Coping with Time Scales in Disease Systems Analysis: Application to Bone Remodeling

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Bone Remodeling

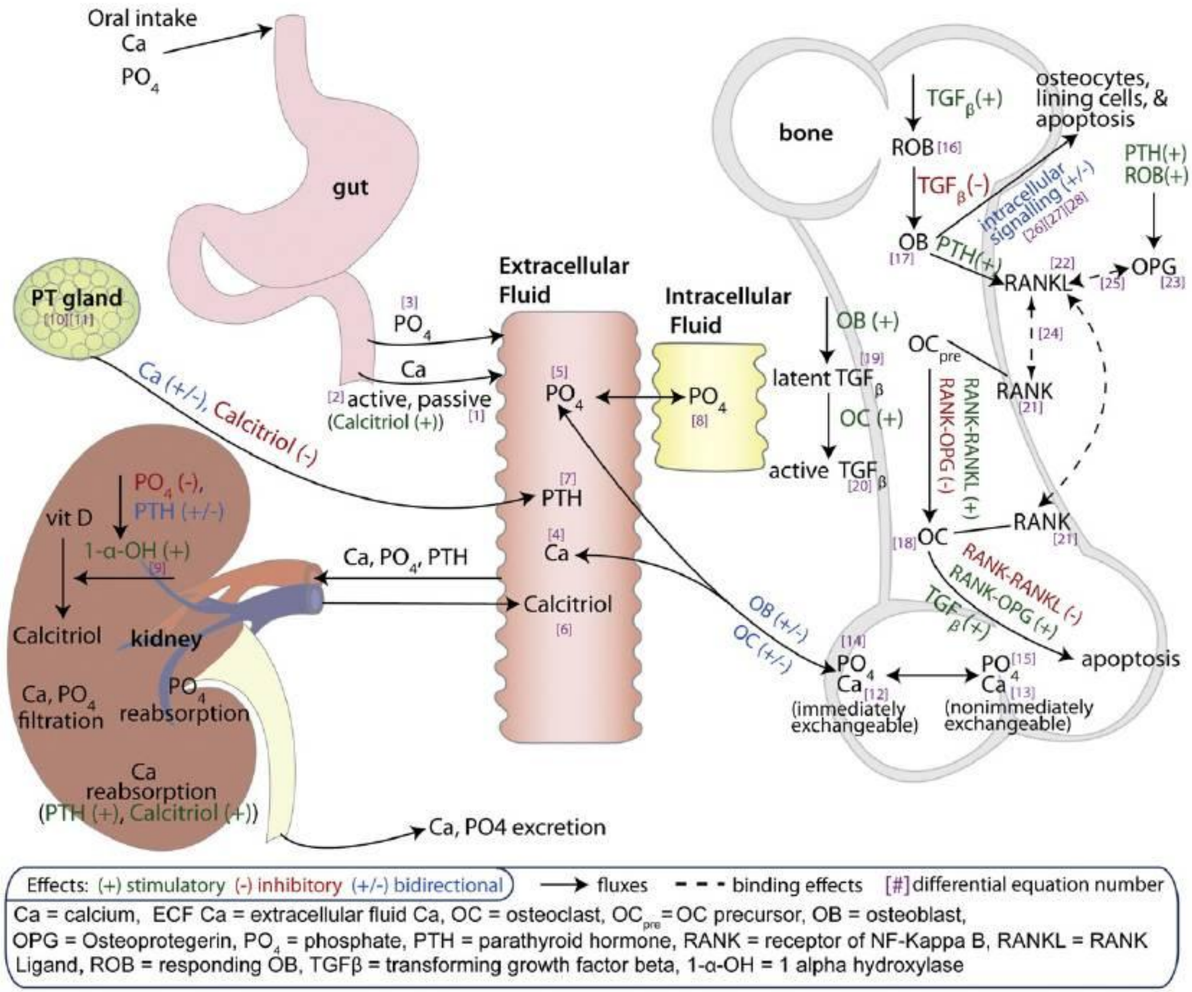
- Bone remodeling is accomplished by groups of:
  - bone forming cells (osteoblasts) and
  - bone removing cells (osteoclasts)

