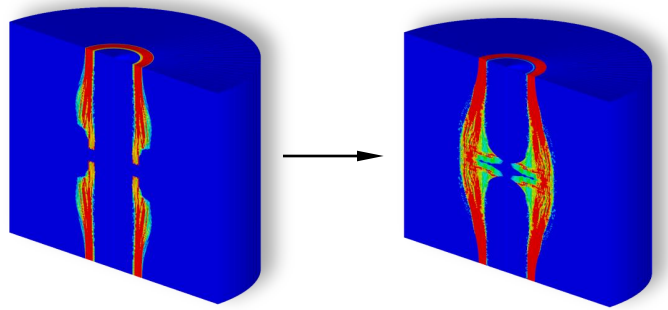
Mechanical stimuli $\boldsymbol{m}(\boldsymbol{x}, t) = \boldsymbol{\mathcal{M}}(\boldsymbol{x}, t, \boldsymbol{c}(\cdot, t_0 \dots t), \boldsymbol{u}_{\mathrm{BC}}, \boldsymbol{F}_{\mathrm{BC}})$
Biological stimuli $\boldsymbol{b}(\boldsymbol{x}, t) = \boldsymbol{\mathcal{B}}(\boldsymbol{x}, t, \boldsymbol{c}(\cdot,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

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

Numerical Implementation





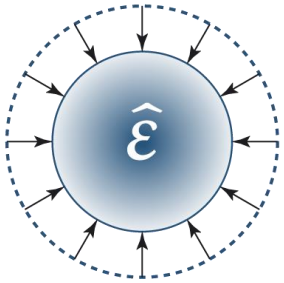


t_n t_{n+1}

Niemeyer 2013

Mechanical Stimuli

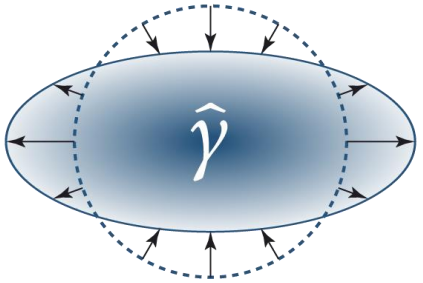
Dilatational strain



Pure volume change

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

Distortional strain



Pure shape change

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

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

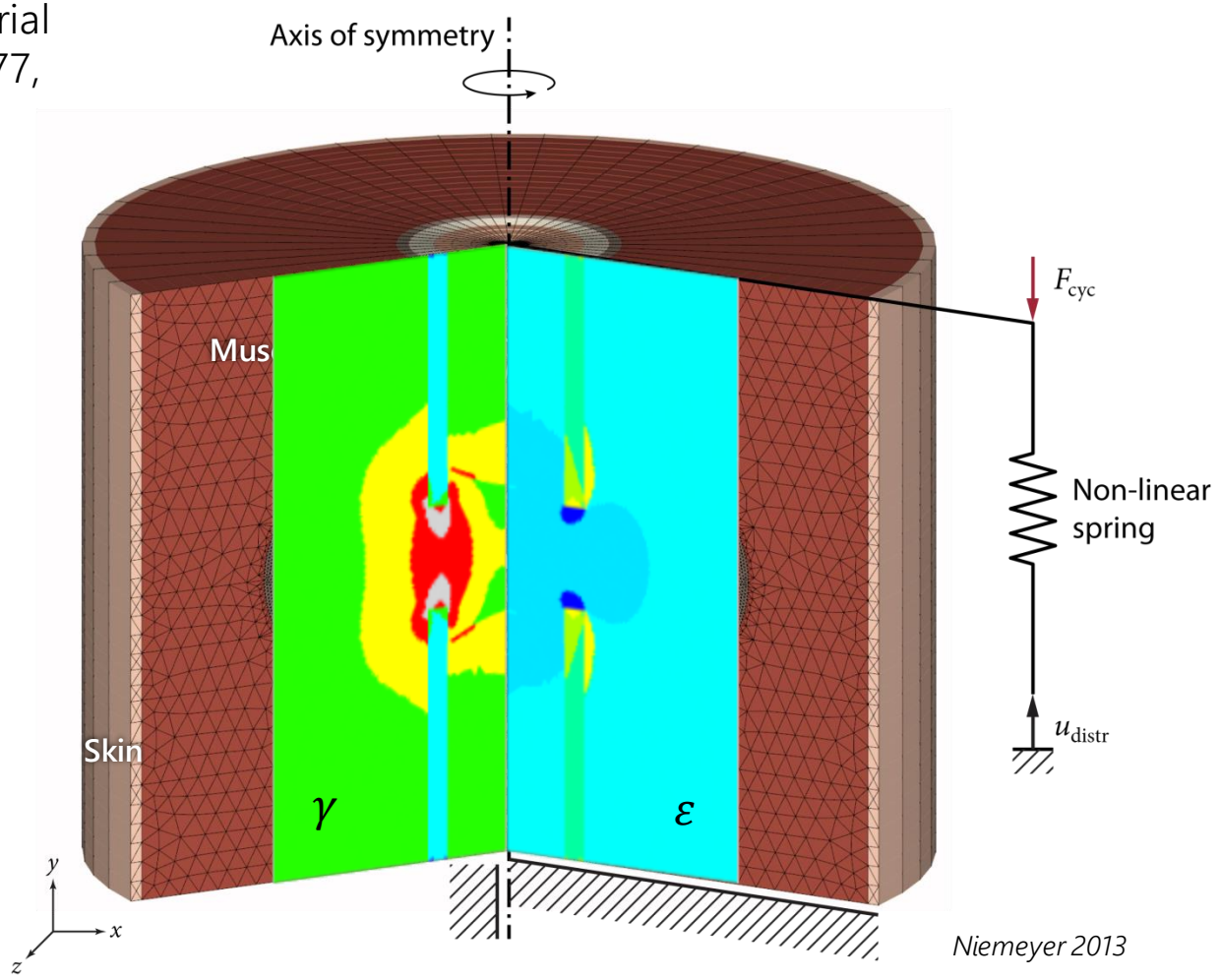
Simon et al. 2002, 2010, Shefelbine et al. 2005

Rule of Mixture & Structural Analysis (FEA)

