A model of bone turnover in the framework of generalized continuum mechanics

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Advances in ELAstoDYNamics of architected materials and BIOmaterials

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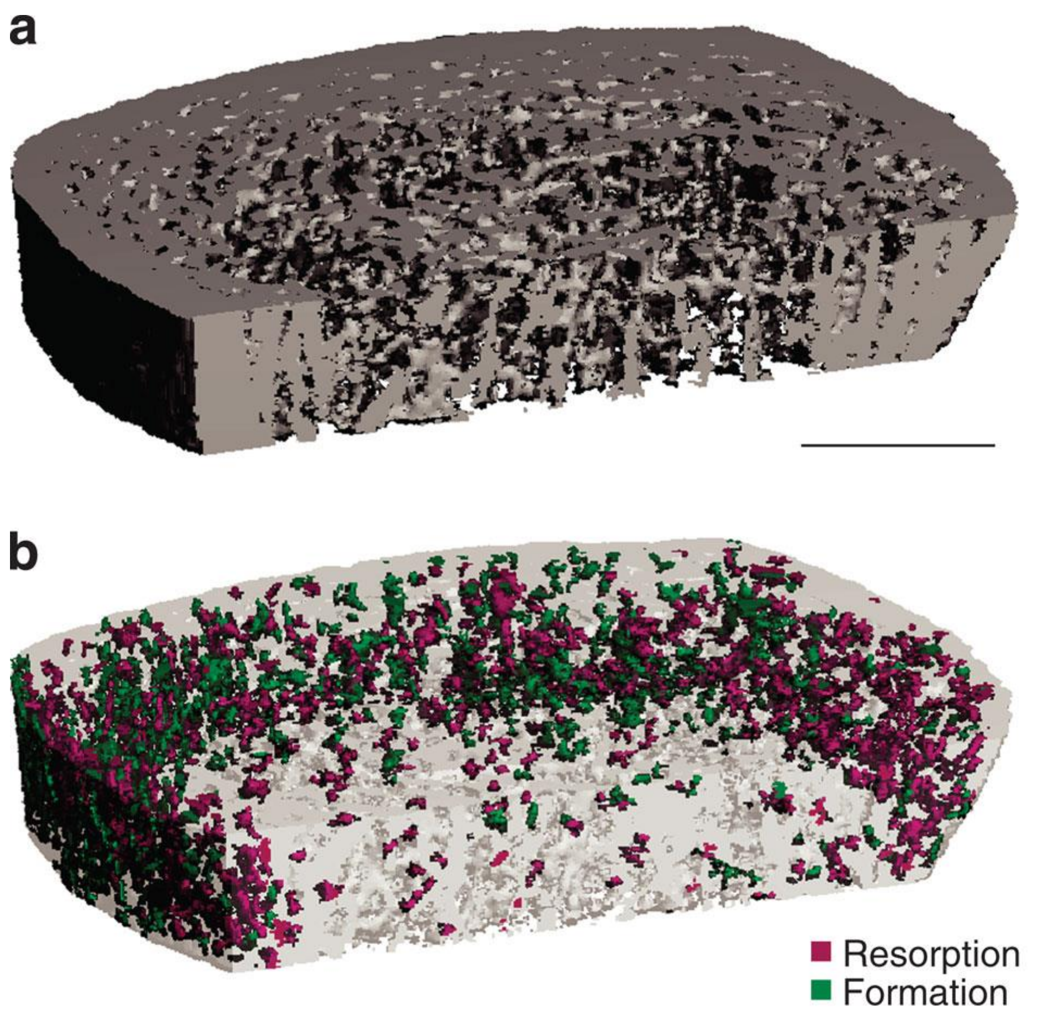
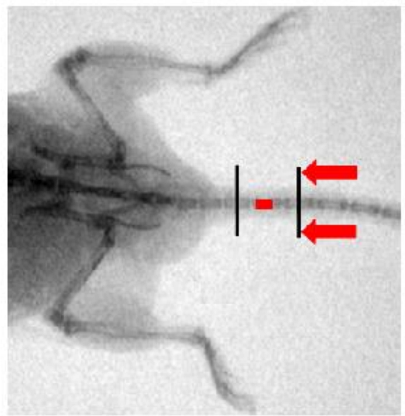
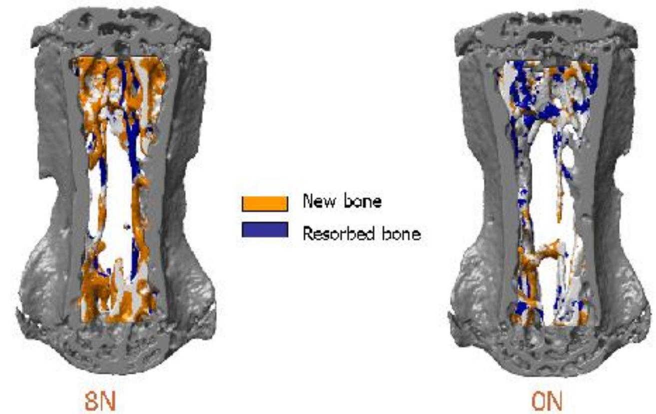
Bone remodeling / What is it about?



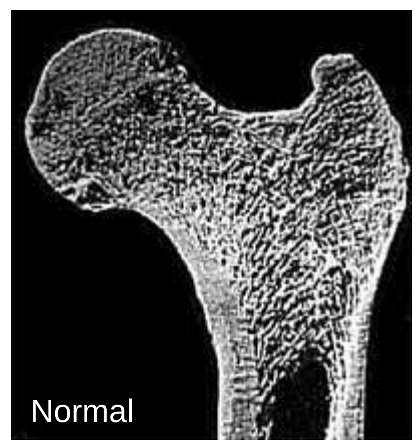
Bone remodeling / What matters?