- Bone turnover = ratio between bone formation and bone removal

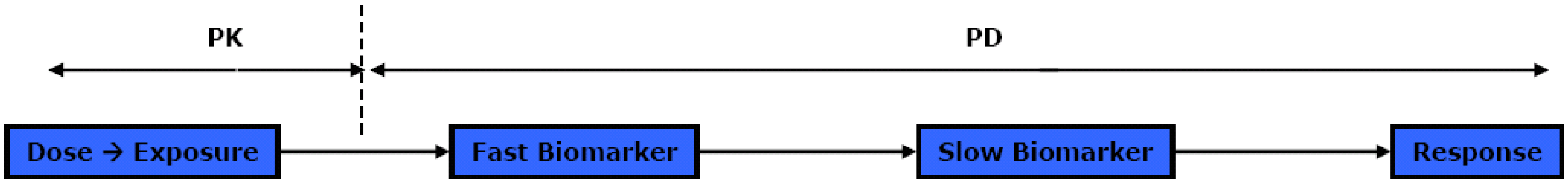
- Interaction between osteoblasts and osteoclasts is highly regulated → temporally and spatially coordinated process

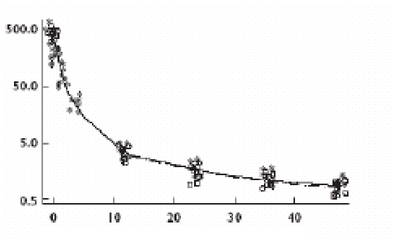
- Disturbances in regulation of the osteoblast-osteoclast interaction can result in pathophysiological conditions, such as osteoporosis

What Are the Challenges?

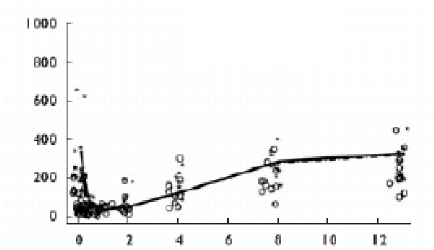


What Are the Challenges?

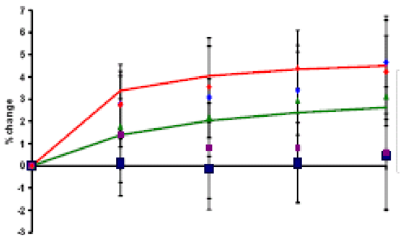




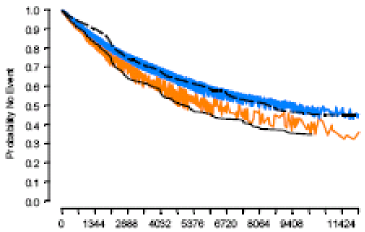
Drug (hours)



Bone turnover markers (weeks)



Bone mineral density (months)



Fracture probability (years)

Understanding the Critical Processes & their Relative Speeds

One hour corresponds to the time taken by a pointer to move 1/12th of the perimeter …

Is the speed of the pointer directly linked to the behaviour of each individual cogged wheel?