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

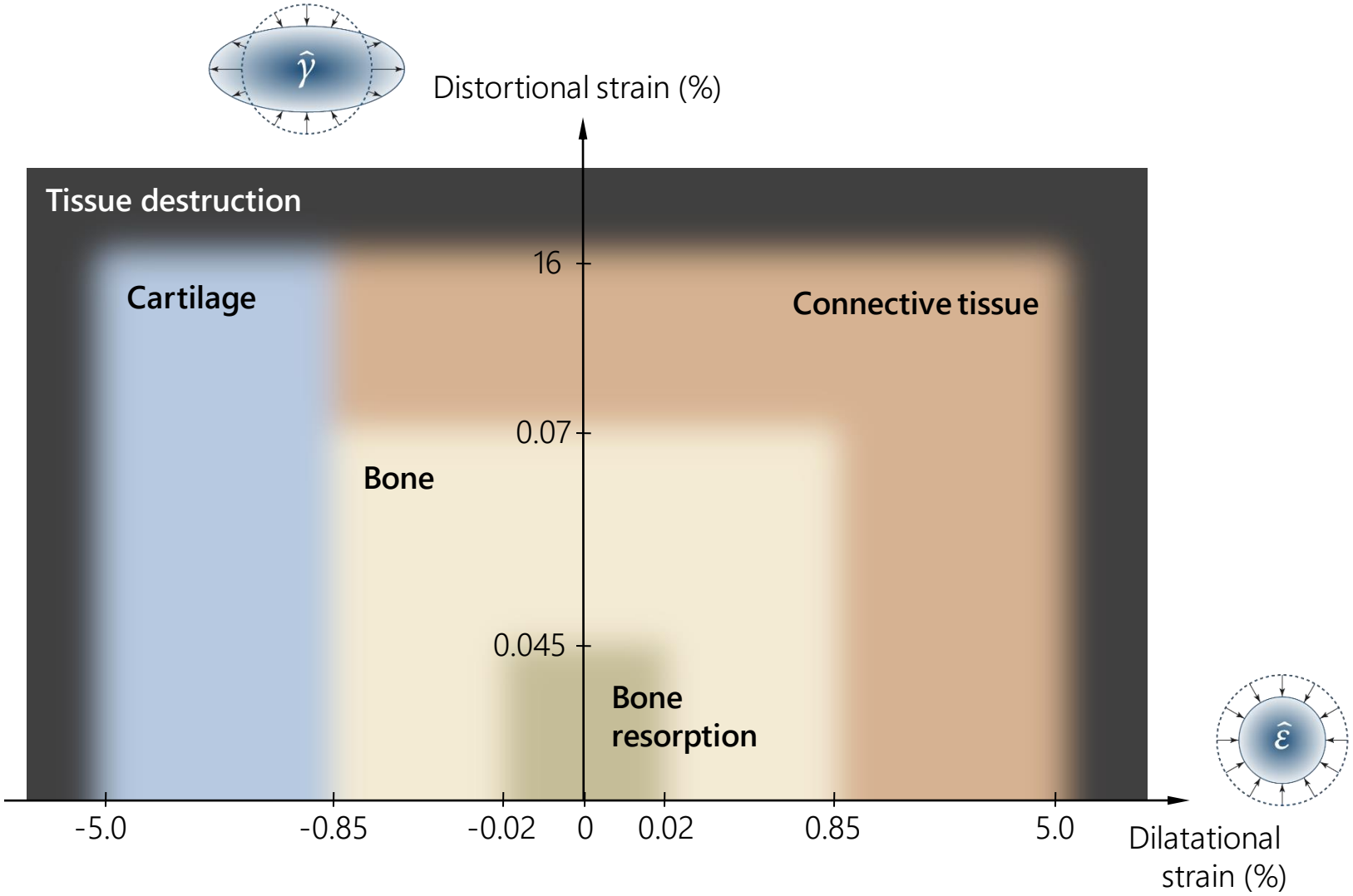
$$E(\boldsymbol{x},t) = \sum_{i \in T} E_i c_i^3(\boldsymbol{x},t)$$

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



Niemeyer 2013

Mechano-regulated Tissue Differentiation

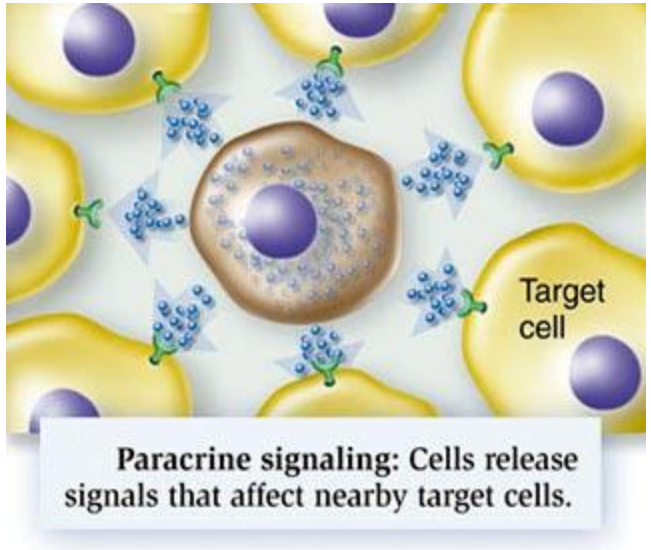


Simon et al. 2002, 2010, Shefelbine et al. 2005, Niemeyer 2013

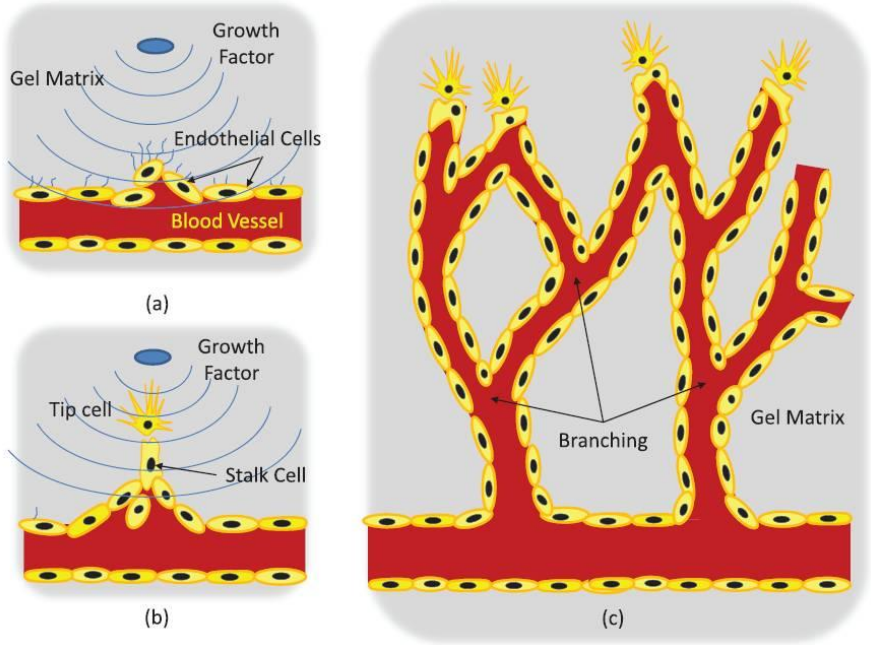
Biological Stimuli

$$\boldsymbol{b} = [c_{\text{woven}}, c_{\text{lamellar}}, c_{\text{cartilage}}, c_{\text{soft}}, c_{\text{vascularity}}, \underbrace{S_{\text{b}}, S_{\text{v}}}]$$

