Formal Analysis of Bone Clinical Pathologies

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joint work with
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Outline

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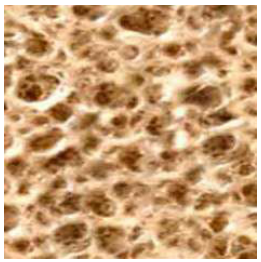
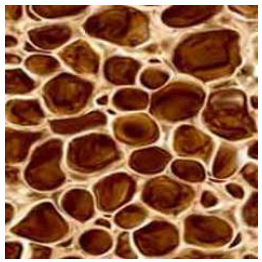
Bone remodeling

- **Bone remodeling (BR)** is the process by which *aged bone is continuously renewed in a balanced alternation of bone resorption and formation*
- BR is driven by **osteoclasts** (the diggers) and **osteoblasts** (the fillers), forming *Basic Multi-cellular Units (BMUs)*
- Imbalances between resorption and formation lead to bone pathologies (e.g. in osteoporosis *resorption* $>$ *formation*)

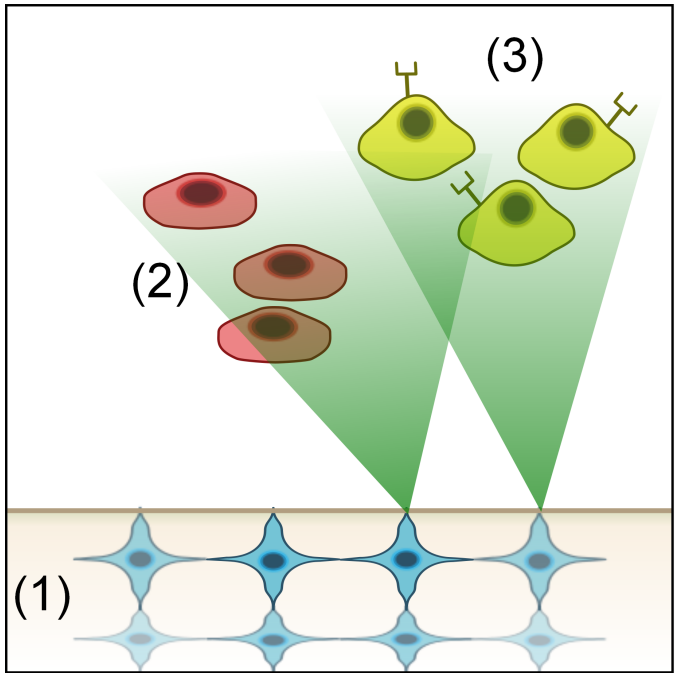


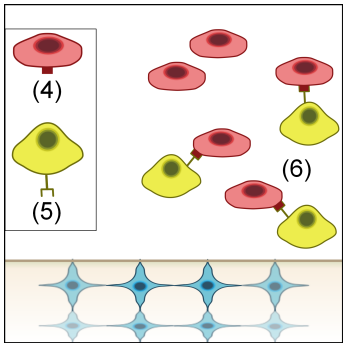
Normal

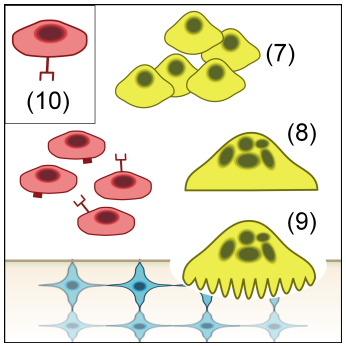


Osteoporotic

Key events in BR (1/2)

