CMDR Journal Club
Math Modeling for Bone-Cell Dynamics

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Overview

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.

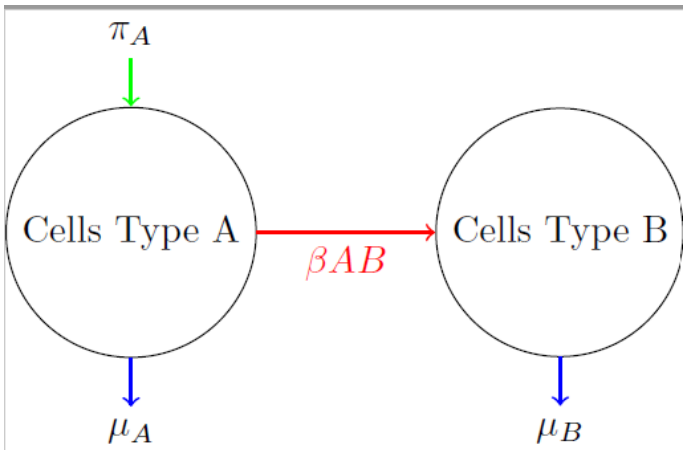
Compartmental Models

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)

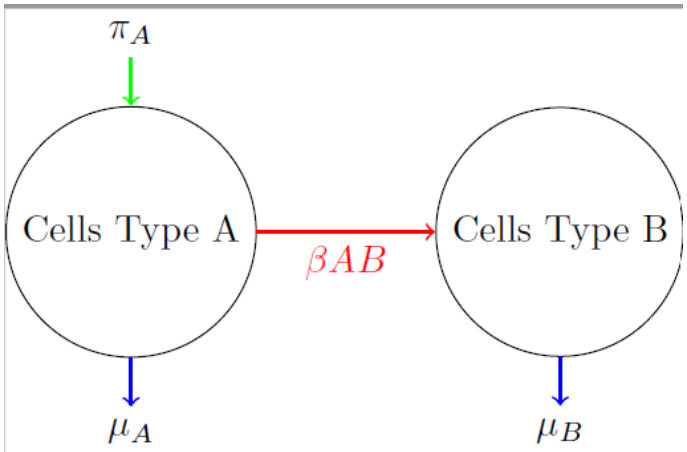
- Cells are entering (some progenitor cell) into the A compartment at a certain rate π_A.
- Cells leave the compartment (cell death) at the rate μ_A and μ_B, respectively.
- Cells evolve from Type A into Type B at a rate proportional to their abundance at a constant rate β.



Compartmental Model Math

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

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



"Solving" the equations

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.

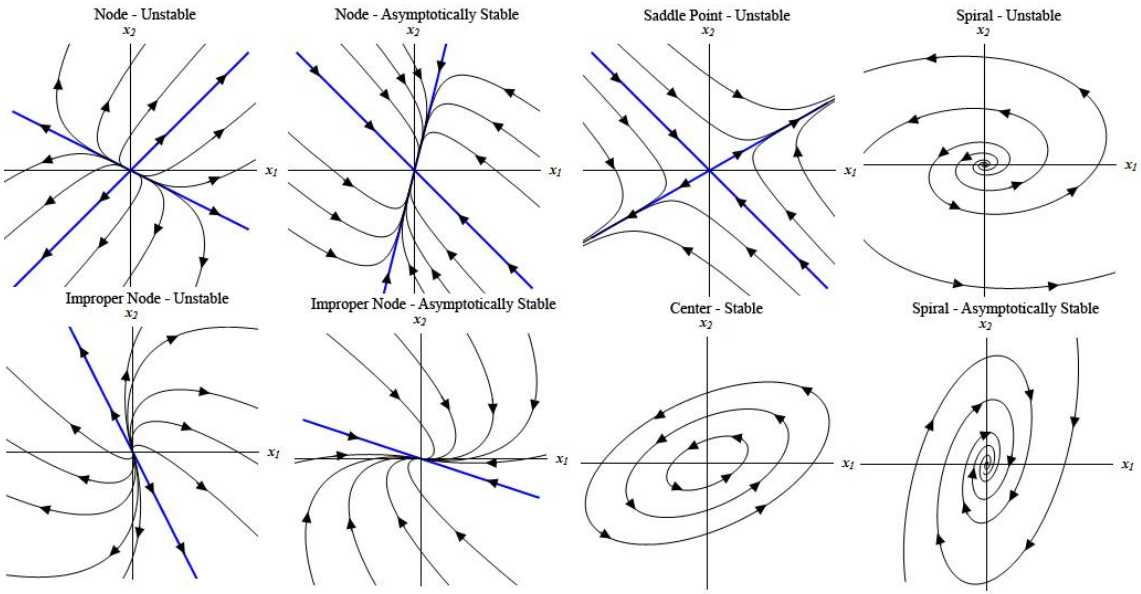
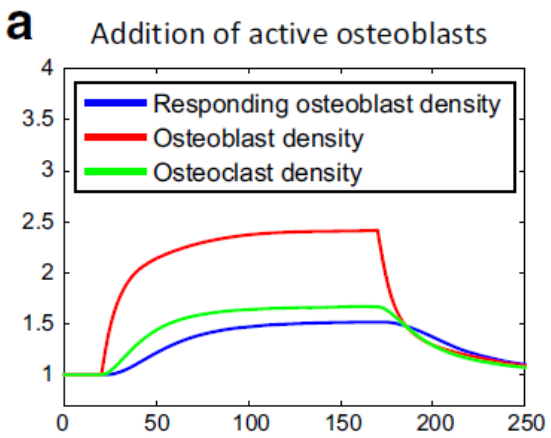


