

# CMDR Journal Club

## Math Modeling for Bone-Cell Dynamics

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# Overview

Math Modeling

Basic Ideas

Paper

Main Model

Ligands Competition

Parameters

Model Simulations

Conclusions

*Mathematicians are a kind of Frenchman. They translate into their own language whatever is said to them and forthwith the thing is utterly changed.*  
*Johann Wolfgang von Goeth*

# Why Math Modeling?

- ▶ It is an attempt to introduce theoretical foundations to biological processes.
- ▶ It can also explain also some of the paradoxical observations.
- ▶ Based on "mechanistic" assumptions, models can produce useful predictions.
- ▶ Once a model is "calibrated", it can accommodate extensions based on new biological findings.

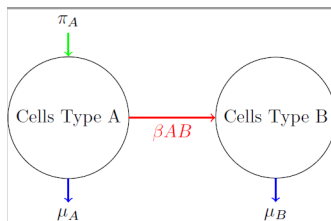
# Compartmental Models

The so-called **Compartmental Models** try to describe the dynamics of cell interactions among two or more well-characterized cell types. Some basic implicit assumptions about cell populations

- ▶ The evolution of the population is described by rates (i.e., instant changes in population numbers).
- ▶ Cells are indistinguishable among the same type ( $A$  and  $B$  below).
- ▶  $A$  and  $B$  represent abundance of the given type.

## Compartmental Models (cont)

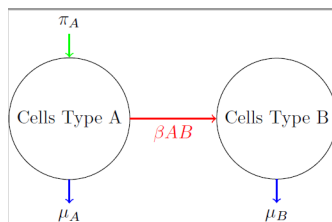
- ▶ Cells are entering (some progenitor cell) into the  $A$  compartment at a certain rate  $\pi_A$ .
- ▶ Cells leave the compartment (cell death) at the rate  $\mu_A$  and  $\mu_B$ , respectively.
- ▶ Cells evolve from Type  $A$  into Type  $B$  at a rate proportional to their abundance at a constant rate  $\beta$ .



## Compartmental Model Math

The translation of this interaction is translated in the following system of (ordinary) differential equations

$$\begin{aligned}A' &= \pi_A - \beta AB - \mu_A A \\ B' &= \beta AB - \mu_B B\end{aligned}\tag{1}$$



For the above system, we can calculate the "steady state(s)". This means the point(s) that the trajectories will end up reaching (after potentially some very long time) or they are getting away from.

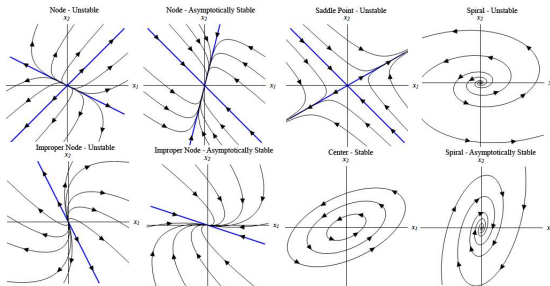


Figure: dynamical systems

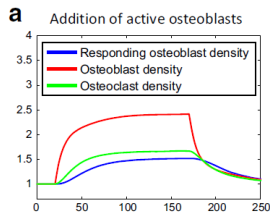


## "Solving" the equations (cont)

In general, it is relatively hard to calculate those steady states and determine (locally) their behavior (attractor or repeler)

(Mathematical issue)

Instead, we solve the equations "numerically". Meaning, we write code to simulate trajectories (e.g., Matlab) for a given set of parameters ( $\pi_A$ ,  $\beta$ , etc.)



# In Silico Simulations

A great deal of time is spent calculating the parameters from a given established system

- ▶ Using other literature sources
- ▶ Making simulations based on newly produced data

The ultimate goal is to produce a tuned *in silico* system based on equations that mimic fundamental biological concepts. Then, we can explore scenarios and test biological hypothesis.