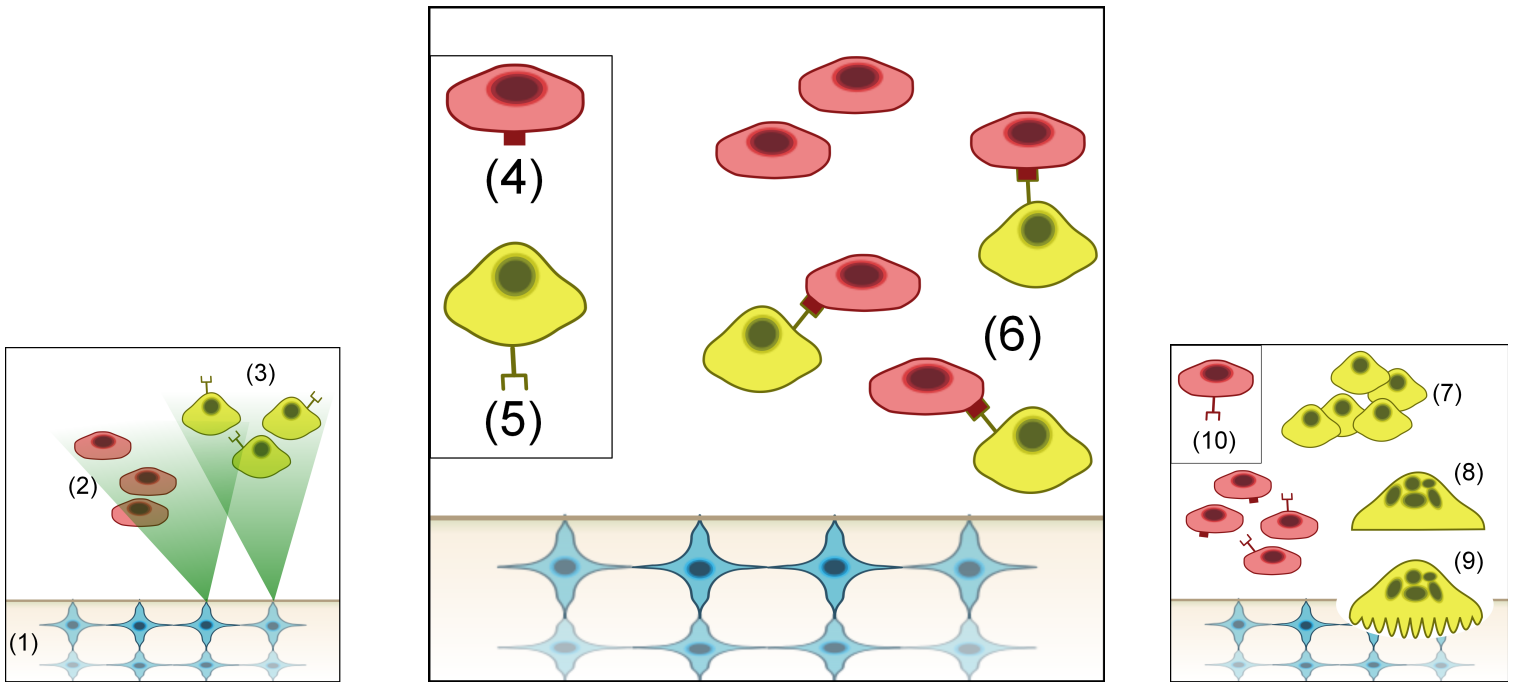






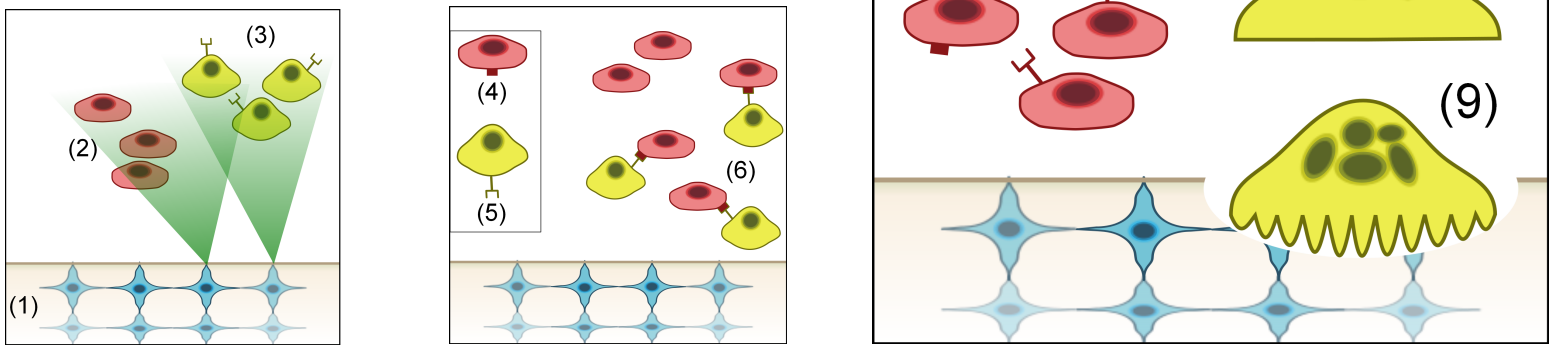
Osteocytes$^{(1)}$ send signals to the fluid part, activating **Pre-osteoblasts**$^{(2)}$ (Pb) and **Pre-osteoclasts**$^{(3)}$ (Pc)

Key events in BR (1/2)