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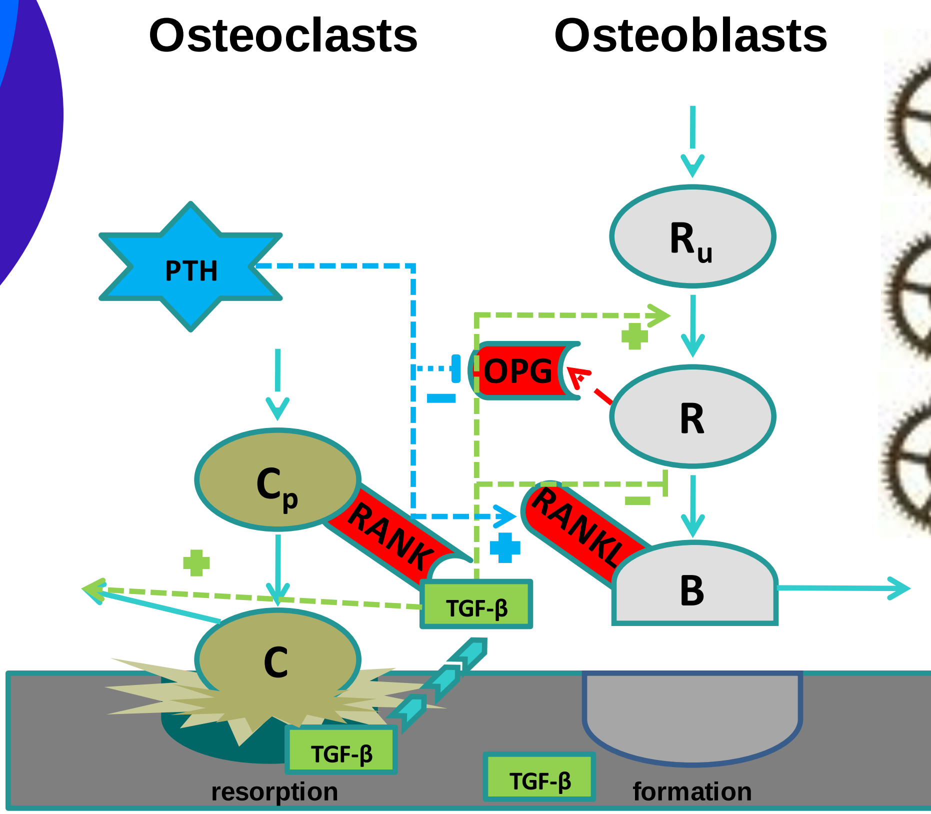
The Bone Cell Interaction Model by Lemaire *et al.*



$$\frac{dR}{dt} = D_R \cdot \pi_C - \frac{D_B}{\pi_C} \cdot R$$

$$\frac{dB}{dt} = \frac{D_B}{\pi_C} \cdot R - k_B \cdot B$$

$$\frac{dC}{dt} = D_C \cdot \pi_L - D_A \cdot \pi_C \cdot C$$

with

$$\pi_C = \frac{C + f_0 C^s}{C + C^s}, \quad \pi_L = \frac{\alpha B}{1 + \beta R}$$

***R**: responding osteoblasts, **B**: active osteoblasts, **C**: active osteoclasts, **RANK**: receptor activator of NF-κB, **RANKL**: RANK ligand, **OPG**: osteoprotegerin, **PTH**: parathyroid hormone, **TGF-β**: transforming growth factor β, **π_C**: TGF- β receptor occupancy, **π_L**: RANK occupancy*

Adapted from: Lemaire et al. (2004) J Theor Biol 229:293-309.

How to Determine the Critical Components of the System?

To identify the characteristic properties of the Lemaire model, it is important to assess:

1) The relative importance of the individual model terms

2) The relative speed/time scales of the processes involved

Dimensionless analysis:

An approach to compare 2 models by evaluating their time scales and dynamics on a common basis

→ creation of a reference system

What Should Be Used as Reference Concentration?

Baseline Concentrations of responding osteoblasts (R_0), active osteoblasts (B_0), and active osteoclasts (C_0):

$$x = \frac{R}{R_0}, \qquad y = \frac{B}{B_0}, \qquad z = \frac{C}{C_0}$$

$$\begin{aligned}
\frac{dR}{dt} &= D_R \cdot \pi_C - \frac{D_B}{\pi_C} \cdot R \\
\frac{dB}{dt} &= \frac{D_B}{\pi_C} \cdot R - k_B \cdot B \\
\frac{dC}{dt} &= D_C \cdot \pi_L - D_A \cdot \pi_C \cdot C
\end{aligned}
\quad \Rightarrow \quad
\begin{cases}
\dfrac{dx}{dt} = \dfrac{D_R}{R_0} \pi_Z(z) - D_B \dfrac{x}{\pi_Z(z)} \\
\dfrac{dy}{dt} = D_B \dfrac{R_0}{B_0} \dfrac{x}{\pi_Z(z)} - k_B y \\
\dfrac{dz}{dt} = D_C \dfrac{B_0}{C_0} \dfrac{\alpha y}{1+\beta R_0 x} - D_A \pi_Z(z) z
\end{cases}$$

What Are the Relationships within the System?