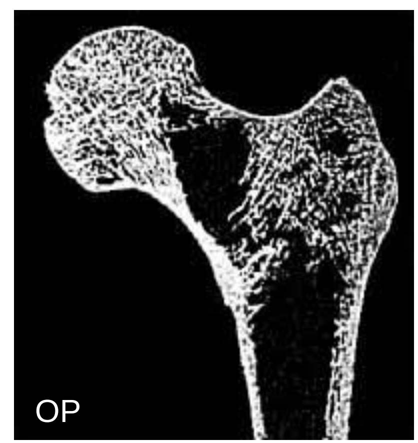
- Mechanics





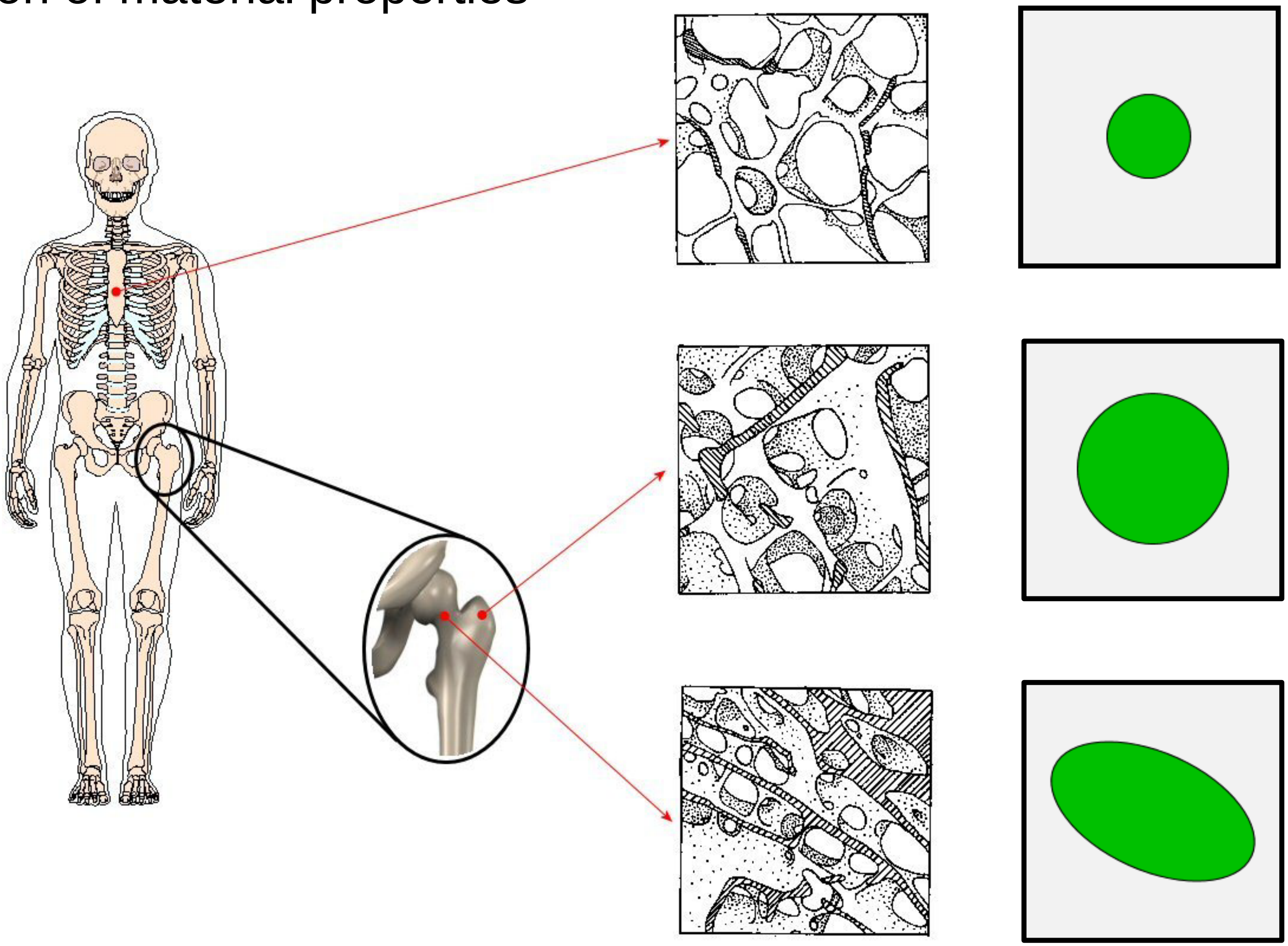
- Biology, Biochemistry



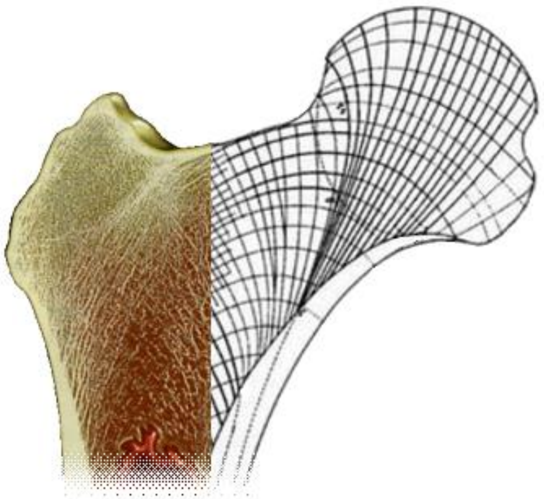


Modeling bone remodeling at the tissue scale

► Evolution of material properties



Modeling bone remodeling at the tissue scale



- Adaptive elasticity Cowin & Hegedus ‘70
- Mechanostat Frost ‘80
- Adaptive bone remodeling Huiskes ‘80
- Optimisation Carter & Fyhrie ‘80, Beaupre & Jacobs ‘90
- Optimal response Lekszycki ‘90
- Volumetric growth Ganghoffer ‘00, Kuhl ‘00
- Microdamage McNamara, Prendergast & Taylor ‘00
- Continuum damage mechanics Doblare & Garcia ‘00
- Generalized continuum mechanics DiCarlo ‘00, Sansalone ‘10
- Mechanobiology dell’Isola, George, Giorgio, Martin, Pivonka, Sansalone, Scheiner… ‘10
- ...