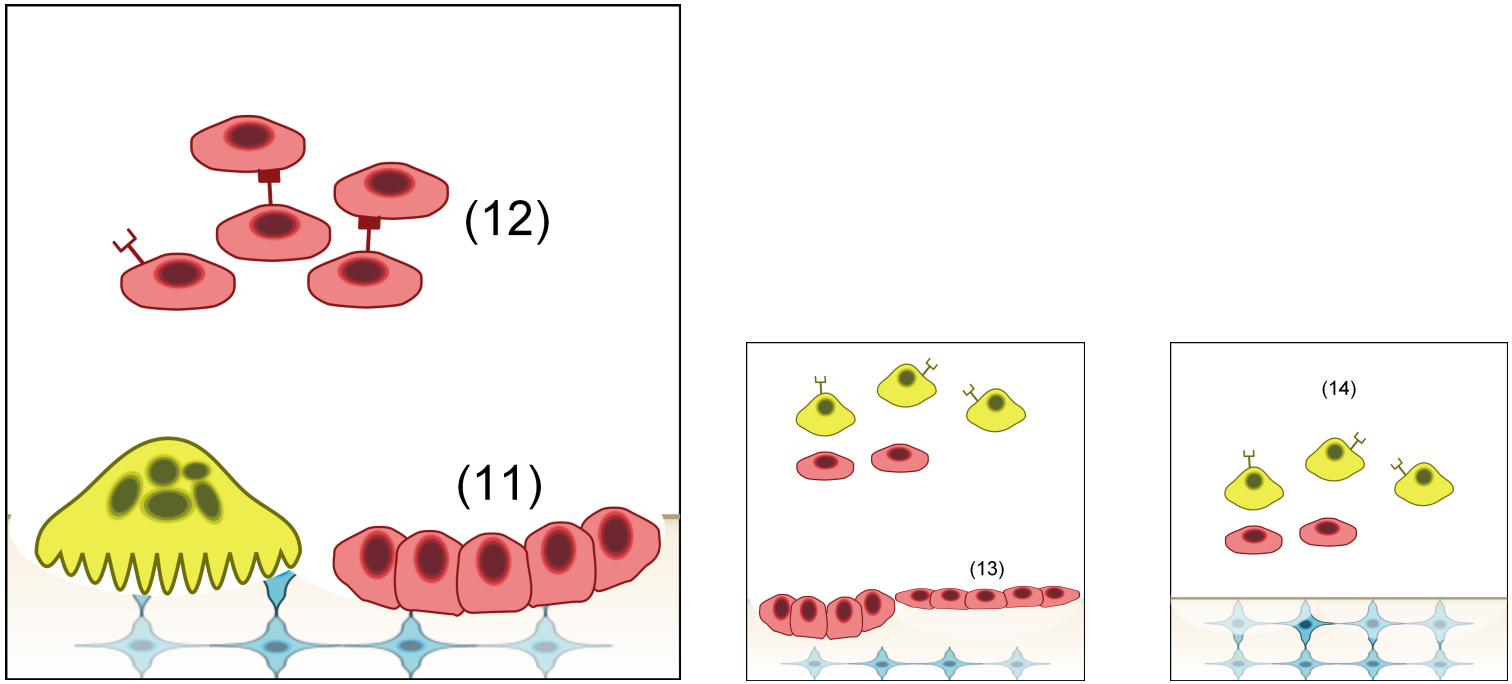
*Pb*s express **RANKL**$^{(4)}$. *Pc*s express **RANK**$^{(5)}$ receptor.

Key events in BR (1/2)



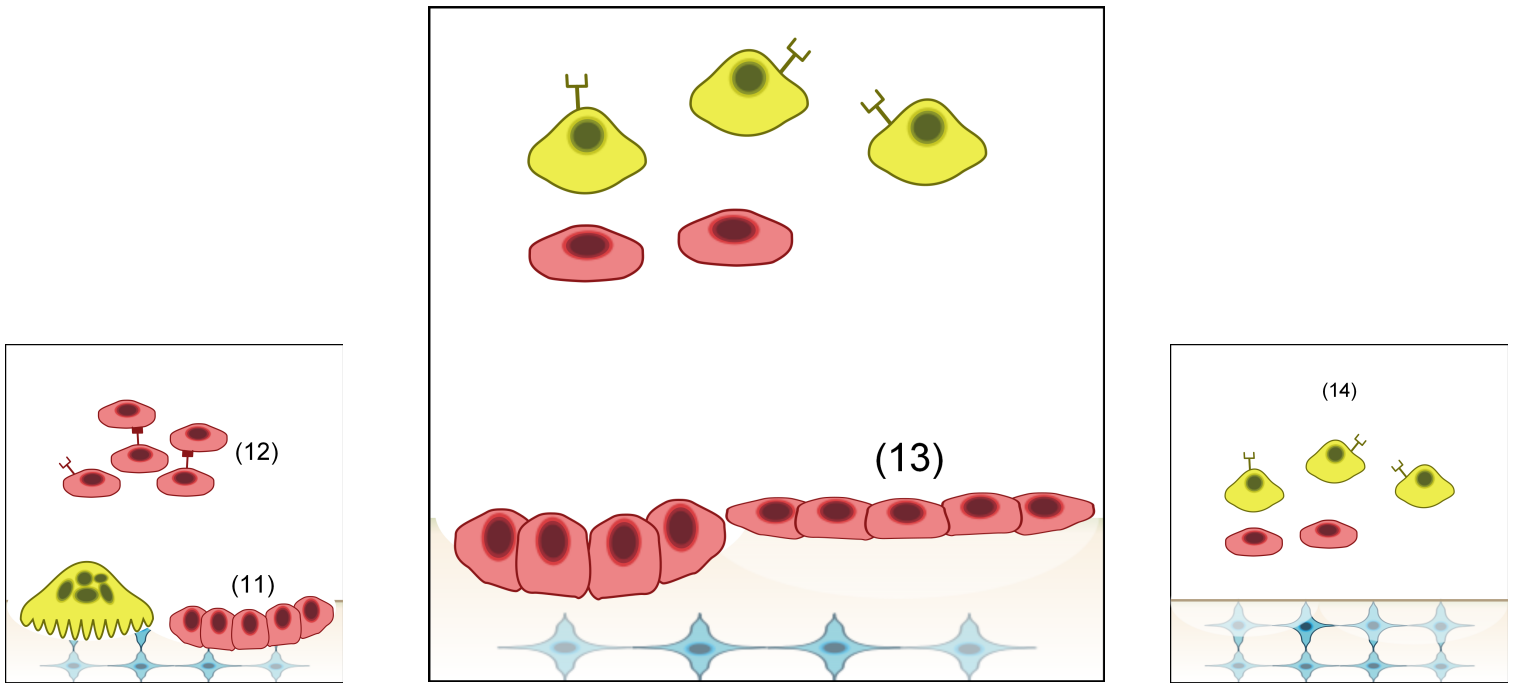
RANK/RANKL binding(6) induces **Pcs' proliferation**(7). *Pcs* enlarge and fuse, forming mature **Osteoclasts**(8) which start bone **Resorption**(9). Mature osteoblasts express the decoy receptor **OPG**(10).