Non-local influence

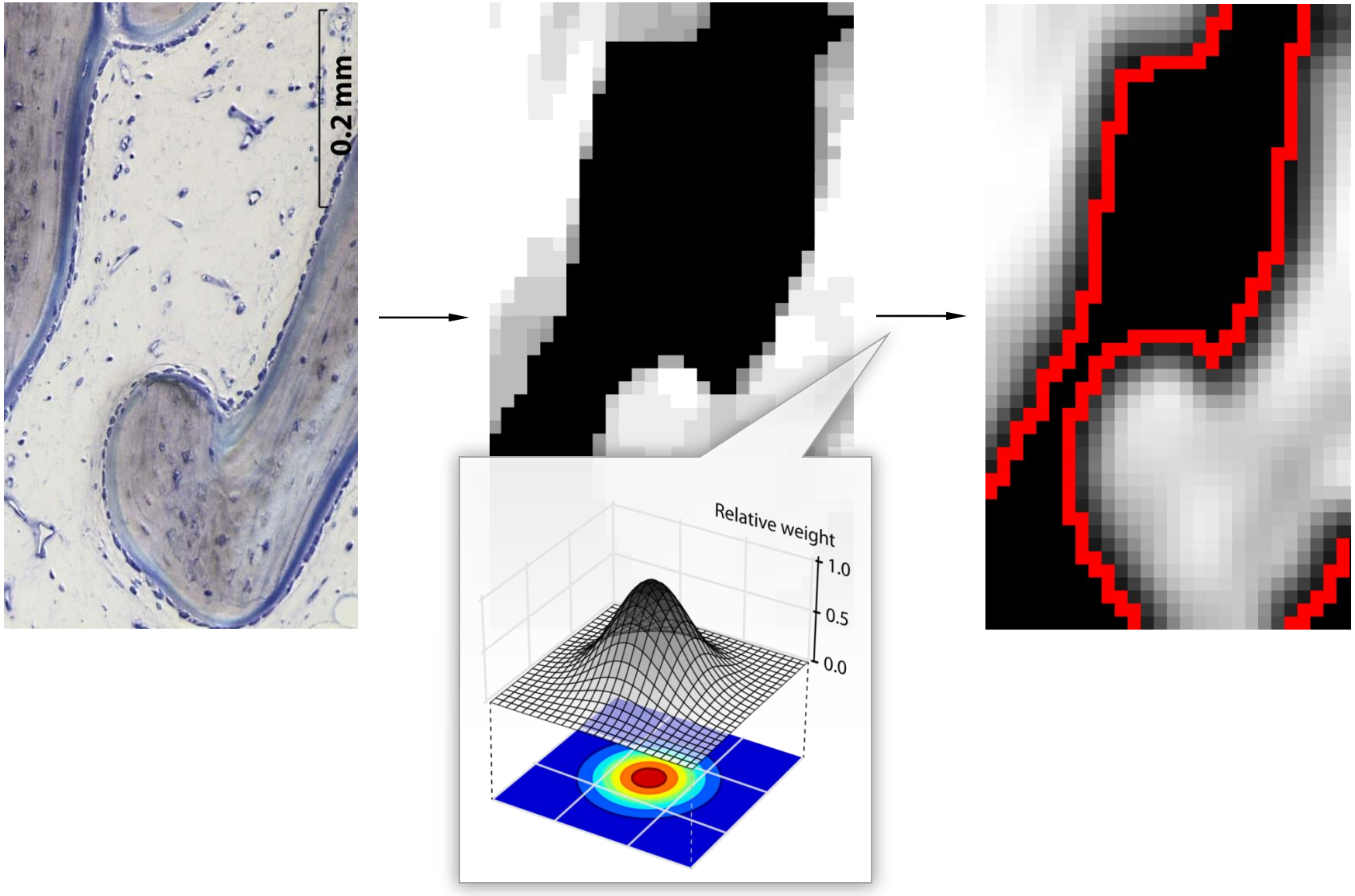


http://www.snipview.com/q/Paracrine_signaling



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

Appositional Growth



Biological Stimuli

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

Non-local influence

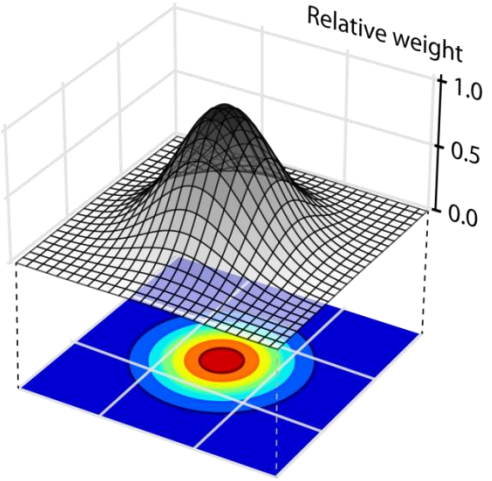
$$s_{\text{b}}(\boldsymbol{x}, t) = (c_{\text{bone}}(\cdot, t) * G_\sigma)(\boldsymbol{x})$$

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

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

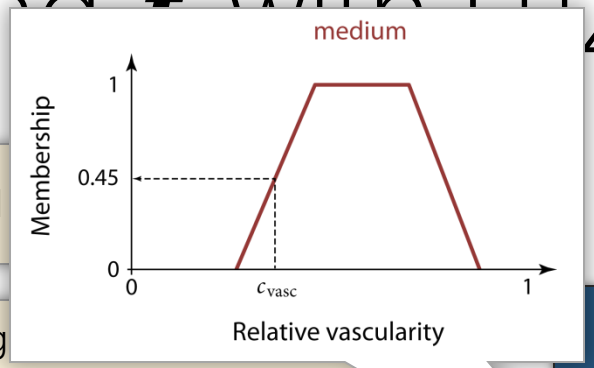
e.g. in two spatial dimensions

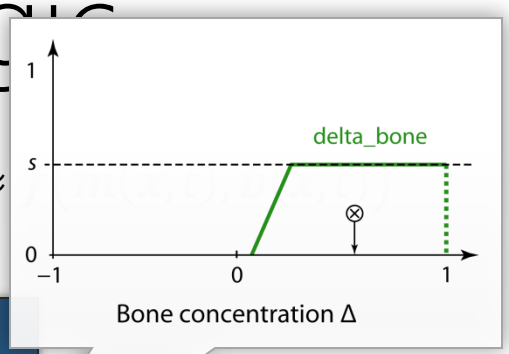
$$G_\sigma(x, y) \propto \frac{1}{2\pi\sigma^2} \exp \frac{-x^2 - y^2}{2\sigma^2}$$