# Today's paper

Bulletin of Mathematical Biology (2019) 81:3575–3622  
<https://doi.org/10.1007/s11538-018-0533-0>



**SPECIAL ISSUE: MATHEMATICS TO SUPPORT DRUG  
DISCOVERY AND DEVELOPMENT**

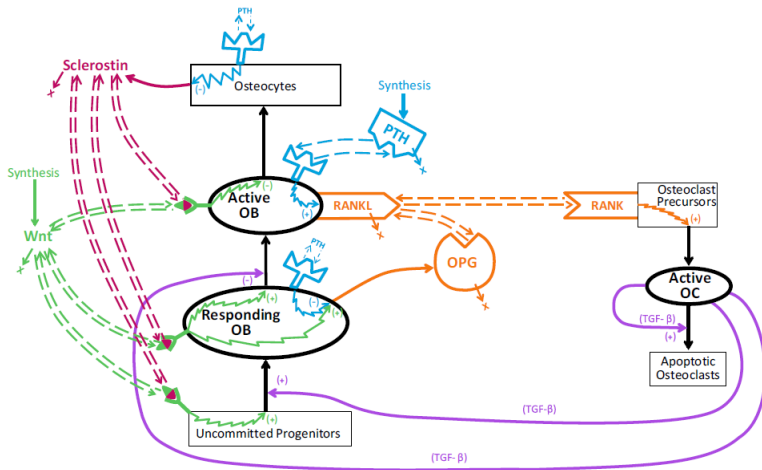


## Dynamics of Bone Cell Interactions and Differential Responses to PTH and Antibody-Based Therapies

Vincent Lemaire<sup>1,2</sup>  · David R. Cox<sup>1</sup>

Received: 17 June 2017 / Accepted: 1 November 2018 / Published online: 20 November 2018  
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# Picture First



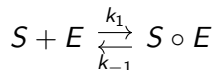
# Cell Compartment Equations

$$\begin{aligned}
 R' &= D_R \pi_C \pi_W - D_B \frac{\pi_W}{\pi_C} R \\
 B' &= D_B \frac{\pi_W}{\pi_C} R - \frac{k_e^B}{\pi_W} B \\
 C' &= D_C \pi_L - k_e^C \pi_C C
 \end{aligned} \tag{2}$$

According to the model  $D_R$ ,  $D_B$  and  $D_C$  are constant differentiation rates,  $k_e^B$ , and  $k_e^C$  are constant elimination rates.

## Ligands Models

The modeling follows the enzymatic theory of Michaelis-Menten. In brief, if we have a substrate  $S$  reacting with an enzyme  $E$  to form a complex  $SE$  can be modeled as

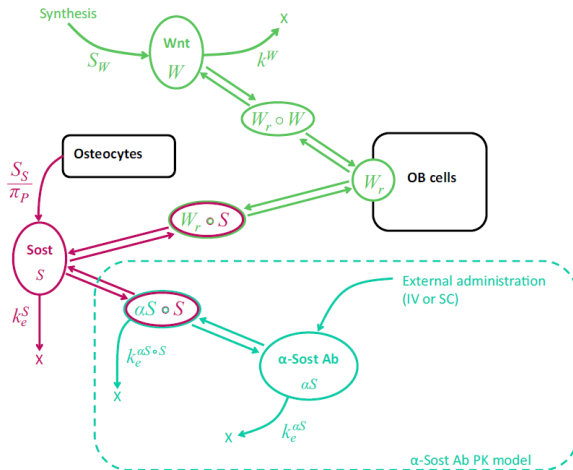


$$\frac{dS \circ E}{dt} = k_1 S \cdot E - k_{-1} S \circ E \quad (3)$$

When the text refers that equations are considered at "steady state" it means that

$$k_1 S \cdot E = k_{-1} S \circ E$$

# Ligand Models (cont)



# Binding to LPR5/6

The attachment of Wnt to the receptor  $W_r$  is taken at the steady state. The equations for binding of Wnt receptor and sclerostin are

$$\begin{aligned}\frac{dW_r \circ S}{dt} &= k_9 S \cdot W_r - k_{10} W_r \circ S \\ \frac{d\alpha S \circ S}{dt} &= k_{13} S \cdot \alpha S - k_{14} \alpha S \circ S - k_e^{\alpha S \circ S} \alpha S \circ S\end{aligned}\tag{4}$$