Key events in BR (2/2)



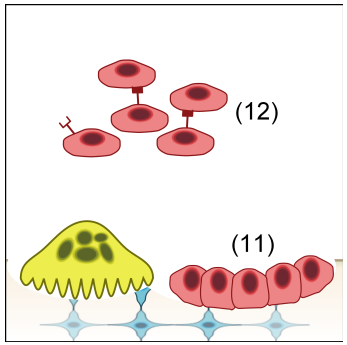
Osteoblasts start the bone **Formation**(11) process. **RANKL/OPG binding**(12) inhibits RANKL, protecting bone from excessive resorption.

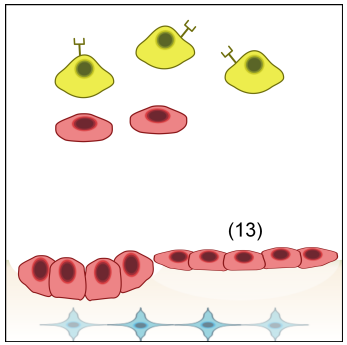
Key events in BR (2/2)

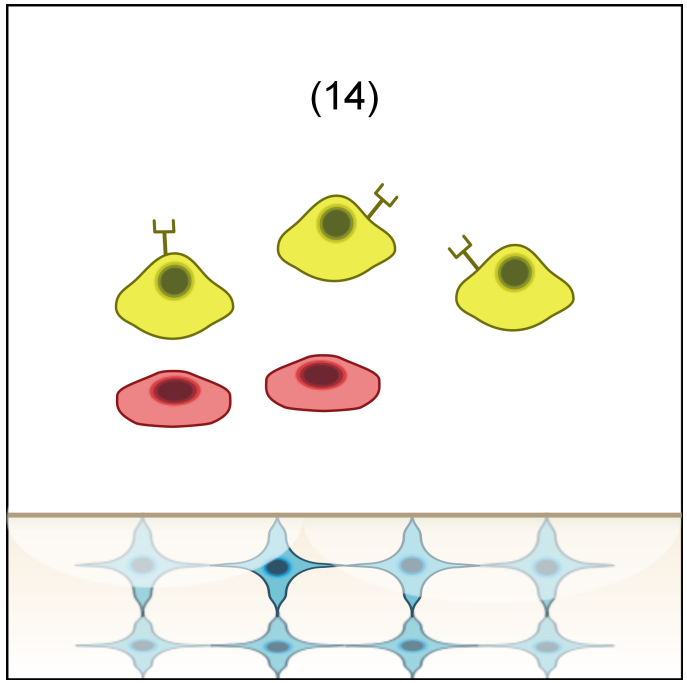


During the **Mineralization**(13) process, osteoids secreted by osteoblasts calcify.

Key events in BR (2/2)







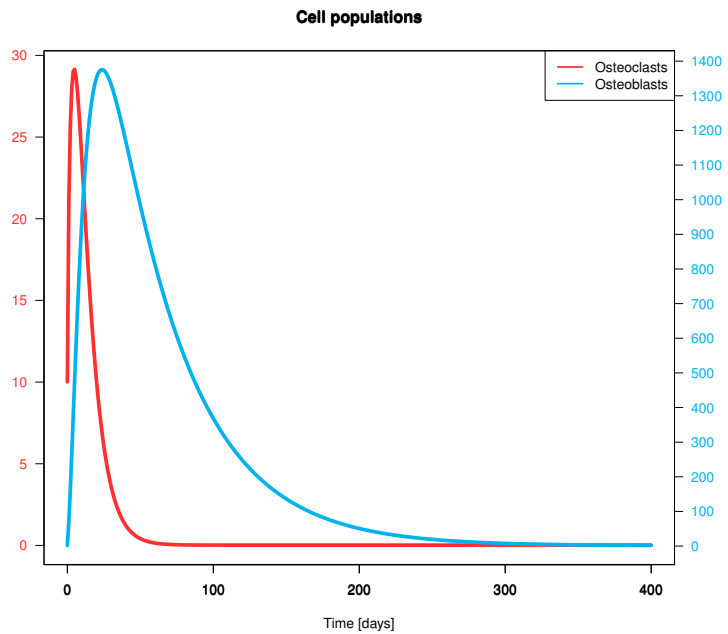
Resting$^{(14)}$: the initial situation is re-established