Evaluating $\boldsymbol{f}$ with Fuzzy Logic

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





Local

Weig
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

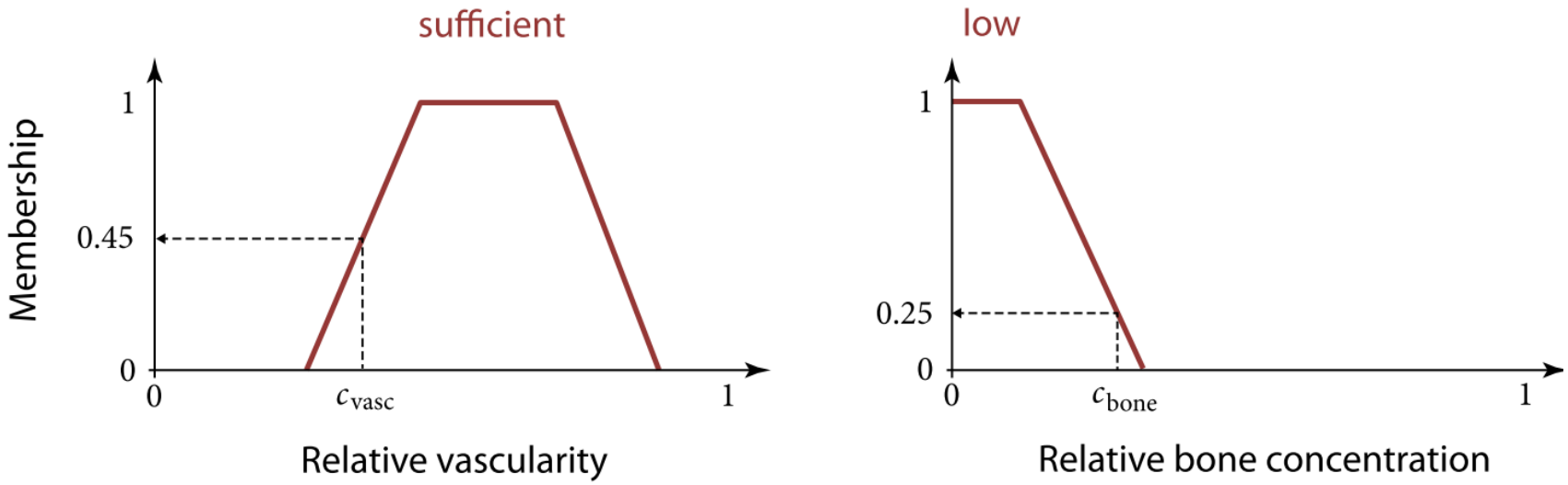
Change in cartilage concentration

Change in vascularity

```
if vascularity is medium and not bone is low
and dist_strain_eff is low
    then delta_bone is positive
```

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

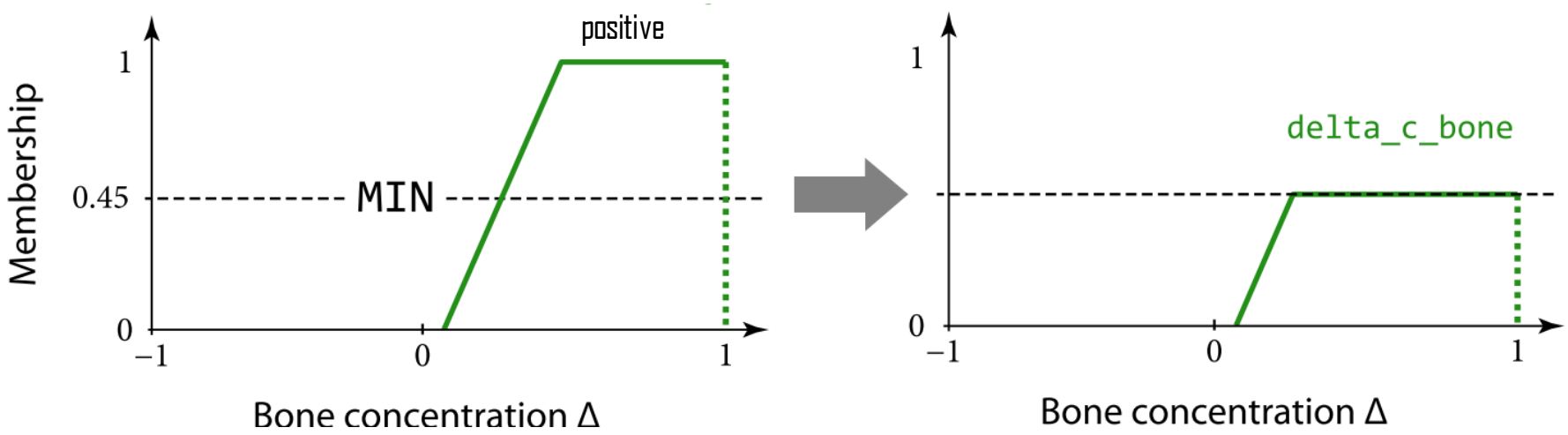
```
if c_vasc is sufficient and not c_bone is low
    then delta_c_bone is positive
```



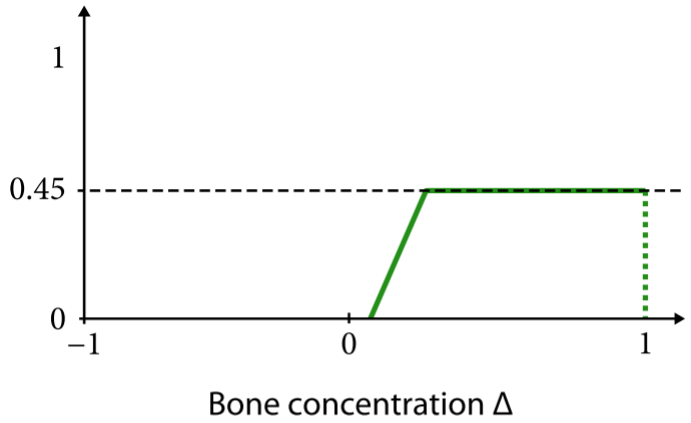

```
c_vasc is sufficient  and not  c_bone is low

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

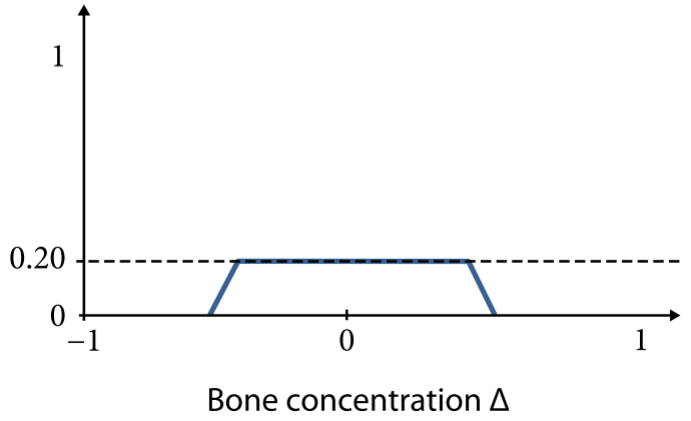
Example (2/3): Implication

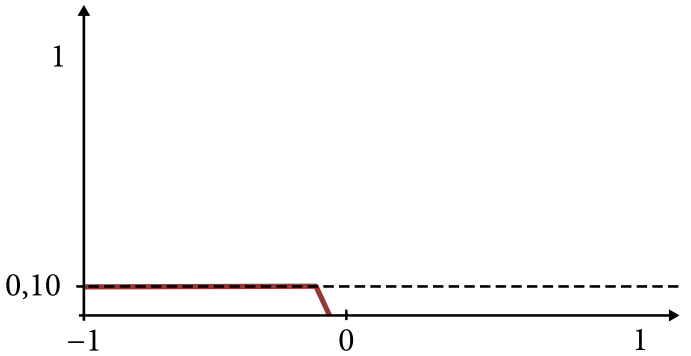
```
c_vasc is sufficient and not c_bone is low