GCM / Extended kinematics

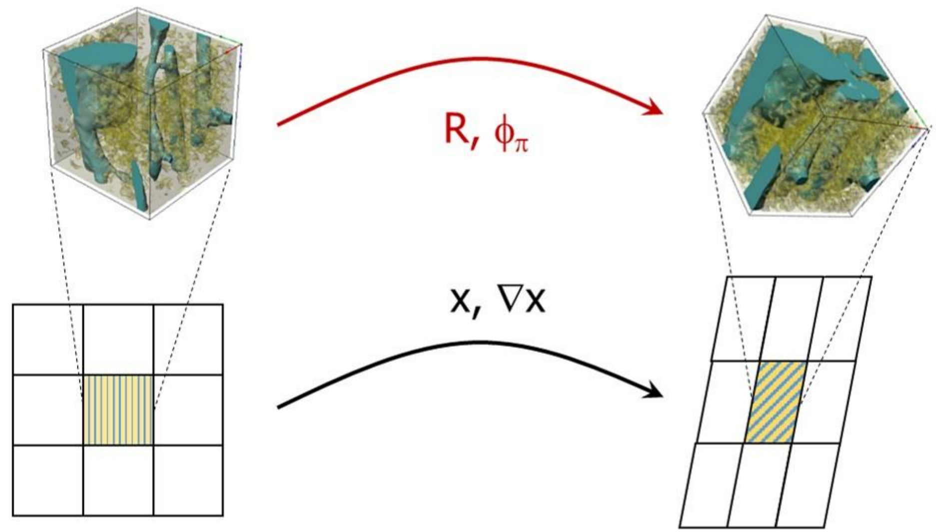
- ► Visible deformation

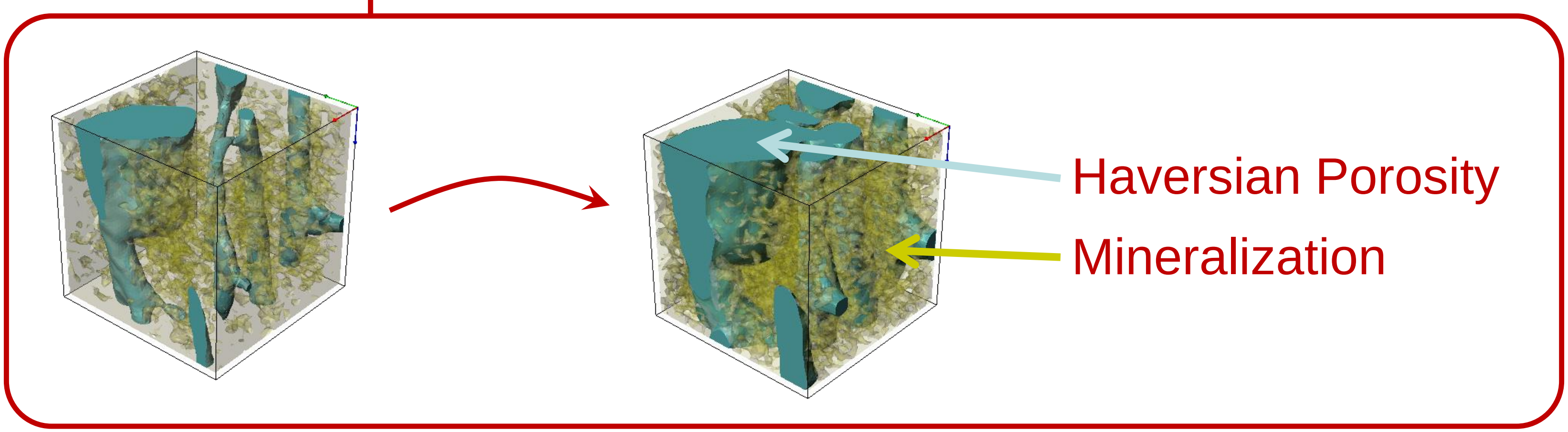
  ∇x

- ► Remodeling

  R … Fabric

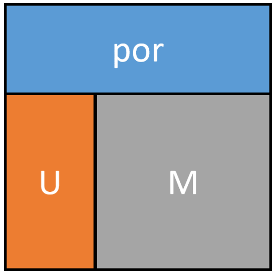
  ϕ_π … Composition





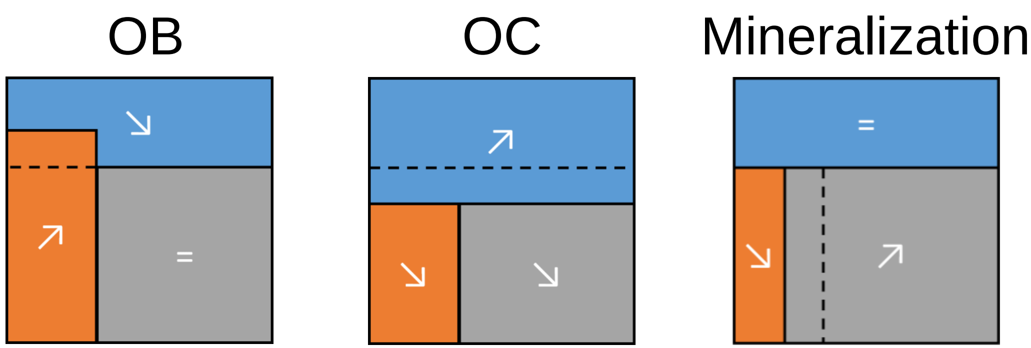
GCM / Kinematics of bone turnover

- ▶ Three-phase material
  - ▶ Haversian porosity ϕ_{por}
  - ▶ Unmineralized matrix ϕ_U
  - ▶ Mineralized matrix ϕ_M



$\phi_{por} + \phi_U + \phi_M = 1$

- ▶ Three-way evolution of bone composition



$$\dot{\phi}_U = \dot{\phi}_U^{OB} + \dot{\phi}_U^{OC} + \dot{\phi}_U^{\chi}$$

$$\dot{\phi}_M = \dot{\phi}_M^{OC} + \dot{\phi}_M^{\chi}$$

with

$$\dot{\phi}_U^{\chi} = -\dot{\phi}_M^{\chi}$$

$$\dot{\phi}_{por} = -(\dot{\phi}_U + \dot{\phi}_M)$$

GCM / Extended balance

- Virtual power principle

Test velocity: $\tilde{\mathfrak{v}} = (\tilde{\mathrm{v}}, \tilde{\mathrm{V}}, \tilde{\nu}_{\mathrm{U}}^{\mathrm{OB}}, \tilde{\nu}_{\mathrm{U}}^{\mathrm{OC}}, \tilde{\nu}_{\mathrm{U}}^{\chi}, \tilde{\nu}_{\mathrm{M}}^{\mathrm{OC}}, \tilde{\nu}_{\mathrm{M}}^{\chi})$

Turnover velocity

$$\overset{\mathrm{i}}{\mathscr{P}}(\tilde{\mathfrak{v}}) + \overset{\mathrm{o}}{\mathscr{P}}(\tilde{\mathfrak{v}}) = 0 \qquad \forall \tilde{\mathfrak{v}}$$

$$\overset{\mathrm{i}}{\mathscr{P}}(\tilde{\mathfrak{v}}) = \int_{\mathcal{P}} \Big(-\mathrm{S} : \nabla \tilde{\mathrm{v}} + \overset{\mathrm{i}}{\mathrm{T}} : \tilde{\mathrm{V}} + \overset{\mathrm{i}}{\lambda}{}_{\mathrm{U}}^{\mathrm{OB}} \tilde{\nu}_{\mathrm{U}}^{\mathrm{OB}} + \overset{\mathrm{i}}{\lambda}{}_{\mathrm{U}}^{\mathrm{OC}} \tilde{\nu}_{\mathrm{U}}^{\mathrm{OC}} + \overset{\mathrm{i}}{\lambda}{}_{\mathrm{U}}^{\chi} \tilde{\nu}_{\mathrm{U}}^{\chi} + \overset{\mathrm{i}}{\lambda}{}_{\mathrm{M}}^{\mathrm{OC}} \tilde{\nu}_{\mathrm{M}}^{\mathrm{OC}} + \overset{\mathrm{i}}{\lambda}{}_{\mathrm{M}}^{\chi} \tilde{\nu}_{\mathrm{M}}^{\chi} \Big)$$

Turnover inner actions

$$\overset{\mathrm{o}}{\mathscr{P}}(\tilde{\mathfrak{v}}) = \int_{\mathcal{P}} \Big(\mathrm{b} \cdot \tilde{\mathrm{v}} + \overset{\mathrm{o}}{\mathrm{T}} : \tilde{\mathrm{V}} + \overset{\mathrm{o}}{\lambda}{}_{\mathrm{U}}^{\mathrm{OB}} \tilde{\nu}_{\mathrm{U}}^{\mathrm{OB}} + \overset{\mathrm{o}}{\lambda}{}_{\mathrm{U}}^{\mathrm{OC}} \tilde{\nu}_{\mathrm{U}}^{\mathrm{OC}} + \overset{\mathrm{o}}{\lambda}{}_{\mathrm{U}}^{\chi} \tilde{\nu}_{\mathrm{U}}^{\chi} + \overset{\mathrm{o}}{\lambda}{}_{\mathrm{M}}^{\mathrm{OC}} \tilde{\nu}_{\mathrm{M}}^{\mathrm{OC}} + \overset{\mathrm{o}}{\lambda}{}_{\mathrm{M}}^{\chi} \tilde{\nu}_{\mathrm{M}}^{\chi} \Big) + \int_{\partial \mathcal{P}} (\mathrm{t}_{\partial} \cdot \tilde{\mathrm{v}})$$