At baseline: $x = \dfrac{R}{R_0} = 1, \qquad y = \dfrac{B}{B_0} = 1, \qquad z = \dfrac{C}{C_0} = 1$

Assumption: system is at steady-state at baseline

$$\begin{cases} \dfrac{dx}{dt} = \dfrac{D_R}{R_0}\pi_Z(z) - D_B \dfrac{x}{\pi_Z(z)} \\ \dfrac{dy}{dt} = D_B \dfrac{R_0}{B_0}\dfrac{x}{\pi_Z(z)} - k_B y \\ \dfrac{dz}{dt} = D_C \dfrac{B_0}{C_0}\dfrac{\alpha y}{1+\beta R_0 x} - D_A \pi_Z(z) z \end{cases} \Longrightarrow \begin{cases} \dfrac{dx}{dt} = \dfrac{D_B}{\pi_z(1)}\left(\sigma(z) - \dfrac{x}{\sigma(z)}\right) \\ \dfrac{dy}{dt} = k_B\left(\dfrac{x}{\sigma(z)} - y\right) \\ \dfrac{dz}{dt} = D_A \pi_z(1)\left(\dfrac{1+\beta R_0}{1+\beta R_0 x} y - \sigma(z) z\right) \end{cases}$$

with $\sigma(z) = \dfrac{\pi_z(z)}{\pi_z(1)}$

Selection of a Characteristic Time Scale

Elimination of active osteoblasts (y) is given by k_B:

$$\frac{dy}{dt} = k_B\left(\frac{x}{\sigma(z)} - y\right) \quad \Rightarrow \quad t_{1/2} = \frac{\ln(2)}{k_B}$$

This suggests a characteristic time scale (T) :

$$T = \frac{1}{k_B} \qquad \Rightarrow \qquad \tau = \frac{t}{T} = k_B t$$

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How to Determine the Relative Speeds within the System?

$$\begin{cases} \varepsilon \dfrac{dx}{d\tau} = \sigma(z) - \dfrac{x}{\sigma(z)} \\ \dfrac{dy}{d\tau} = \dfrac{x}{\sigma(z)} - y \\ \dfrac{dz}{d\tau} = \mu\left(\dfrac{1+\beta R_0}{1+\beta R_0 x} y - \sigma(z) z\right) \end{cases}$$

$$\varepsilon = \frac{k_B}{D_B}\pi_z(1)$$

and

$$\mu = \frac{D_A}{k_B}\pi_z(1)$$

For the parameter values provided by Lemaire *et al.*: $\varepsilon \ll 1 < \mu$

→ equation for **x(τ)** is fast relative to **y(τ)** and **z(τ)**

Adapted from: Lemaire et al. (2004) J Theor Biol 229:293-309.

The Reduced System

Reduced System

$$0 = \sigma(z) - \frac{x}{\sigma(z)}$$

$$\Rightarrow x = \sigma^2(z)$$

$$\begin{cases} \dfrac{dy}{d\tau} = \sigma(z) - y \\ \dfrac{dz}{d\tau} = \mu\left(\dfrac{1+\beta R_0}{1+\beta R_0 \sigma^2(z)} y - \sigma(z) z\right) \end{cases}$$

Original Variables

$$0 = D_R \pi_C(C) - \frac{D_B}{\pi_C(C)} R$$

$$\Rightarrow R(C) = \left(\frac{D_R}{D_B}\right) \pi_C^2(C)$$

$$\begin{cases} \dfrac{dB}{dt} = D_R \pi_C(C) - k_B B \\ \dfrac{dC}{dt} = D_C \pi_L\big(R(C), B\big) - D_A \pi_C(C) C \end{cases}$$