      = 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
```



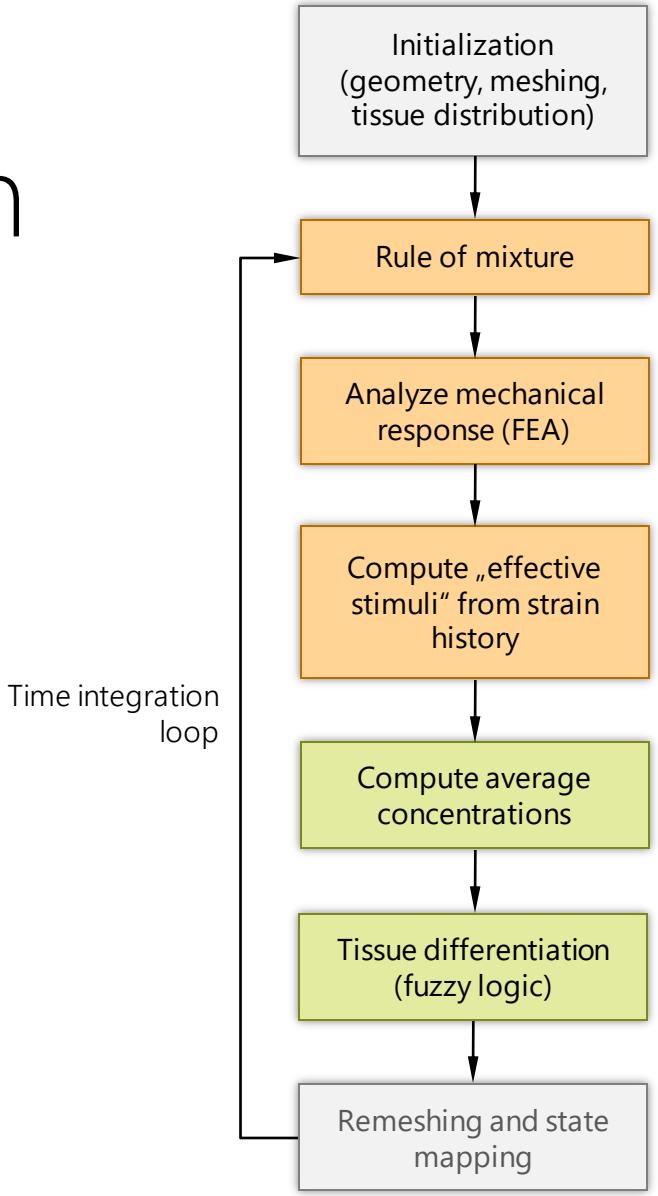
Example (3/3)

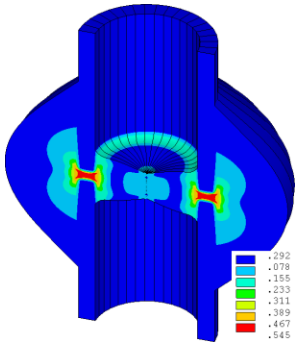

1
0.45
0
−1
0
1
Bone concentration Δ

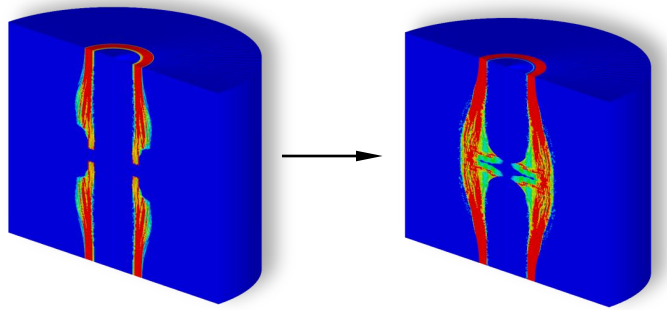

1
0.20
0
−1
0
1
Bone concentration Δ


1
0,10
−1
0
1

Numerical Implementation

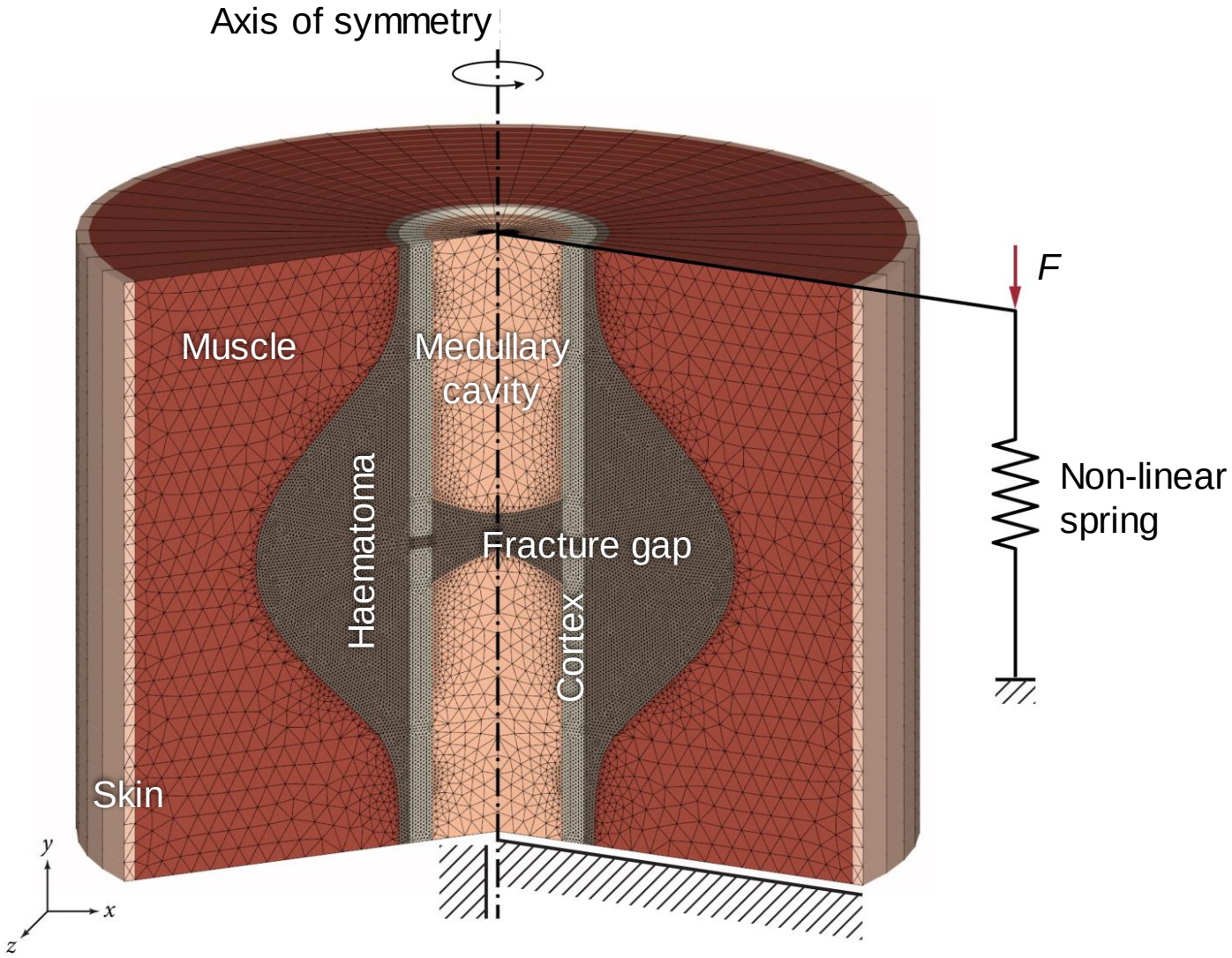






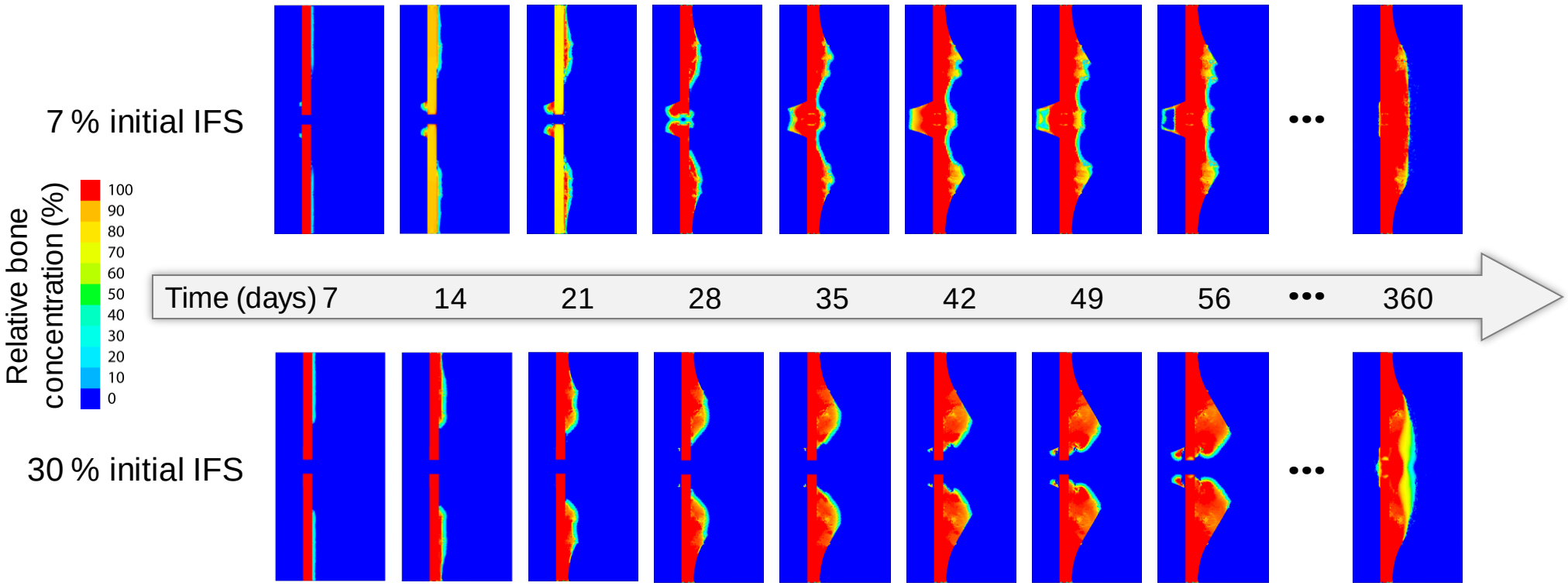
Niemeyer 2013

Callus Healing (Sheep, External Fixator)



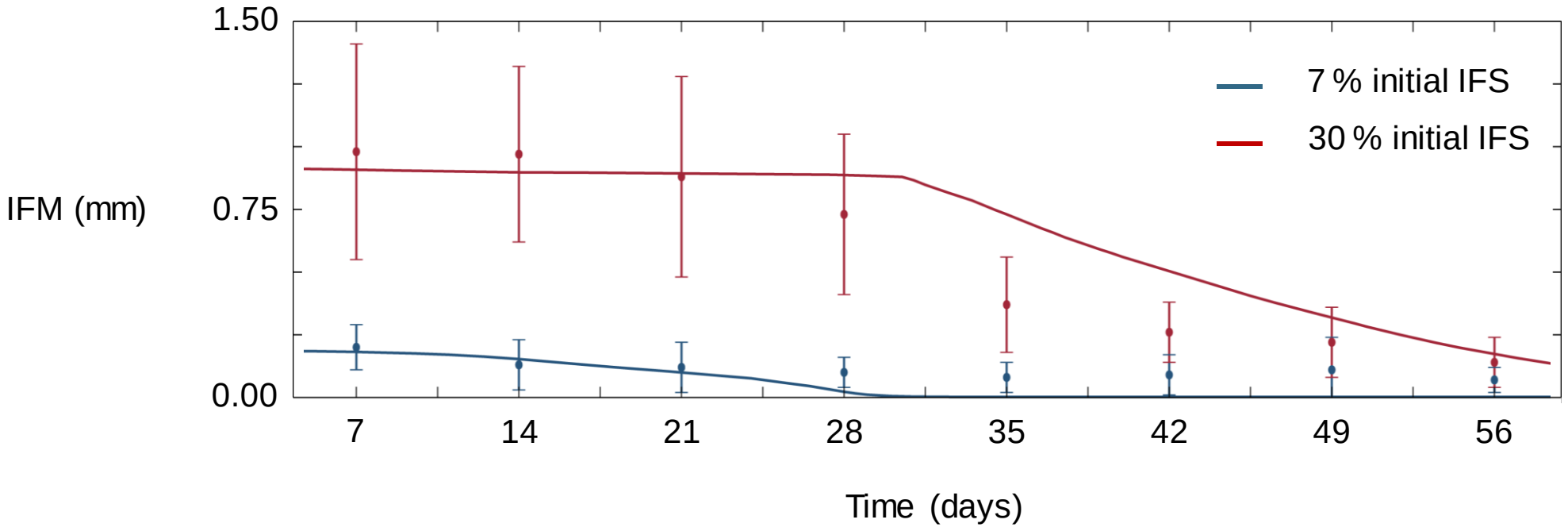
Simon & Niemeyer, 2015

Simulation Results



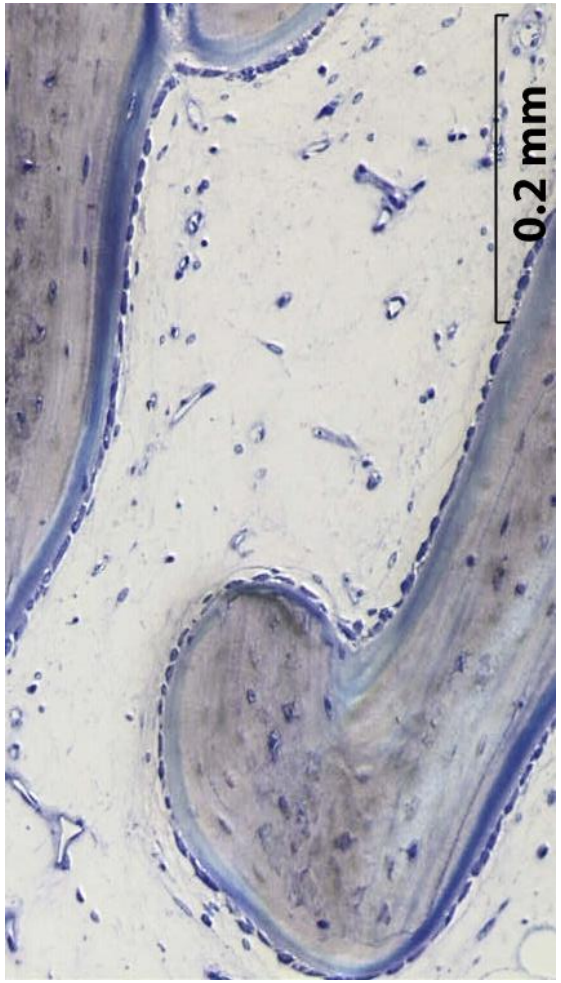
Simon & Niemeyer, 2015