Turnover outer actions

GCM / Extended balance

► Balance equations

$$\mathrm{div}\,\mathrm{S} + \mathrm{b} = 0\,, \quad \mathrm{S}\,\mathrm{n}_\partial = \mathrm{t}_\partial$$

$$\overset{\mathrm{i}}{\mathrm{T}} + \overset{\mathrm{o}}{\mathrm{T}} = 0$$

$$\overset{\mathrm{i}}{\lambda}{}^{\mathsf{OB}}_{\mathsf{U}} + \overset{\mathrm{o}}{\lambda}{}^{\mathsf{OB}}_{\mathsf{U}} = 0$$

$$\overset{\mathrm{i}}{\lambda}{}^{\mathsf{OC}}_{\mathsf{U}} + \overset{\mathrm{o}}{\lambda}{}^{\mathsf{OC}}_{\mathsf{U}} = 0$$

$$\overset{\mathrm{i}}{\lambda}{}^{\mathsf{OC}}_{\mathsf{M}} + \overset{\mathrm{o}}{\lambda}{}^{\mathsf{OC}}_{\mathsf{M}} = 0$$

$$\Delta\overset{\mathrm{i}}{\lambda}{}^{\chi} + \Delta\overset{\mathrm{o}}{\lambda}{}^{\chi} = 0 \quad \text{with: } \Delta\overset{\mathrm{i}}{\lambda}{}^{\chi} = \overset{\mathrm{i}}{\lambda}{}^{\chi}_{\mathsf{M}} - \overset{\mathrm{i}}{\lambda}{}^{\chi}_{\mathsf{U}}\,, \quad \Delta\overset{\mathrm{o}}{\lambda}{}^{\chi} = \overset{\mathrm{o}}{\lambda}{}^{\chi}_{\mathsf{M}} - \overset{\mathrm{o}}{\lambda}{}^{\chi}_{\mathsf{U}}$$

GCM / Constitutive theory

► Free energy density

$$\psi = \widehat{\psi}(\mathrm{E}, \mathrm{R}, \phi_{\mathsf{U}}, \phi_{\mathsf{M}}) \quad = \widehat{\psi}_{\mathsf{mech}}(\mathrm{E}, \mathrm{R}, \phi_{\mathsf{U}}, \phi_{\mathsf{M}}) + \widehat{\psi}_{\mathrm{chem}}(\phi_{\mathsf{U}}, \phi_{\mathsf{M}})$$

$$\psi_{\mathsf{mech}} = \frac{1}{2}\,\mathrm{E} \cdot \mathbb{C}\,\mathrm{E} \qquad \psi_{\mathsf{chem}} = \sum_{\mathsf{phases}} \phi_\pi\, \bar{\mu}_\pi$$

► Extended dissipation inequality

$$\overset{\circ}{\mathscr{P}}(\mathfrak{v}) - \dot{\psi} \geq 0$$

$$\overset{+}{\mathrm{T}} : \dot{\mathrm{R}}\,\mathrm{R}^{\mathsf{T}} + \overset{+}{\lambda}{}_{\mathsf{U}}^{\mathsf{OB}}\,\dot{\phi}_{\mathsf{U}}^{\mathsf{OB}} + \overset{+}{\lambda}{}_{\mathsf{U}}^{\mathsf{OC}}\,\dot{\phi}_{\mathsf{U}}^{\mathsf{OC}} + \overset{+}{\lambda}{}_{\mathsf{M}}^{\mathsf{OC}}\,\dot{\phi}_{\mathsf{M}}^{\mathsf{OC}} + \Delta\overset{+}{\lambda}{}^{x}\,\dot{\phi}_{\mathsf{M}}^{x} \geq 0$$

$$\overset{+}{\lambda} = \overset{\circ}{\lambda} - \partial\psi$$

Turnover dissip. actions

Focusing on biochemistry

- Working hypothesis
  - No strain $\Rightarrow$ $\psi = \psi_{\text{chem}}\,,\quad \sum \overset{+}{\lambda}\,\dot{\phi} \geq 0$
  - Linear dissipation $\Rightarrow$ $\overset{+}{\lambda} = d\,\dot{\phi}$

Resistance to turnover $\in \mathbb{R}^+$

- Evolution laws

$$\begin{cases} \dot{\phi}_{\mathsf{U}}^{\mathsf{OB}} = \dfrac{1}{d_{\mathsf{U}}^{\mathsf{OB}}}\left(\overset{\circ}{\lambda}{}_{\mathsf{U}}^{\mathsf{OB}} - \lambda_{\mathsf{U}}^{\mu}\right) \\ \dot{\phi}_{\mathsf{U}}^{\mathsf{OC}} = \dfrac{1}{d_{\mathsf{U}}^{\mathsf{OC}}}\left(\overset{\circ}{\lambda}{}_{\mathsf{U}}^{\mathsf{OC}} - \lambda_{\mathsf{U}}^{\mu}\right) \\ \dot{\phi}_{\mathsf{M}}^{\mathsf{OC}} = \dfrac{1}{d_{\mathsf{M}}^{\mathsf{OC}}}\left(\overset{\circ}{\lambda}{}_{\mathsf{M}}^{\mathsf{OC}} - \lambda_{\mathsf{M}}^{\mu}\right) \\ \dot{\phi}_{\mathsf{M}}^{\chi} = \dfrac{1}{d^{\chi}}\left(\Delta\overset{\circ}{\lambda}{}^{\chi} - \Delta\lambda^{\mu}\right) \\ \dot{\phi}_{\mathsf{U}}^{\chi} = -\dot{\phi}_{\mathsf{M}}^{\chi} \end{cases} \Rightarrow \begin{cases} \dot{\phi}_{\mathsf{U}} = \dot{\phi}_{\mathsf{U}}^{\mathsf{OB}} + \dot{\phi}_{\mathsf{U}}^{\mathsf{OC}} + \dot{\phi}_{\mathsf{U}}^{\chi} \\ \dot{\phi}_{\mathsf{M}} = \dot{\phi}_{\mathsf{M}}^{\mathsf{OC}} + \dot{\phi}_{\mathsf{M}}^{\chi} \end{cases}$$

$$\dot{\phi} = \frac{1}{d}\left(\overset{\circ}{\lambda} - \partial\psi\right)$$

Focusing on biochemistry

$$\dot{\phi} = \frac{1}{d}\left(\overset{\circ}{\lambda} - \partial\psi\right)$$

- Resistance to remodeling:

Cell activity

$$d^{cell} = \frac{\bar{d}^{cell}}{[cell] \cdot f(\phi)}$$

Mineralization

$$d^{\chi} = \frac{\bar{d}^{\chi}}{\phi_U \, \phi_M}$$

$$[cell] = \beta^{cell} \, S_v$$

- External actions:

Cell activity

$\lambda^{OB} > 0$ ⇨ bone ↗

$\lambda^{OC} < 0$ ⇨ bone ↘

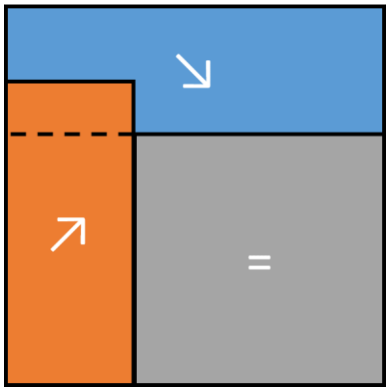
Mineralization

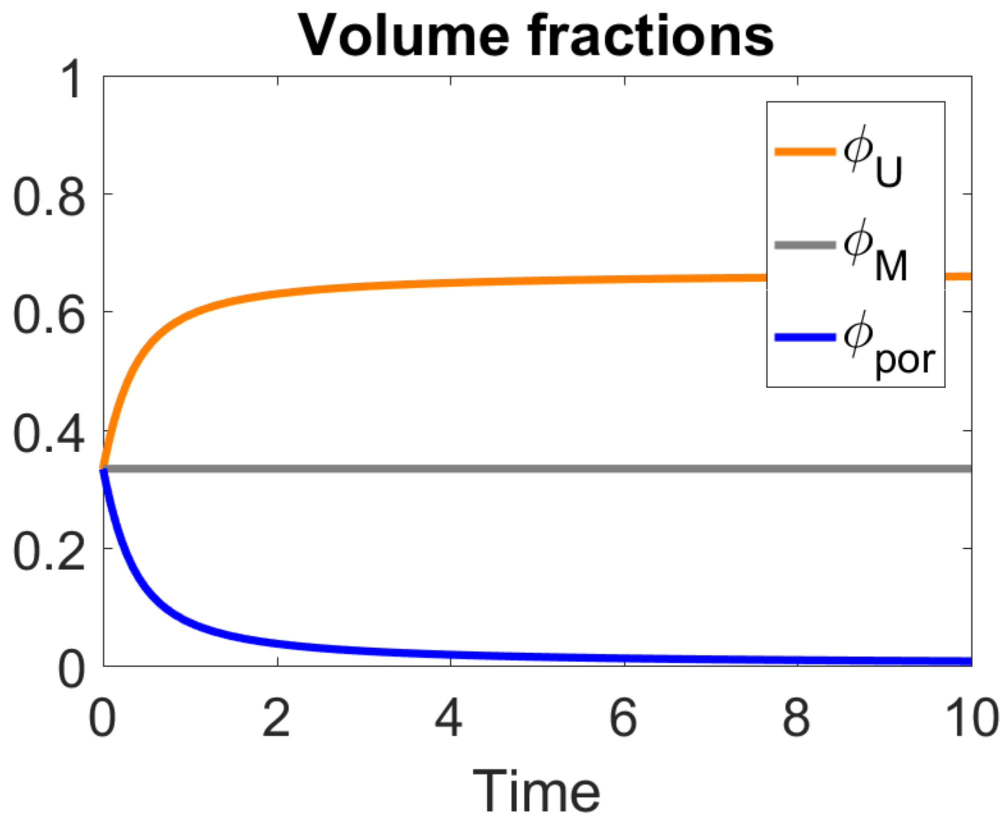
$\Delta\lambda^{\chi} > 0$ ⇨ mineraliz.

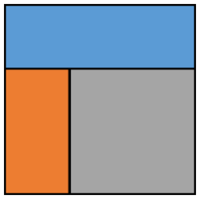
$\Delta\lambda^{\chi} < 0$ ⇨ demineraliz.