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Evaluation of Model Behavior

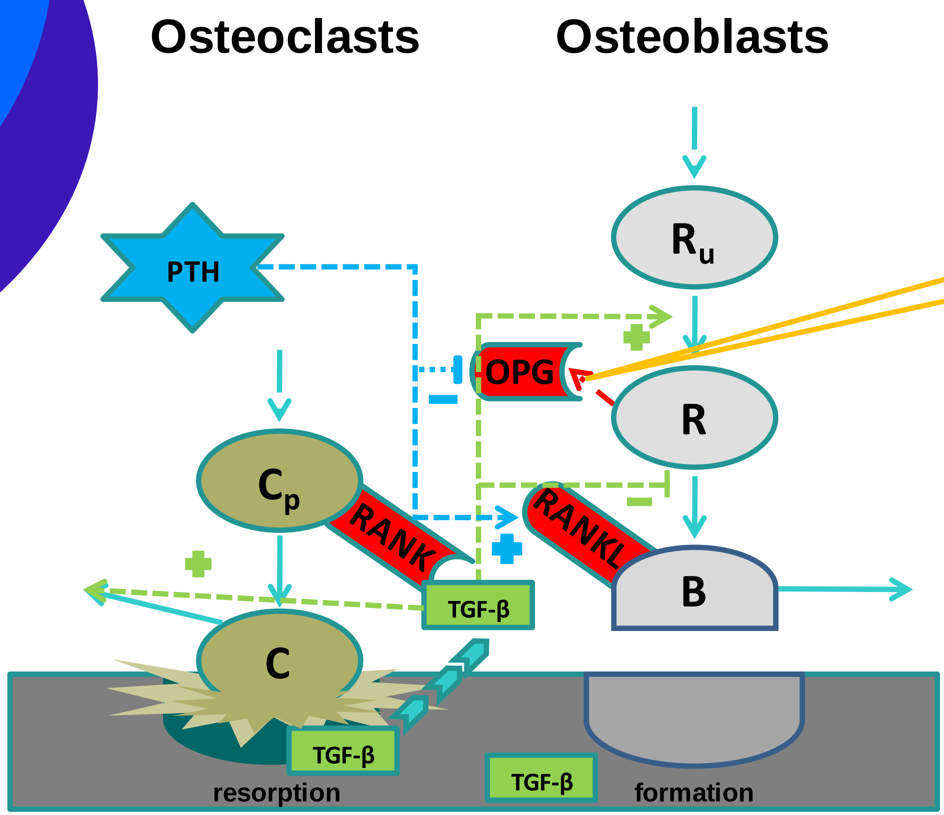
Performance of the full Lemaire model and the reduced model were evaluated in simulations using physiologically meaningful scenarios:

1) Estrogen deficiency/Estrogen replacement therapy
2) Vitamin D deficiency
3) Ageing
4) Glucocorticoid treatment (chronic)/treatment cessation

Parameter values (normal & diseased) provided by Lemaire *et al.* were used for simulations

Lemaire et al. (2004) J Theor Biol 229:293-309.

Estrogen Deficiency



Estrogen stimulates the production of OPG (K_O^P)

$$K_O^P \downarrow \Rightarrow \pi_L \uparrow = \frac{\alpha B}{1 + \beta \downarrow R}$$