Figure: dynamical systems

"Solving" the equations (cont)

In general, it is relatively hard to calculate those steady states and determine (locally) their behavior (attractor or repelor) (Mathematical issue)
Instead, we solve the equations "numerically". Meaning, we write code to simulated the trajectories (e.g., Matlab) for a given set of parameters (π_A, β, 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

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Society for Mathematical Biology

SPECIAL ISSUE: MATHEMATICS TO SUPPORT DRUG DISCOVERY AND DEVELOPMENT

CrossMark

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

Vincent Lemaire[1,2] · David R. Cox[1]

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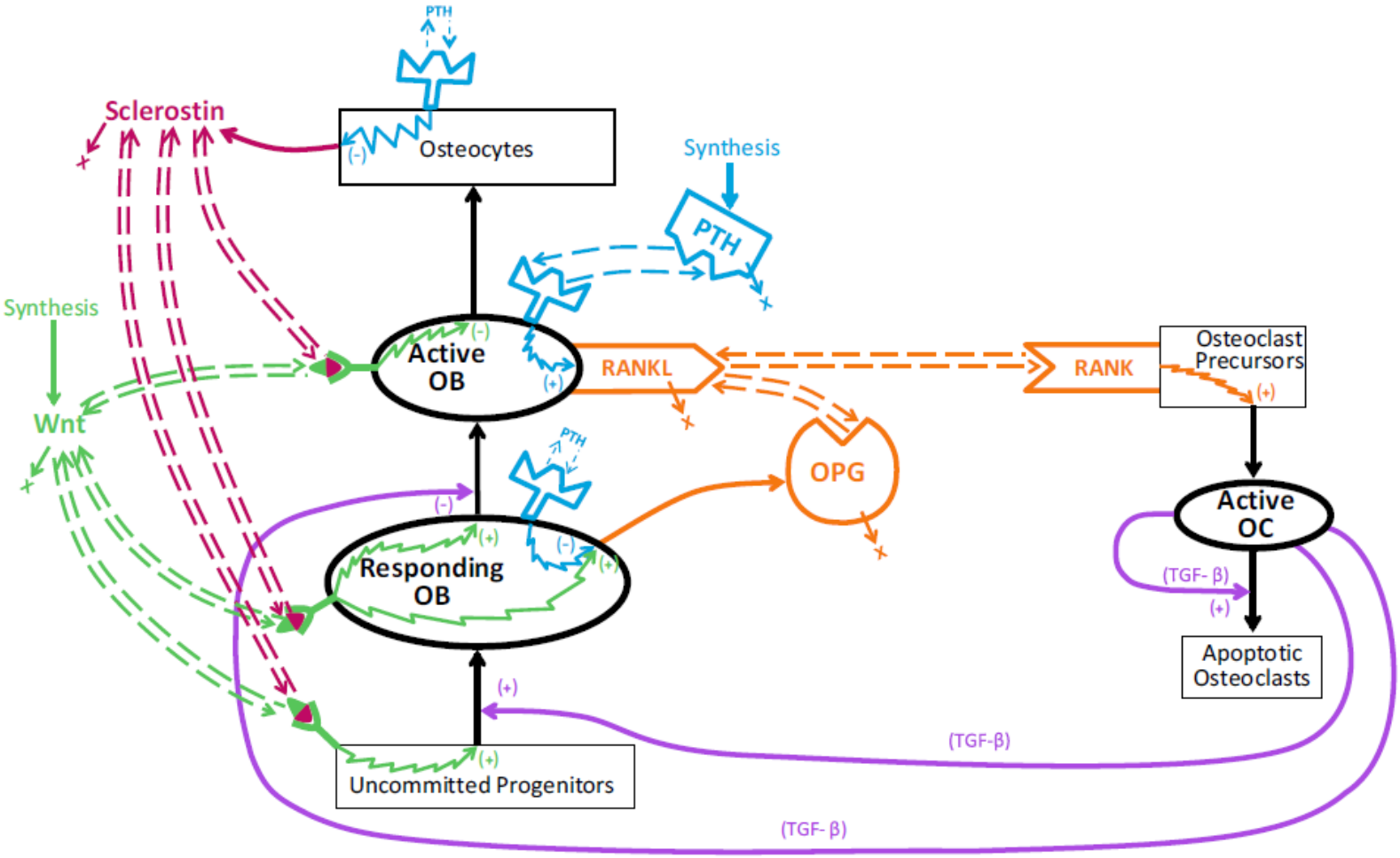
Picture First