The second equation represents the presence of an antibody for Sost



# Parameter Estimation

**Table 2** These are the parameters of the bone model which were determined by optimization (fitting parameters)

Symbol	Unit	Value	Description
$D_R$	pM/day	$1.28 \times 10^{-4}$	Differentiation rate of osteoblast progenitors into responding osteoblasts [see Eq. (1)]
$f_0$	None	$3.39 \times 10^{-2}$	Minimal TGF- $\beta$ receptor occupancy [see Eq. (2)]
$C_{50}$	pM	$1.25 \times 10^{-6}$	Osteoclast density to achieve half TGF- $\beta$ receptor occupancy [see Eq. (2)]
$D_B$	day $^{-1}$	3.47	Differentiation rate of responding osteoblasts into active osteoblasts [see Eq. (1)]
$k_e^B$	day $^{-1}$	$1.21 \times 10^{-3}$	Rate of elimination/death of active osteoblasts [see Eq. (1)]
$D_C$	pM/day	$7.12 \times 10^{-3}$	Differentiation rate of osteoclast progenitors into active osteoclasts [see Eq. (1)]
$k_e^C$	day $^{-1}$	$6.46 \times 10^{-2}$	Rate of elimination/death of active osteoclasts [see Eq. (1)]
$K_D^O$	pM	$4.76 \times 10^{-6}$	Mixed parameter representing a typical density of OPG-producing cells [see Eq. (36)]
$K_{max}^L$	pmol/pmol of cells	4644.6	Maximum carrying capacity of cell-bound RANKL by osteoblasts [see Eq. (28)]
$k_3$	pM $^{-1}$ day $^{-1}$	0.368	RANK-RANKL association rate [Eq. (25)]
$k_4$	day $^{-1}$	65.64	RANK-RANKL dissociation rate [Eq. (25)]
$K_D^P$	None	20.17	Mixed parameter related to unbound PTH receptors in basal condition [see Eq. (24)]
$K$	pM	0.10	RANK density [see Eq. (26)]
$K_D^S$	None	14.95	Mixed parameter related to unbound sclerostin molecules in basal condition [see Eq. (19)]
$K_D^W$	None	3.70	Mixed parameter related to unbound Wnt molecules in basal condition [see Eq. (19)]

# "Optimization"

This part is not the traditional (formal) optimization process.

The authors try to place some reasonable constraints (i.e. the dynamics reaches steady state in less than 500 days)

The scenarios ("objectives") are mostly a sanity check for the model. The notation  $R \nearrow$  represent a "significant" increase in the steady-state value of the mentioned species should be observed after perturbations (e.g., drug) is applied.

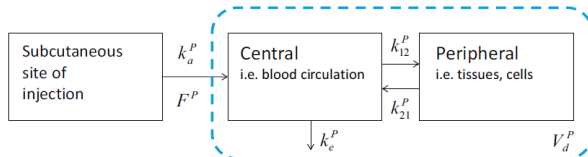
# "Optimization" (cont)

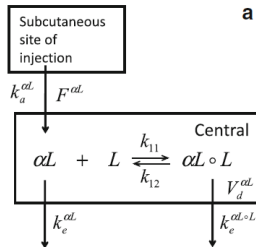
**Table 5** The list of qualitative objectives used for the optimization of the model is summarized in this table

Experiment	Perturbations	Objectives
① Monitoring cell densities	None (unperturbed state)	$10^{-5} \text{ pM} \leq \max(R, B, C) \leq 10^{-2} \text{ pM}$ and $10^{-6} \text{ pM} \leq \min(R, B, C) \leq 10^{-3} \text{ pM}$ $T_{ss} < 500 \text{ days}$
② Addition of active osteoblasts	Adding active osteoblasts at the rate $B _{\text{ref}}/8$ per day	$R \nearrow$ $B \nearrow$ $C \nearrow$ $C/B \searrow$ $T_{ss} < 500 \text{ days}$
③ Addition of active osteoclasts	Adding active osteoclasts at the rate $C _{\text{ref}}/8$ per day	$R \nearrow$ $B \nearrow$ $C \nearrow$ $C/B \nearrow$ $T_{ss} < 500 \text{ days}$ $\frac{\max(\pi_C)}{\min(\pi_C)} > 1.5$