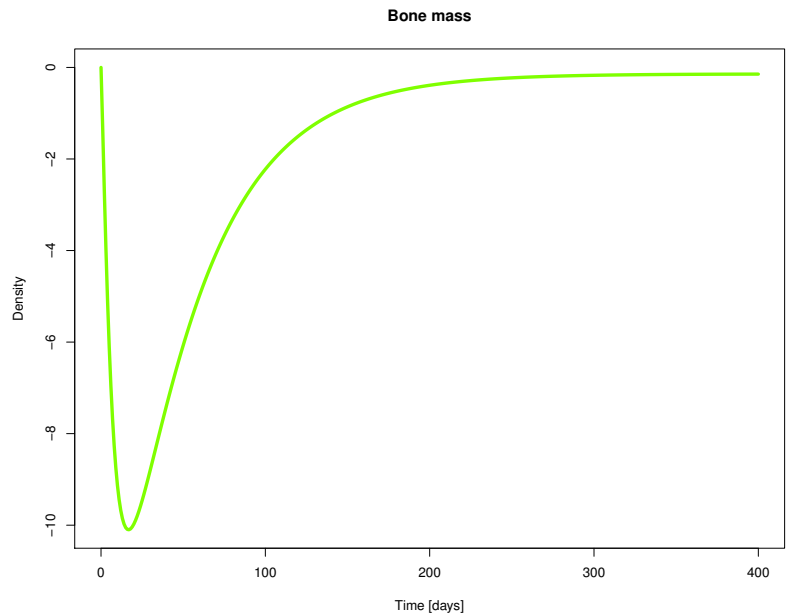
Outline

ODE model

$$\dot{x_1} = \alpha_1 {x_1}^{g_{11}} {x_2}^{g_{21}} - \beta_1 x_1$$
$$\dot{x_2} = \alpha_2 {x_1}^{g_{12}} {x_2}^{g_{22}} - \beta_2 x_2$$
$$\dot{z} = -k_1 x_1 + k_2 x_2$$

- Osteoclasts
- Osteoblasts
- Bone mass





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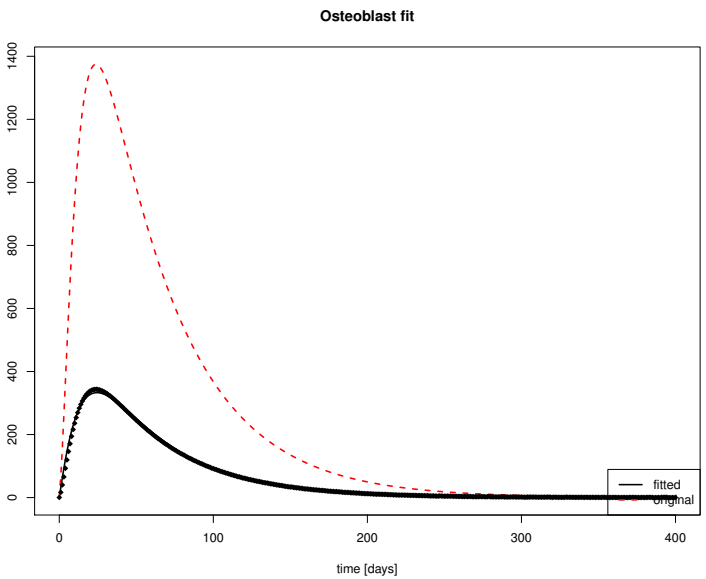
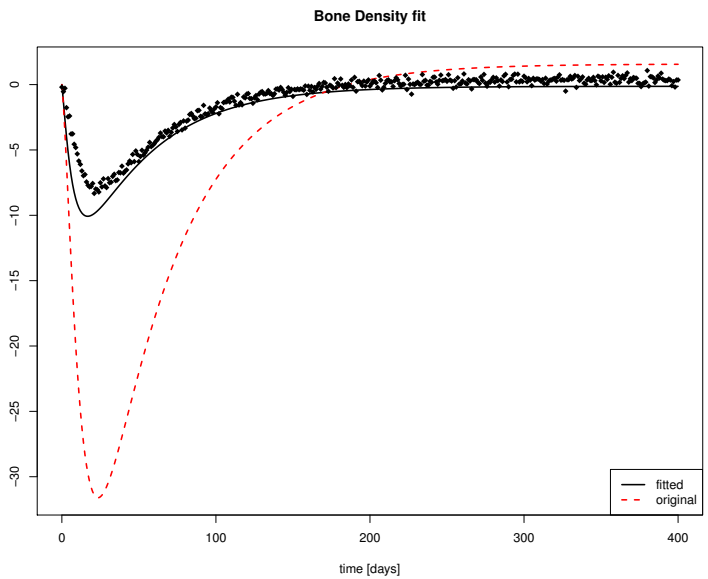
1. **Modeling a portion of BMU**
   - Parameter sensitivity and identifiability
   - New parameters after model fitting operations