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

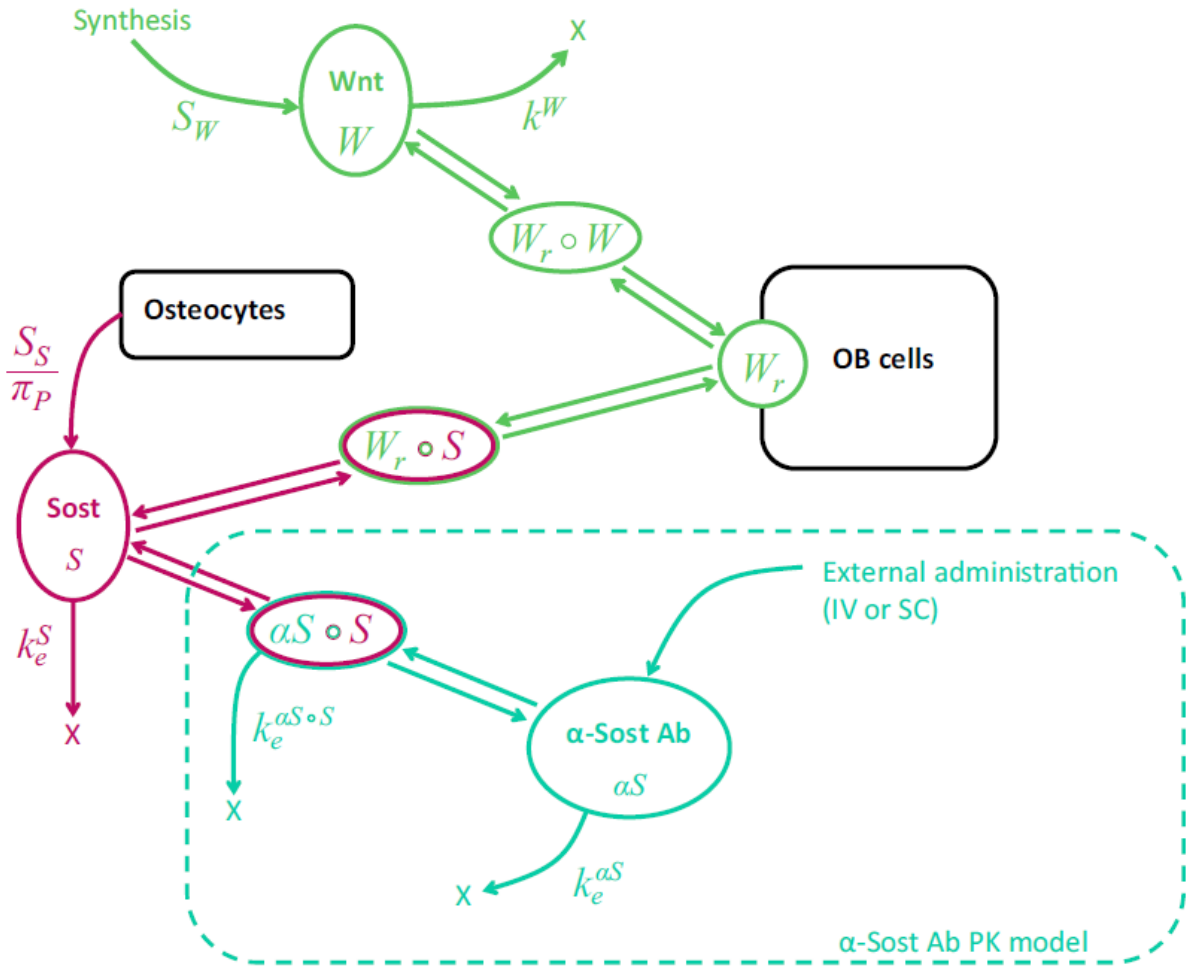
$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} S \circ E$$