2 x 10^5 pM day^{-1}/pM cells

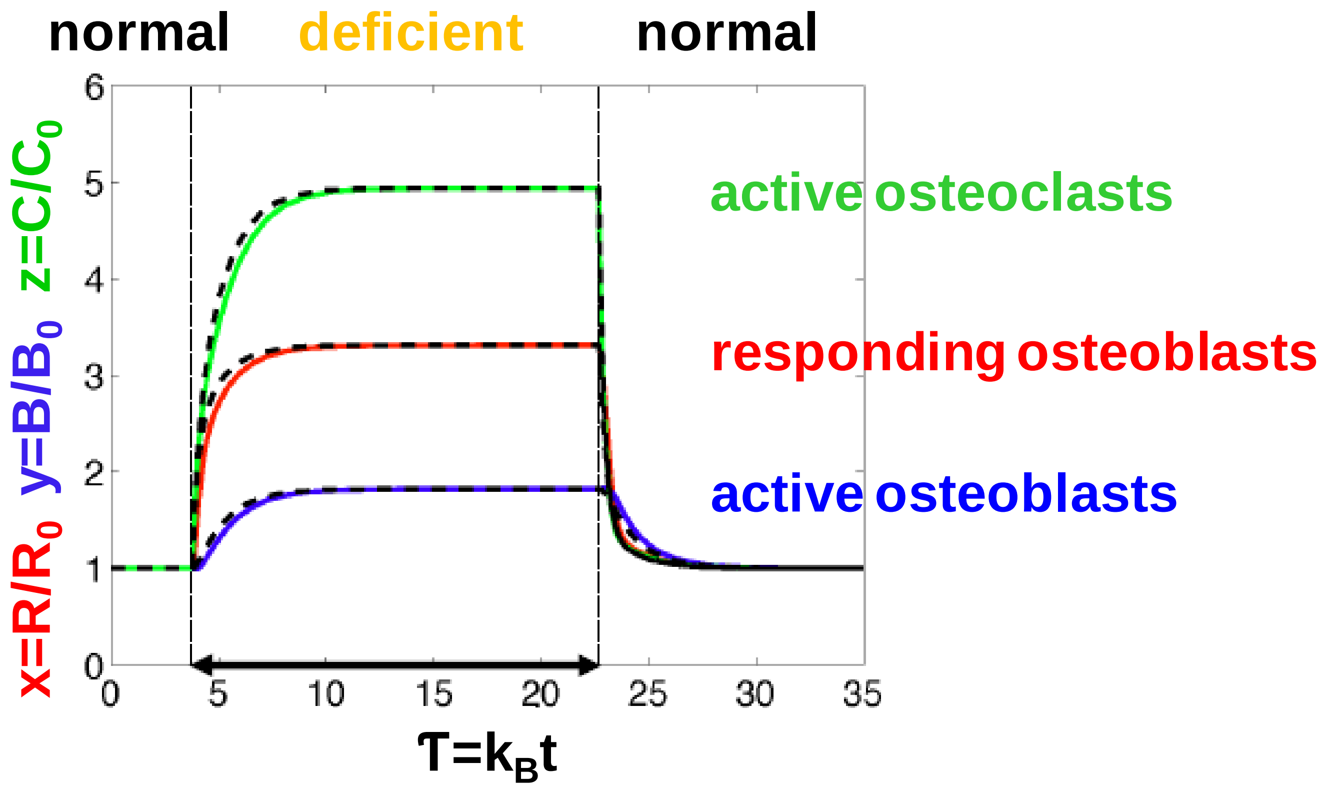
↓

158 pM day^{-1}/pM cells

***R**: responding osteoblasts, **B**: active osteoblasts, **C**: active osteoclasts, **RANK**: receptor activator of NF-κB, **RANKL**: RANK ligand, **OPG**: osteoprotegerin, **PTH**: parathyroid hormone, **TGF-β**: transforming growth factor β, π_L: RANK occupancy, K_O^P: OPG production rate*

Adapted from: Lemaire et al. (2004) J Theor Biol 229:293-309.