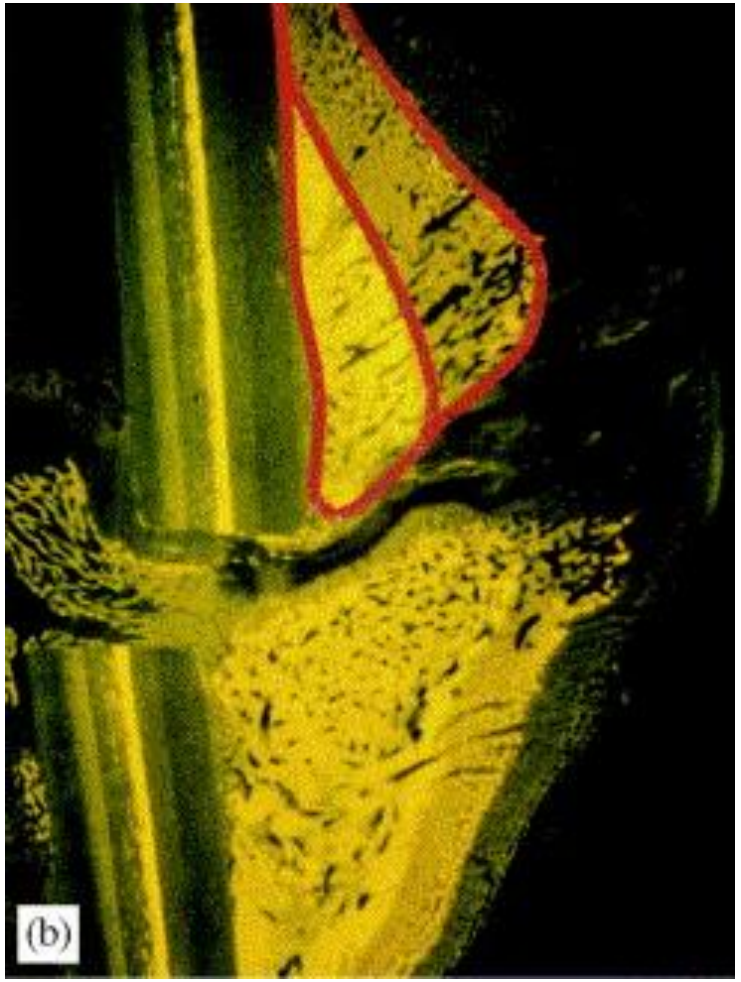
Simulation Results



Simon & Niemeyer, 2015

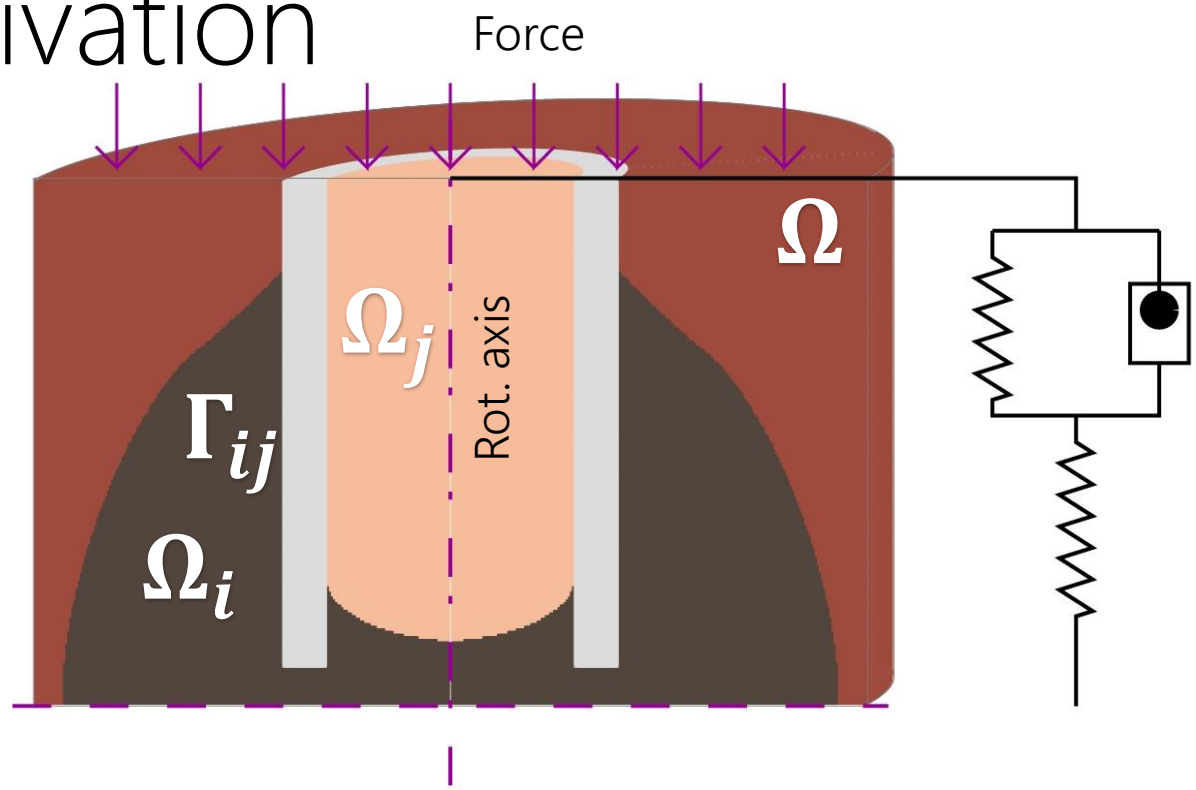
Interface Capturing Motivation





Interface Capturing Motivation

- Simulation area Ω
- Subdomains $\bigcup_i^N \Omega_i = \Omega$
- Interfaces $\Omega_i \cap \Omega_j = \Gamma_{ij}$
- Rotational symmetry (3D problem)



	Old	New
Value of interest	$c_i : \mathbb{R}_0^+ \times \Omega \to [0,1]$	$\Gamma_{ij}(t) \subseteq \Omega$
Tissue growth	$\dot{c}_i : \mathbb{R}_0^+ \times \Omega \to \mathbb{R}$	$v_{ij} : \Gamma_{ij}(t) \to \mathbb{R}^2$

Tissue growth description

- Phase volume fraction α_i