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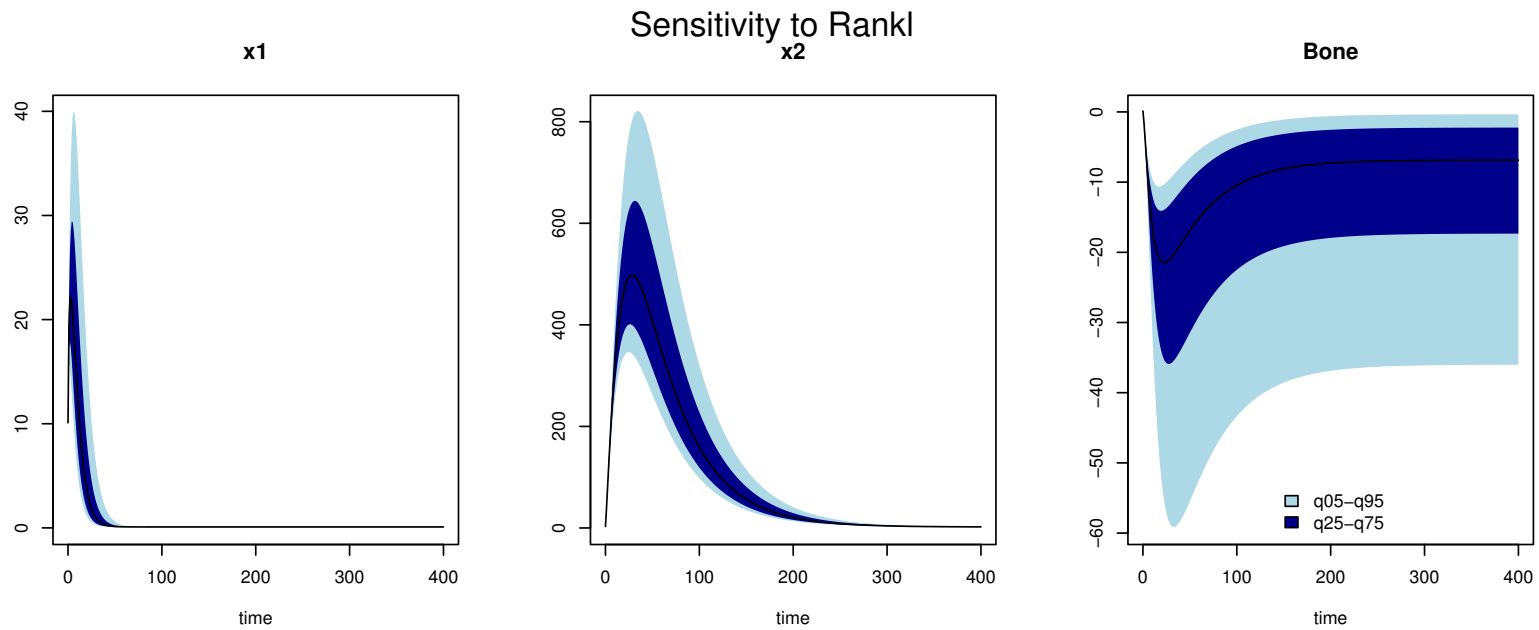
2. RANKL and aging paramaters

- *RANKL* strongly affects the resorption phase
- *Aging* expressed as reduced cellular activity