Step-Decrease in Estrogen Production



Responding osteoblasts, active osteoblasts, active osteoclasts. ***Solid lines****: full model,* ***dashed lines****: reduced model,* ***black arrow****: duration of deficiency.*

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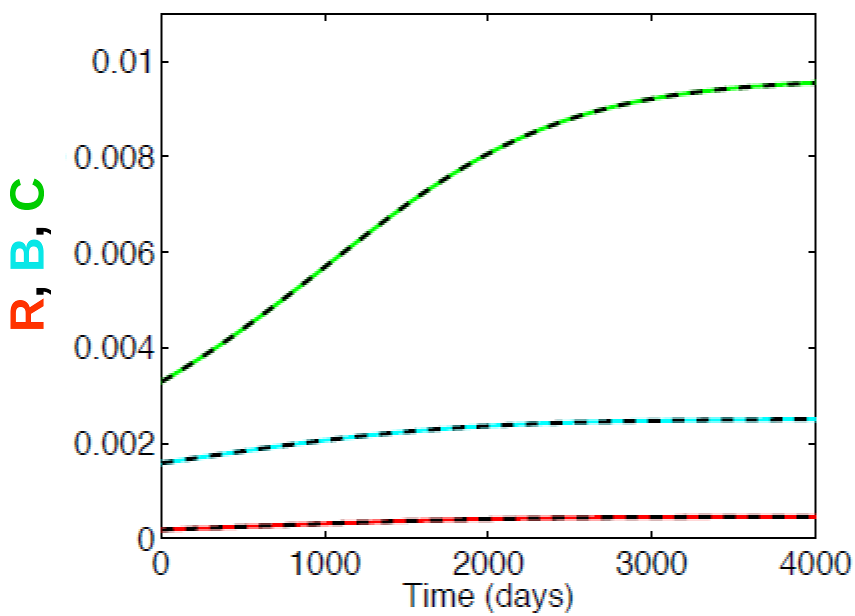
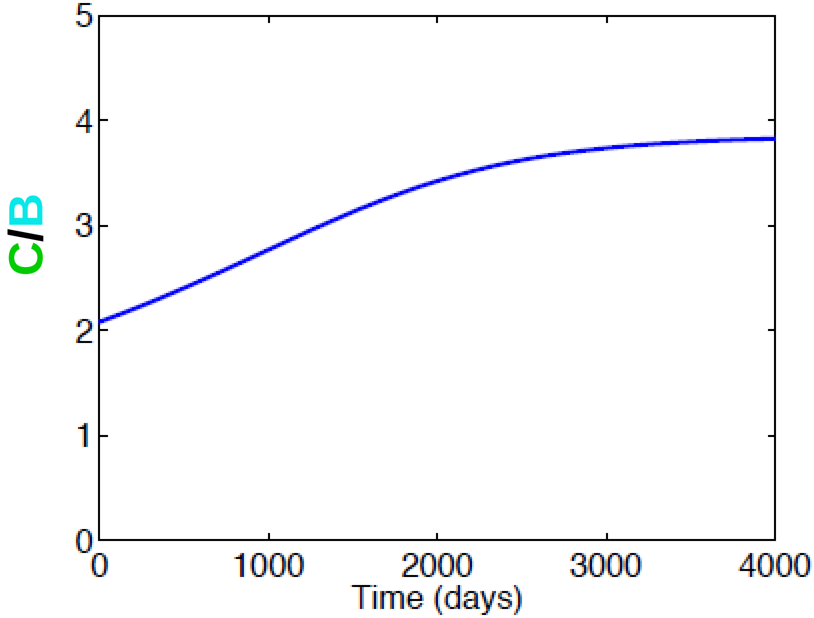
Physiological Change in Estrogen Production