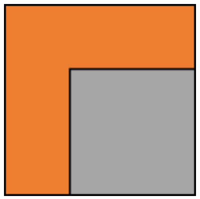
Individual mechanisms of remodeling

- ▶ Only OB



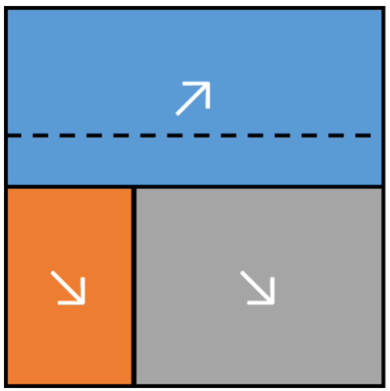


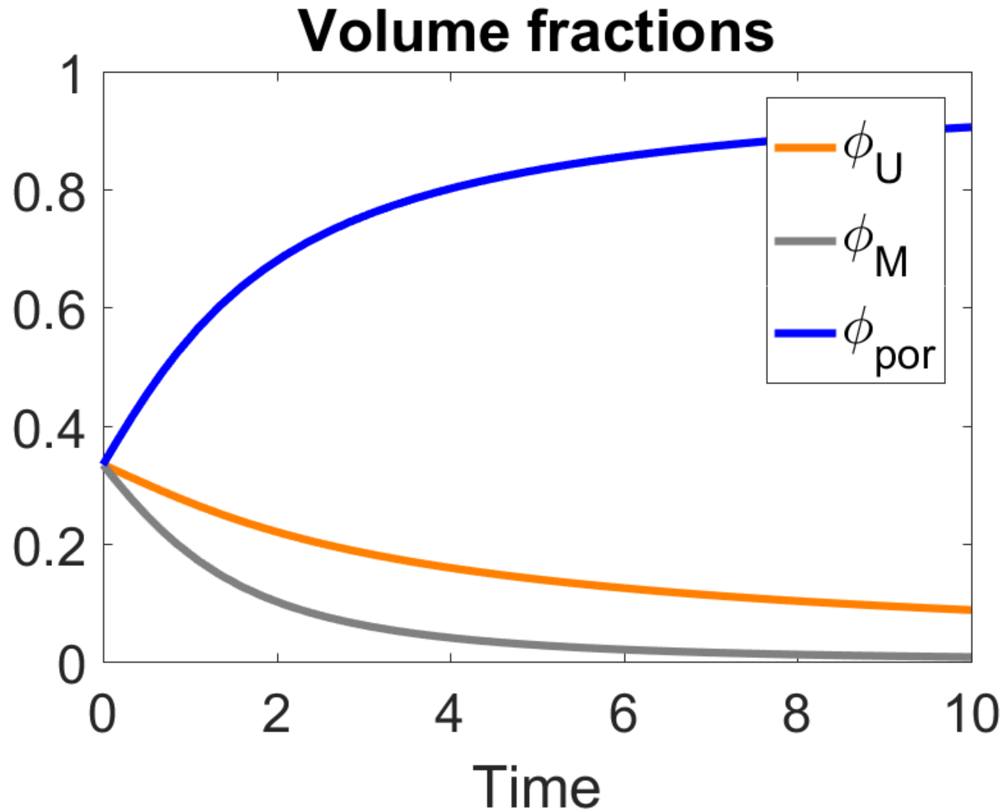


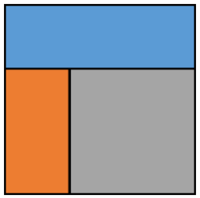


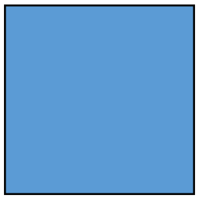
Individual mechanisms of remodeling

▶ Only OC



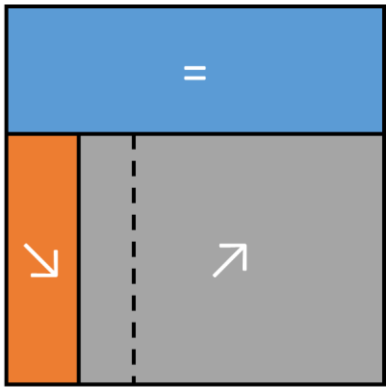


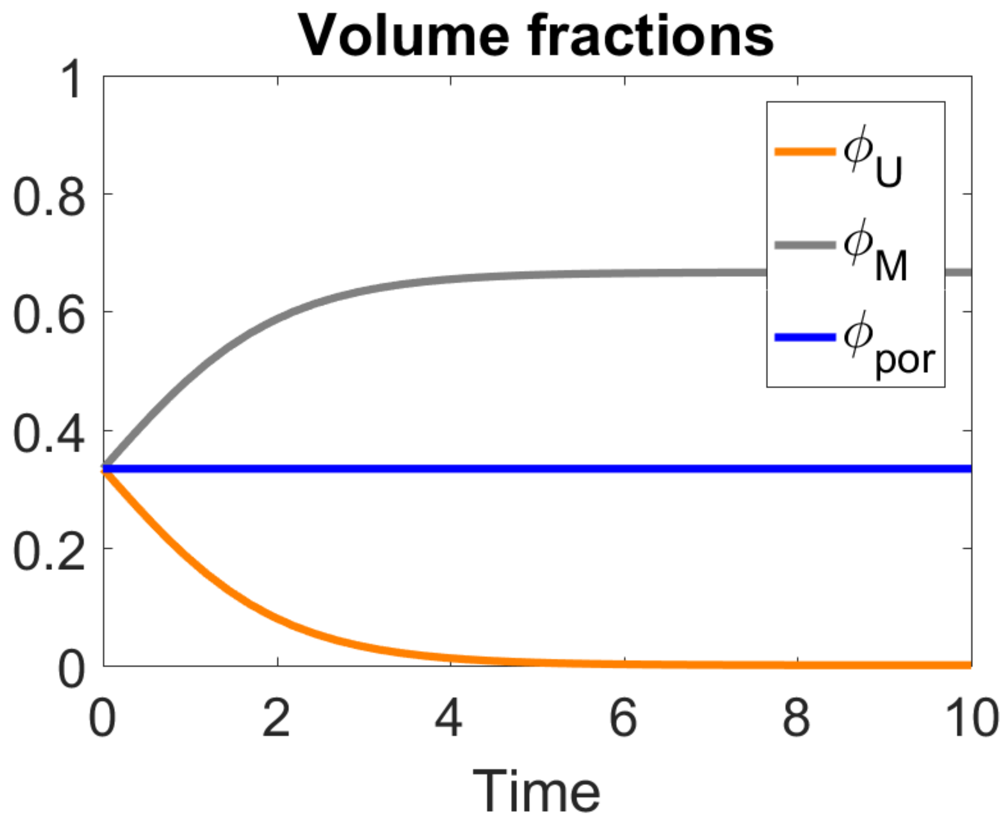


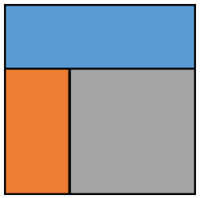


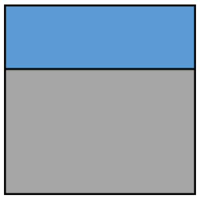
Individual mechanisms of remodeling

▶ Only Mineraliz.



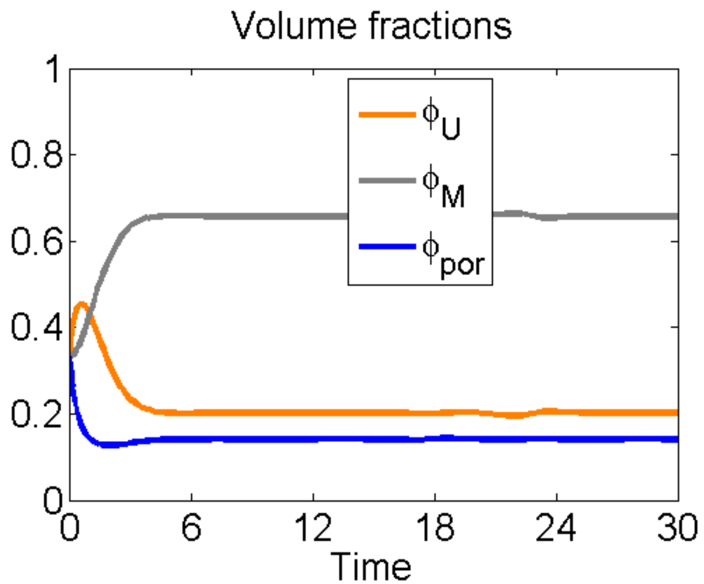






Combined mechanisms of remodeling

Balanced OB and OC activity
+ Mineralization



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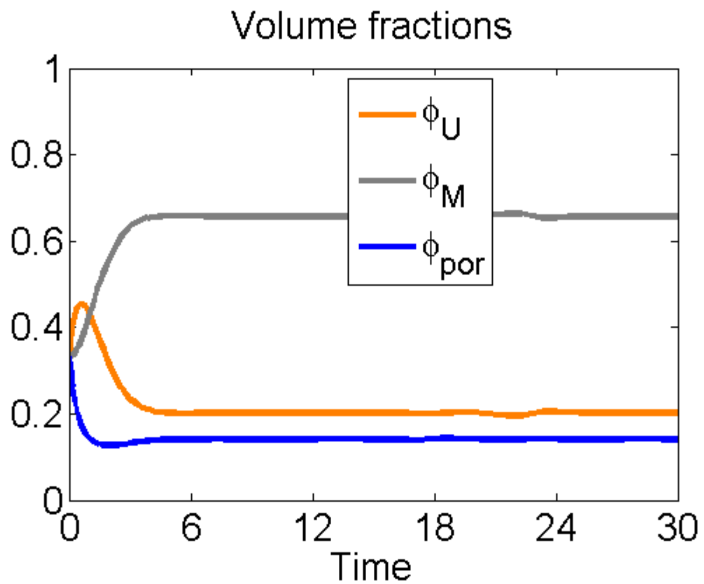
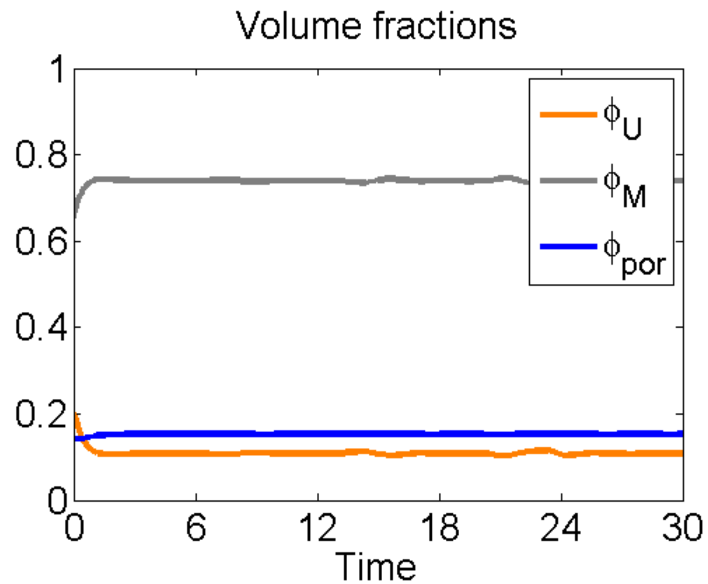