# Adding PK

A two-compartment model for hPTH was used



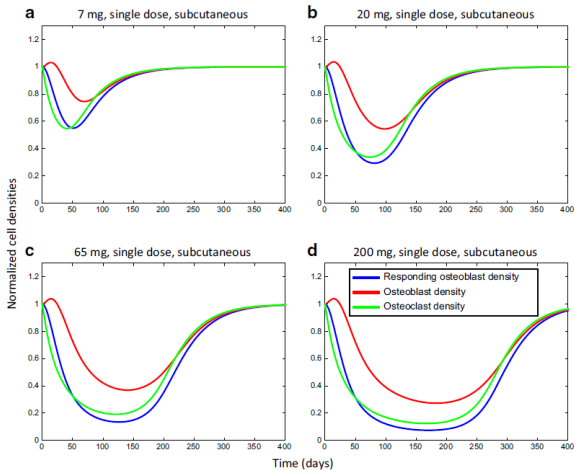


## PK model for Anti-RANKL

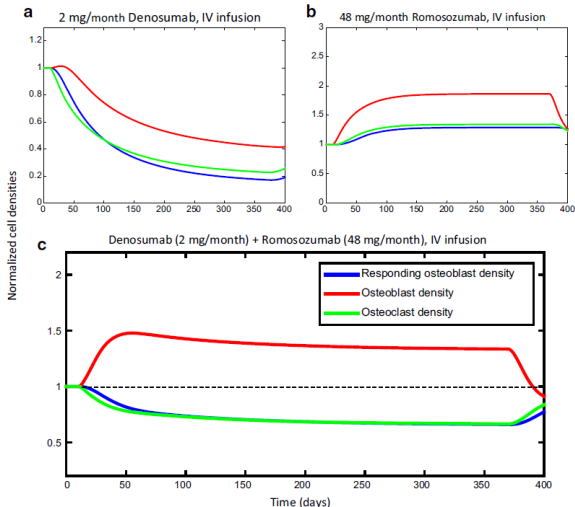
They used a one compartment model described by the equation

$$\begin{aligned}\frac{d\alpha L}{dt} &= P^{\alpha L}(t) - k_e^{\alpha L} \cdot \alpha L - k_e^{\alpha L \circ L} \cdot \alpha L \circ L \\ &= P^{\alpha L}(t) - \left( k_e^{\alpha L} + \frac{k_e^{\alpha L \circ L}}{K_d^{\alpha L}} L \right) \alpha L\end{aligned}\tag{5}$$

# Denosumab single dose simulation

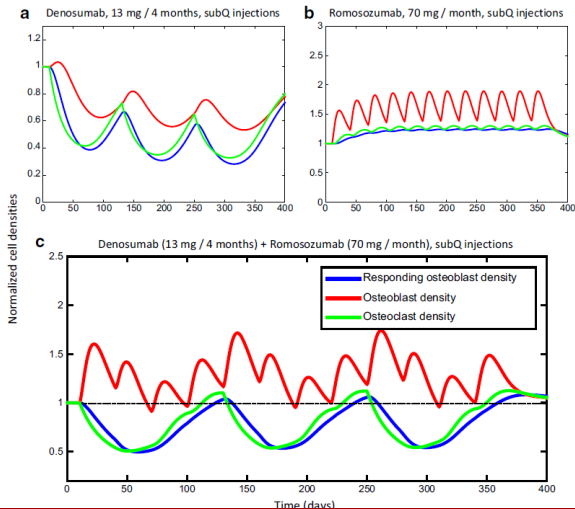


# Combination of Therapies (in silico)





# Multiple injections





## Math Models

- ▶ Several groups around the globe are incorporating math modeling. Notably, Peter Pivonka (Queensland).
- ▶ Most of the publications have referenced the work from this group!
- ▶ There are many extensions to the basic model.
- ▶ If a model requires generating new data, then it is normally a time-series like data that is required.

# Papers

## Osteocytes as a record of bone formation dynamics: A mathematical model of osteocyte generation in bone matrix

Pascal R. Buenzli

*School of Mathematical Sciences, Monash University, Clayton, VIC 3800, Australia*

## Osteocytes as a record of bone formation dynamics: A mathematical model of osteocyte generation in bone matrix

Pascal R. Buenzli

*School of Mathematical Sciences, Monash University, Clayton, VIC 3800, Australia*

## Mathematical Model of Paracrine Interactions between Osteoclasts and Osteoblasts Predicts Anabolic Action of Parathyroid Hormone on Bone

Svetlana V. Komarova

*McGill University, Montreal, Canada H3A 2B2*

Navigation icons: back, forward, search, and other controls.

*If the Lord Almighty had consulted me before embarking  
on creation I should have recommended something simpler*  
*Alphonso X (Alphonso the Wise) 1221-1284*  
*King of Castile and Leon*