Bone cell dynamics



Bone turnover dynamics



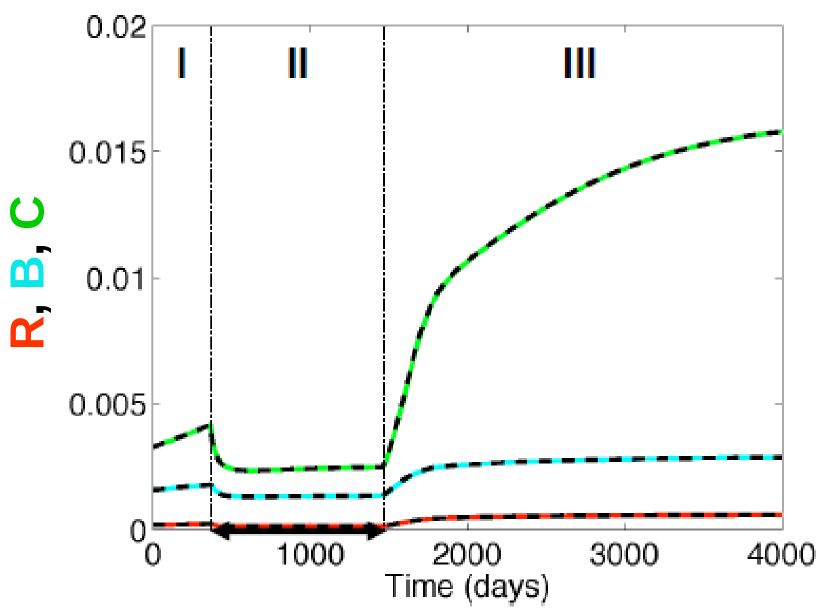
*Responding osteoblasts (R), active osteoblasts (B), active osteoclasts (C). **Solid lines**: full model, **dashed lines**: reduced model.*

Clarke and Khosla (2010) Arch Biochem Biophys 503(1):118-28.

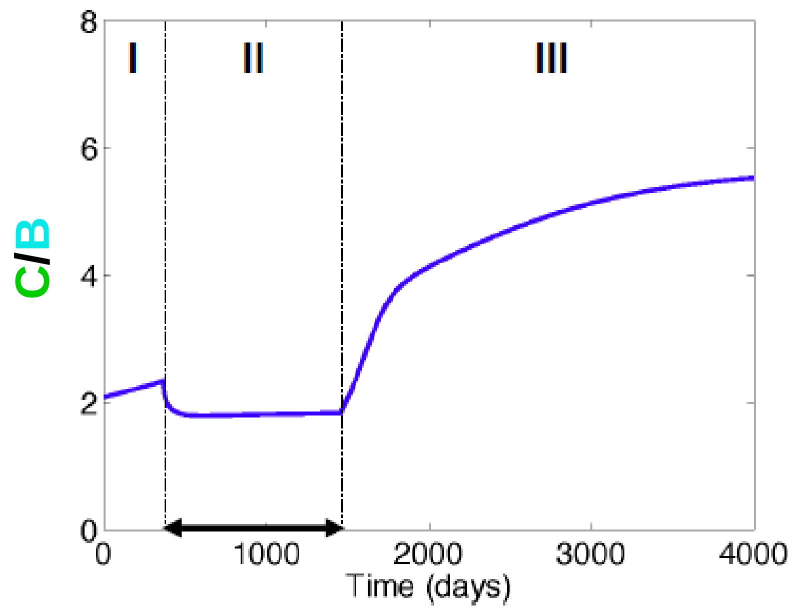
Lemaire et al. (2004) J Theor Biol 229:293-309.

Estrogen Replacement Therapy

Bone cell dynamics



Bone turnover dynamics



*Change in responding osteoblasts (R), active osteoblasts (B), active osteoclasts (C) (**I**) prior to, (**II**) during, and (**III**) following estrogen replacement therapy. **Solid lines**: full model, **dashed lines**: reduced model, **black arrow**: treatment duration (4 years).*

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Summary

- The full Lemaire model was mathematically reduced to a simpler, two-dimensional system
- Negligible differences in the dynamic properties of both models on the time scale of disease progression and therapeutic intervention
- Reduction to a two-dimensional system:
  1) yielded qualitative insight in the difference in time scales (onset and washout of treatment effects),
  2) brought down the number of parameters to be identified while maintaining the dynamic properties of the full Lemaire model
- Provides a tool for developing mechanism-based disease systems models, which can be applied to clinical data

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Hong et al. (2011) abstract at ACoP.

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