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

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	1.28×10^{-4}	Differentiation rate of osteoblast progenitors into responding osteoblasts [see Eq. (1)]
f_0	None	3.39×10^{-2}	Minimal TGF-β receptor occupancy [see Eq. (2)]
C_{50}	pM	1.25×10^{-6}	Osteoclast density to achieve half TGF-β 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}	1.21×10^{-3}	Rate of elimination/death of active osteoblasts [see Eq. (1)]
D_C	pM/day	7.12×10^{-3}	Differentiation rate of osteoclast progenitors into active osteoclasts [see Eq. (1)]
k_e^C	day^{-1}	6.46×10^{-2}	Rate of elimination/death of active osteoclasts [see Eq. (1)]
K_D^O	pM	4.76×10^{-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	$\text{pM}^{-1}\ \text{day}^{-1}$	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 constrains (i.e. the dynamics reaches steady stead 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.

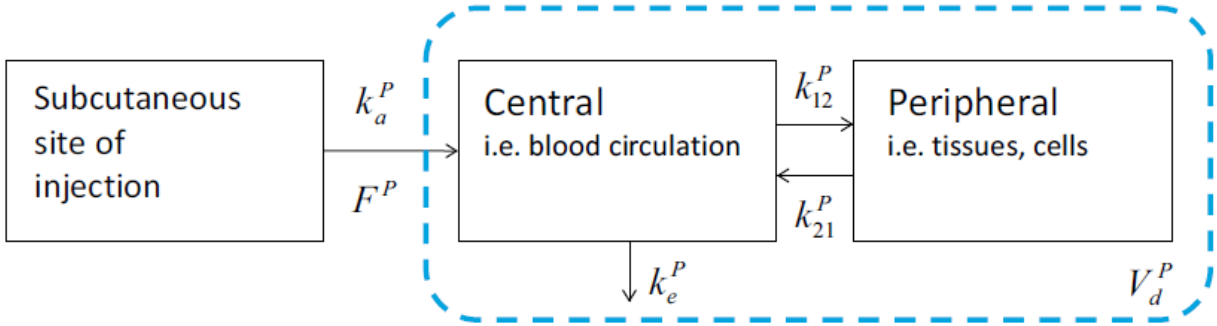
"Optimization" (cont)

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} pM $\leq \max(R, B, C) \leq 10^{-2}$ pM and 10^{-6} pM $\leq \min(R, B, C) \leq 10^{-3}$ pM T_{ss} <500 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 days
③ Addition of active osteoclasts	Adding active osteoblasts at the rate $C\|_{\text{ref}}/_8$ per day	$R \nearrow$ $B \nearrow$ $C \nearrow$ $C/_B \nearrow$ T_{ss} <500 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

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

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