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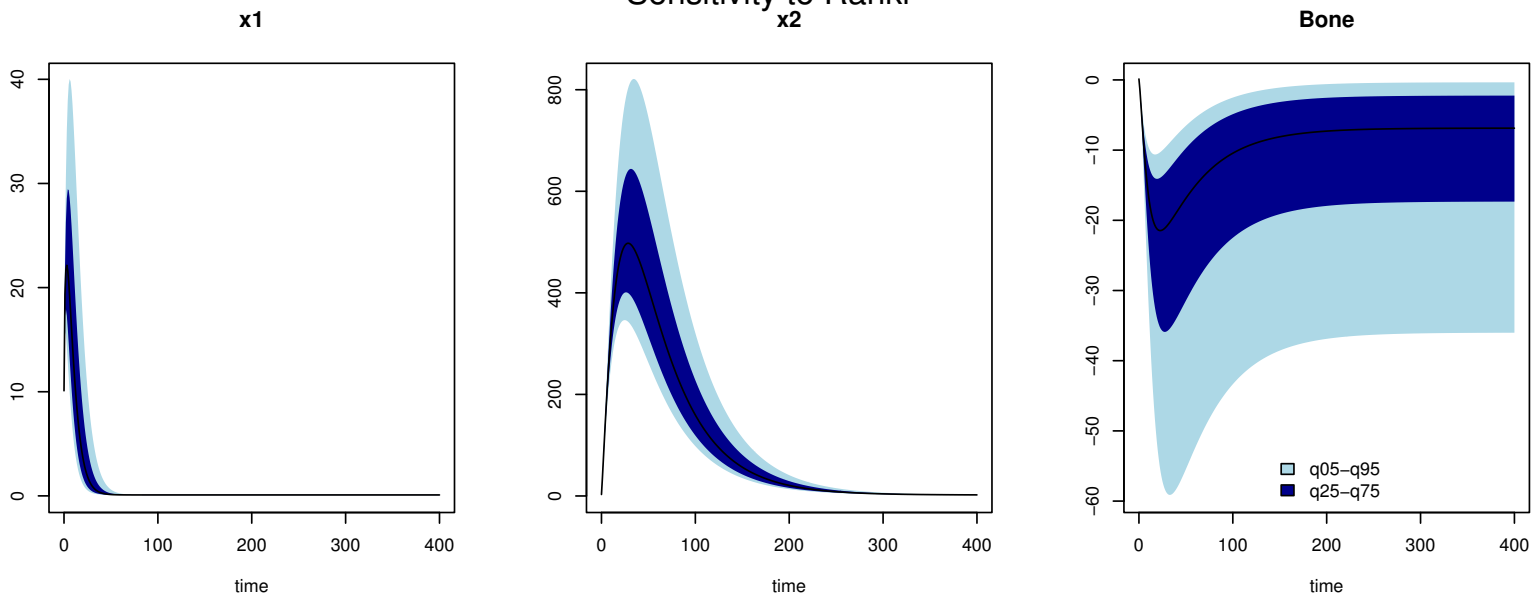
New model

$$\dot{x_1} = \alpha_1 x_1^{g_{11}} x_2^{g_{21}/\underline{\mathbf{rankl}}} - \beta_1 x_1$$
$$\dot{x_2} = \alpha_2 x_1^{g_{12}} x_2^{g_{22}} - \beta_2 x_2$$
$$\dot{z} = -\underline{\mathbf{ag}} k_1 x_1 + \underline{\mathbf{ag}} k_2 x_2$$

Sensitivity to Rankl



Stochastic model

From the modified ODE, we derive a CTMC model for the PRISM model checker.

	Original	**BMU portion**	
States	21,021	5,616	(-73.28%)
Transitions	103,060	27,345	(-73.47%)

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$$\dot{z} = -ag \cdot k_1 x_1 + ag \cdot k_2 x_2$$

Stochastic model

$$[]\ x_1 > 0 \rightarrow \beta_1 x_1 : x_1 = x_1 - 1$$
$$[]\ x_1 < max_{x_1} \rightarrow \alpha_1 x_1^{g_{11}} x_2^{g_{21}/rankl} : x_1 = x_1 + 1$$
$$[resorb]\ x_1 > 0 \rightarrow ag \cdot k_1 x_1 : true$$

$$[]\ x_2 > 0 \rightarrow \beta_2 x_2 : x_2 = x_2 - 1$$
$$[]\ x_2 < max_{x_2} \rightarrow \alpha_2 x_1^{g_{12}} x_2^{g_{22}} : x_2 = x_2 + 1$$
$$[form]\ x_2 > 0 \rightarrow ag \cdot k_2 x_2 : true$$

Model checking bone pathologies

Diagnostic estimators:

1. Bone density monitor
2. Rapidity of density changes

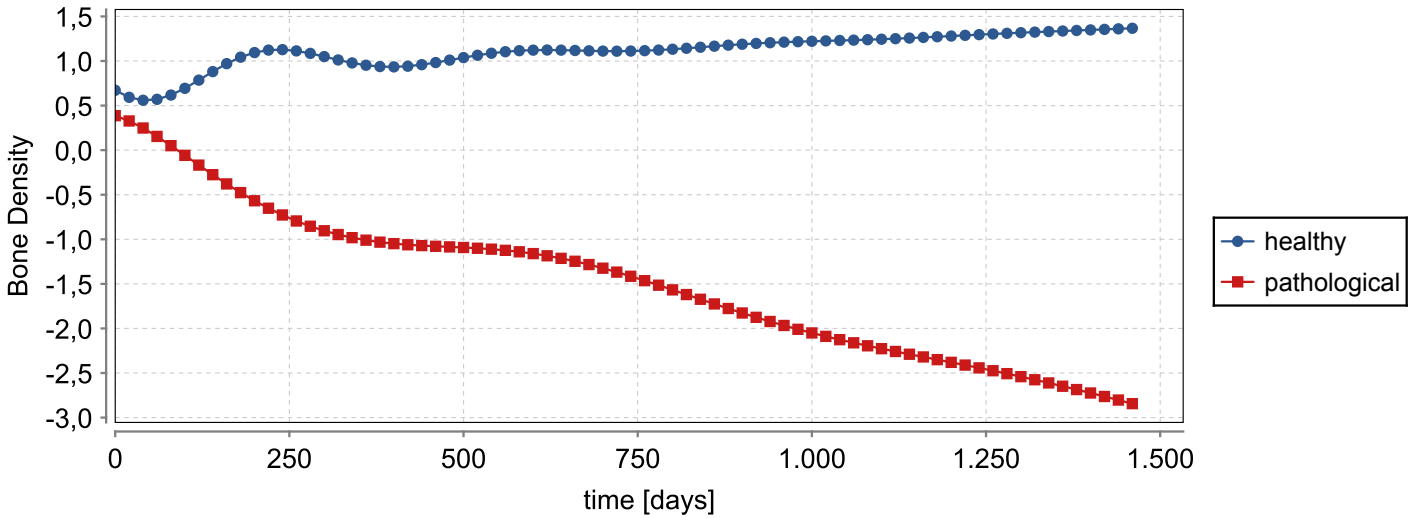
Comparison of two configurations over a 4 years-time:

- **healthy conf:** $rankl = 1$ and $ag = 1$
- **pathological conf:** $rankl = 1.2$ and $ag = 2$

Outline

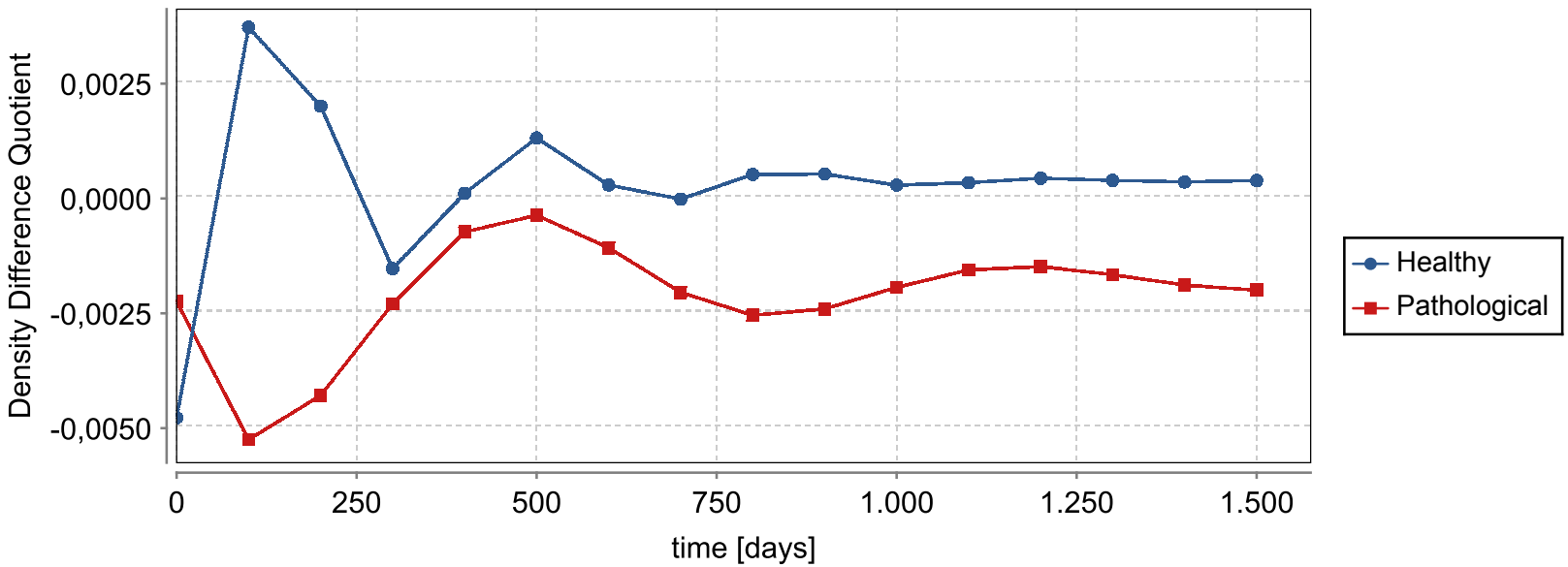
Bone mineral density

$$f_+(t): \ R\{''boneFormed''\} =?[C \leq t],$$
$$f_-(t): \ R\{''boneResorbed''\} =?[C \leq t],$$
$$f_{BD}(t): \ f_+(t) - f_-(t), \quad t = 0, 10, \ldots, 1460.$$



Density change rate

$$\frac{f_{BD}(t+\Delta t) - f_{BD}(t)}{\Delta t}, \quad t = 0, 50, \ldots, 1450.$$



Conclusions

- Statistical analysis of ODE model for reducing the state space and incorporating *RANKL* and *aging* parameters
- Derivation of a stochastic model in PRISM
- Comparison of healthy and pathological configurations
- Probabilistic verification of bone pathologies with clinical estimators

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