Mineralization ↗



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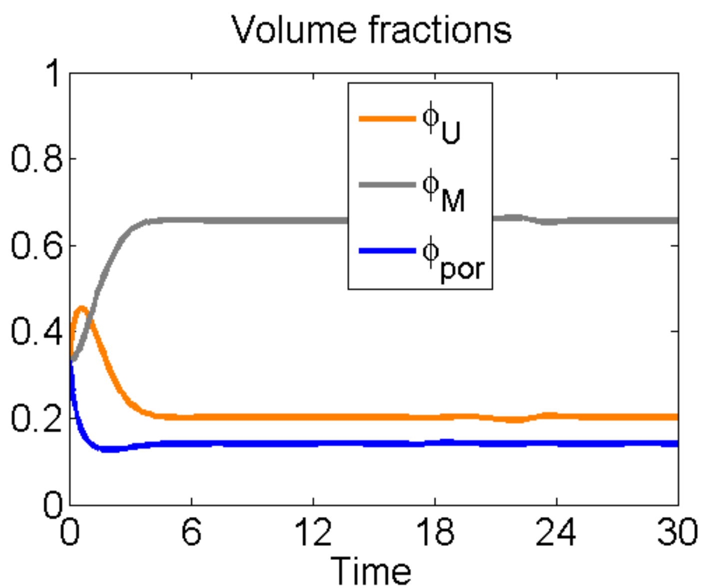
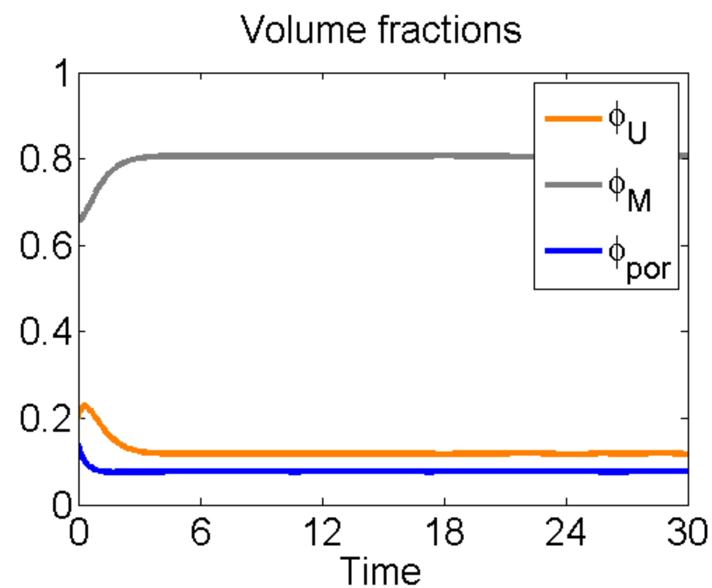


OB activity ↗



Combined mechanisms of remodeling

Balanced OB and OC activity
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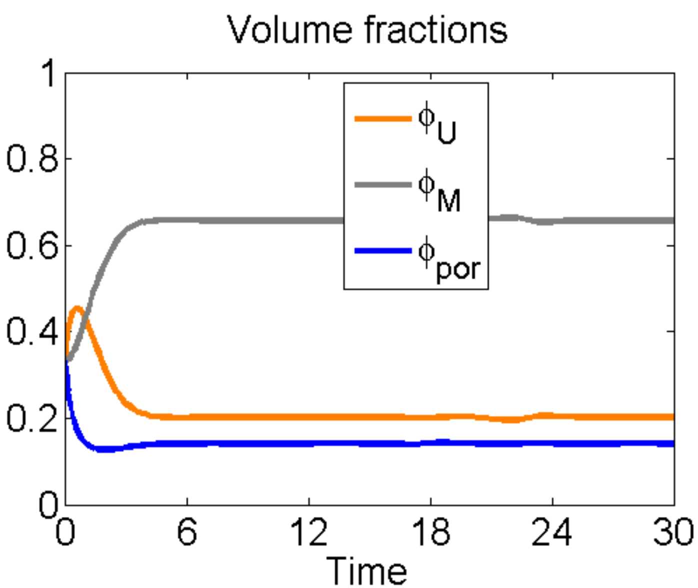
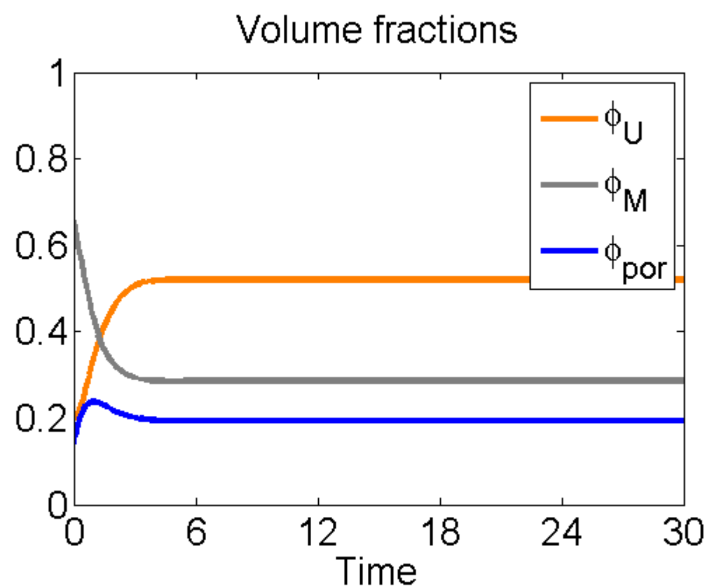
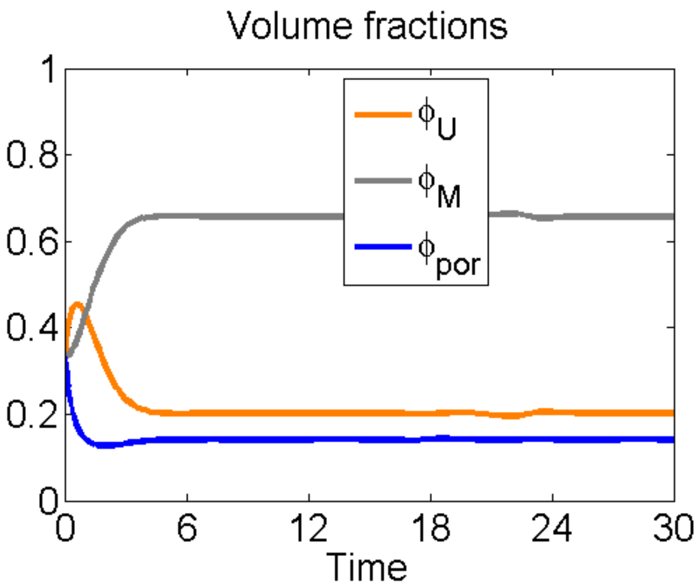