$$\alpha_i : \Omega \times \mathrm{I} \rightarrow [0,1] \quad with \quad \alpha_i = \begin{cases} 1, & on\ \Omega_i \\ 0, & on\ \Omega_j \neq \Omega_i \end{cases}$$

- Advection equation for α_i

$$\frac{\partial \alpha_i}{\partial t} - \sum_{j \in tt} v_{ij} \cdot \nabla \alpha_j = 0$$

- Velocity field

$$v_{ij} = \vartheta_{ij} \cdot n_{ij}$$

with n_{ij} the vector normal to the interface Γ_{ij}

$$\vartheta_{ij} : \mathcal{M}_i(\varepsilon, \gamma) \rightarrow \mathbb{R}$$

0.00	0.00	0.00	0.00	0.00
0.00	0.00	0.00	0.00	0.00
0.00	0.05	0.20	0.07	0.00
0.00	0.75	1.00	0.65	0.00
0.00	0.40	0.98	0.43	0.00

How to get n_{ij}

- **Level-Set function**

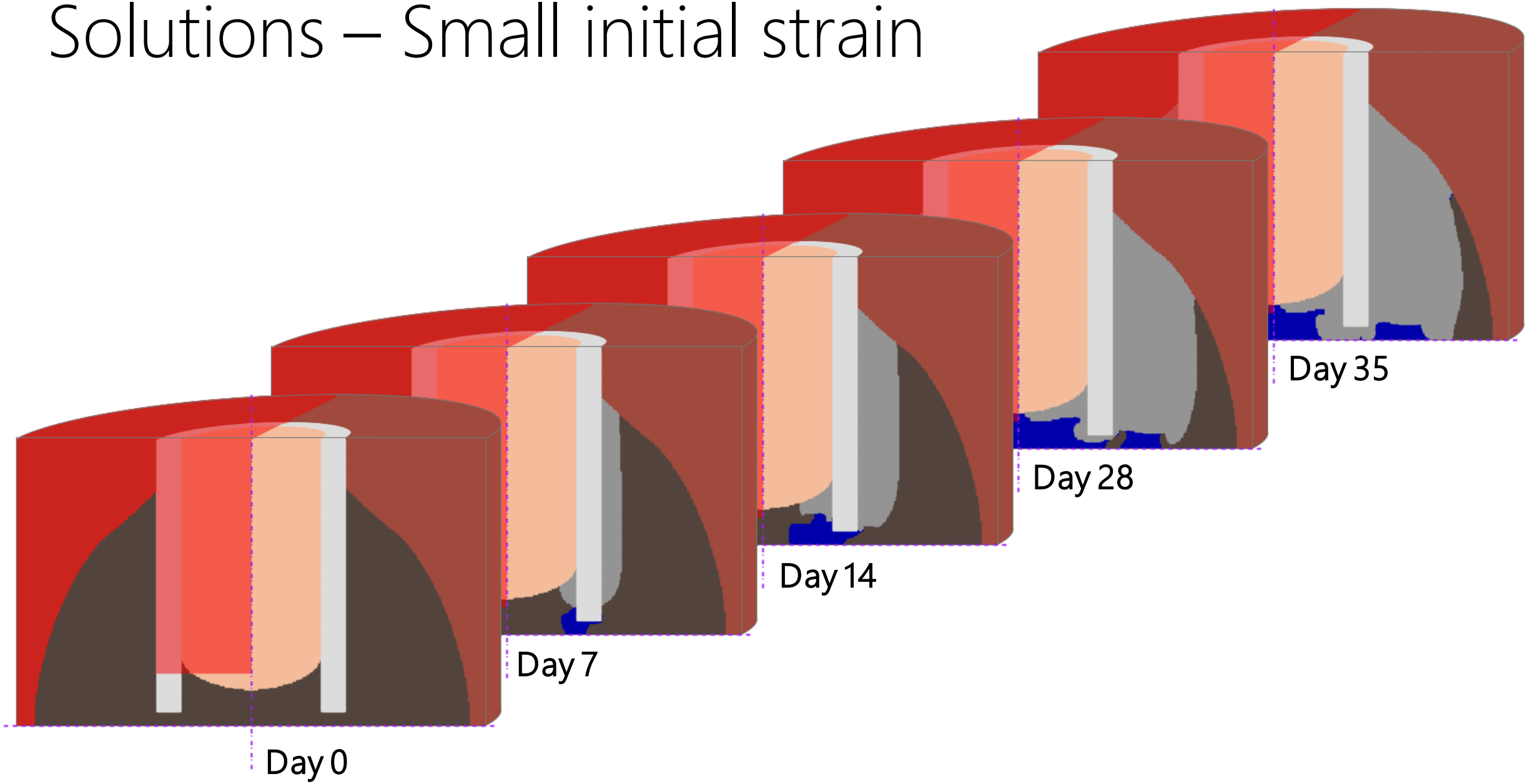
$$\phi_i : \Omega \to \mathbb{R} \quad with \quad \Gamma_i = \{x \in \Omega : \phi_i(x) = 0\}$$

1. $\phi_i^0 = 1.5\Delta x \cdot (\alpha_i - 0.5)$
2. $\phi_i^\tau - \text{sign}(\phi_i^0) \cdot (1 - |\nabla \phi_i^\tau|) = 0$
3. ϕ_i^τ equals signed distance function near Γ_i after few iterations

$$n_{ij} = \frac{\nabla \phi}{|\nabla \phi|} \qquad \kappa_{ij} = \nabla \cdot n_{ij}$$

0.00	0.00	0.00	0.00	0.00
0.00	0.00	0.00	0.00	0.00
0.00	0.05	0.20	0.07	0.00
0.00	0.75	1.00	0.65	0.00
0.00	0.40	0.98	0.43	0.00

Solutions – Small initial strain



Solutions – Big initial strain