OC activity ↗

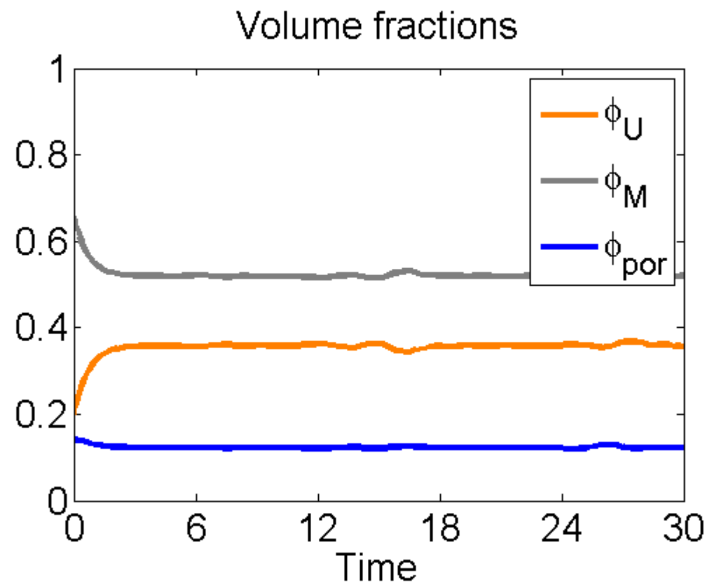


Combined mechanisms of remodeling

Balanced OB and OC activity
+ Mineralization

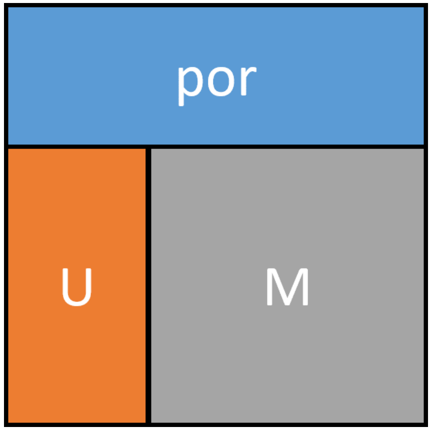


OB, OC activity ↗



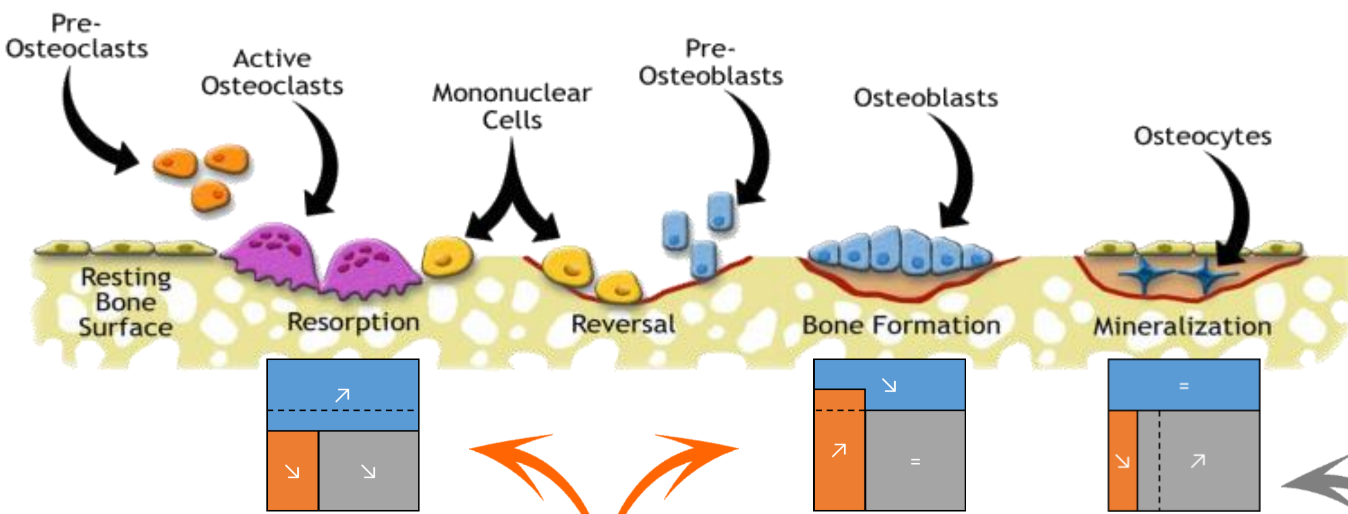
Conclusions

- ► Bone turnover ... 3 competing mechanisms
  - ► Bone apposition by OB
  - ► Bone resorption by OC
  - ► Bone mineralization
- ► Modeling framework
  - ► Generalized Continuum Mechanics
  - ► Thermodynamic consistency
- ► Numerical results
  - ► Individual remodeling mechanisms
  - ► Combined remodeling mechanisms
  - ► Need for mecanobiology coupling

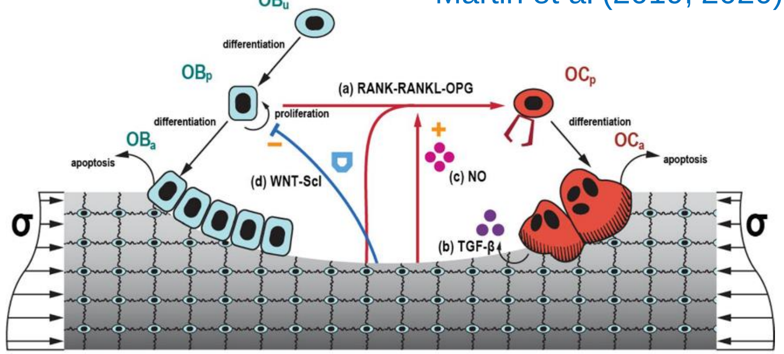


Perspectives

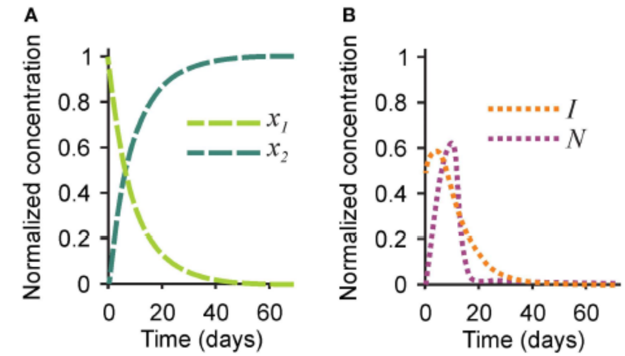
► Cell and Mineralization dynamics ←→ Macroscale model



Martin et al (2019, 2020)



Komarova et al (FCell 2015)



Acknowledgements

- People
  - M. Martin, G. Haïat, T. Lemaire
  - P. Pivonka
- Funding

- Refs
  - Madge et al, JMMB 2019, BMMB 2019, Bone 2020
  - Sansalone et al, MMS (accepted)

Thank you for your attention