# Predicting Nonlinear Changes in BMD Over Time using a Physiologically-Based Mathematical Model

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## Abstract

Purpose: Develop a mathematical model component to extend an existing physiologically-based model of calcium and bone homeostasis and enable prediction of nonlinear changes in bone mineral density (BMD) observed during, and following discontinuation of, anti-osteoporosis treatments.

Methods: The underlying physiologically-based model has been published and is described fully in Bone 46 (2010) 49-63 [1]. Data for denosumab, a receptor activator of NF-kappa B ligand inhibitor being developed for the treatment of osteoporosis, was used for fitting the BMD component. Mean serum C-telopeptide (sCTX), bone-specific alkaline phosphatase (BSAP), and lumbar spine BMD were digitized and extracted from figures contained within a clinical publication describing the on- and off-treatment effects of denosumab over 48 months [2]. Differential equations were constructed to link the prior description of bone resorption and formation markers, scaled appropriately, to provide a prediction of BMD values following treatment with denosumab. Alternate model constructs were then evaluated to ensure the most predictive structure was chosen.

Results: An indirect feedback differential equation model linked the bone markers to BMD. Changes in BMD were described by a zero-order input and first-order elimination, scaled by percentage changes in formation and resorption markers, respectively. The composite model was able to reasonably predict the percentage accumulation ofl umbar spine BMD for the subcutaneously (SC) administered 30 mg every 3 months (q3M) and 210 mg q6M regimens from start of treatment to 24 months, the decline in BMD following discontinuation of these treatments at 24 months, and the return in BMD upon reinstitution of treatment at a SC dose of 60 mg q6M. The observed data demonstrated approximately 7–8% increases in lumbar spine BMD at 24 months, followed by declines to 1–2% at 36 months (12 months after discontinuation). Upon reinstitution of treatment of the 30 mg group at 60 mg q6M, BMD gains returned to approximately 8% within 12 months.

Conclusions: A mathematical model has been developed that is able to reasonably predict nonlinear changes in mean BMD both during, and following discontinuation of, denosumab treatment, and provides a structure to be further generalized to accommodate other osteoporosis treatments.

## Objective

Develop a mathematical component to extend the existing calcium and bone homeostasis model for longitudinal prediction of nonlinear changes in BMD during, after, and upon reinstitution of receptor activator of nuclear factor Kappa-B ligand (RANKL) inhibition.

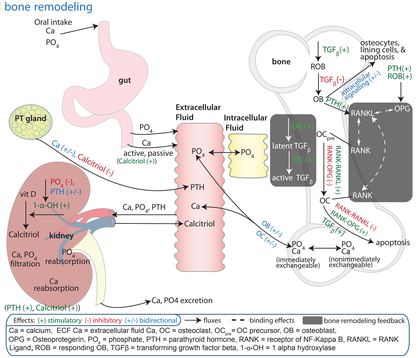
## Background

- Published literature on predicting BMD changes predominantly use correlations (linear regressions) with bone markers, such as:
  - serum C-terminal cross-linking telopeptide of type I collagen (CTx), a marker of osteoclast (OC) function
  - bone specific alkaline phosphatase (BSAP), a marker of osteoblast (OB) function
- Publications demonstrate limited ability for BMD longitudinal predictions
- Denosumab, a known specific inhibitor of RANKL [3] , provides a discrete intercession point within the physiologic system
- Robust longitudinal clinical data (4 years) for denosumab available to develop BMD model component [2]
- Our published physiologically-based model of calcium and bone homeostasis [1] already describes calcium, bone marker, and related paracrine and endocrine longitudinal effects under conditions of:
  - Primary hyperparathyroidism (HPT)
  - Secondary HPT elicited through progressive renal insufficiency
  - Primary hypoparathyroidism
  - Teriparatide (administered once-daily) treatment
  - Denosumab (administered every 3 or 6 months) treatment
- Existing model forms starting point for model extension and predictions of nonlinear changes in lumbar spine BMD (Figure 1)

## Methods

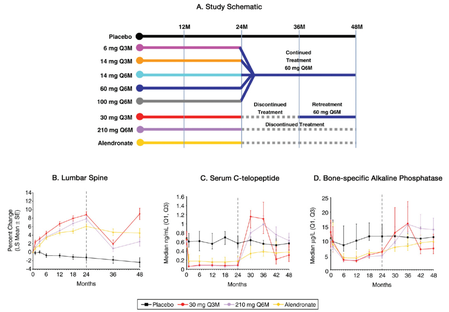
- Extend published mathematical model to predict longitudinal, nonlinear changes in lumbar spine BMD [1] (Figure 1)
- Extract longitudinal clinical data (BMD, CTx and BSAP) describing on- and off-treatment effects of denosumab over 48 months in postmenopausal women from literature [2] (Figure 2):
  - Digitized data using Plot Digitizer, v 2.4.1
  - Model BMD parameters fit to high, moderate and low denosumab dosing regimens (Figure 2)
    - 14 mg Q6M for 24M; switched to 60 mg Q6M for 24M
    - 30 mg Q3M for 24M; switched to 60 mg Q6M at Month 36
    - 210 mg Q6M for 24M; then discontinued
  - Model evaluation using denosumab 60 mg Q6M for 48M regimen
- Two-compartment, parallel linear, saturable clearance model of denosumab pharmacokinetics [4] used to simulate denosumab serum concentrations following the published dosing regimens (Figure 2)
- Model parameters fit using Berkeley Madonna, v 8.0.1 via:
  - Deterministic parameter estimates
  - Ordinary differential equations solved with fixed step size integration Fourth-order Runge-Kutta algorithm
  - Simplex algorithm with least squares minimization (Curve Fit option)
- Predictions required to be consistent with observed data during, following discontinuation of, and after reinstitution of treatment with denosumab

Figure 1: Schematic of physiologic system model to describe calcium homeostasis and bone remodeling




Modified from Figure 1 of Peterson and Riggs, 2010 [1]

Figure 2: Denosumab dose ranging study schematic (A) with resulting effects on mean lumbar spine BMD (B), median CTx (C) and BSAP (D).




Modified from Figures 1 and 4 of Miller et al., 2008 [2]

## Results

- BMD prediction, expressed as percent of baseline (initial condition = 100%), integrated into existing model with an additional differential equation (Equation 1):

$$\frac{d(BMD)_{LS}}{dt} = k_{in,BMD} \cdot \left(\frac{BSAP}{BSAP_{baseline}}\right)^{\gamma_{OB}} - k_{out,BMD} \cdot \left(\frac{CT_x}{CT_{x_{baseline}}}\right)^{\gamma_{OC}} \cdot BMD_{LS} \quad (1)$$

$\gamma_{OB} = 0.0739$
$\gamma_{OC} = 0.0679$
$k_{out,BMD} = 0.000145h^{-1}$

- Equation links nonlinear changes in BMD with longitudinal changes in:
  - CTx, a marker of osteoclast (OC) function
  - BSAP, a marker of osteoblast (OB) function
- Feedback to predict off-treatment or reinstitution-of-treatment observations required no additional mathematical expressions
  - Produced by existing mathematical relationships of the prior model
  - Manifested by endocrine linkages of PTH, RANK/RANKL/osteoprotegerin (OPG), and transforming growth factor beta (TGF- β) (Figure 1)
- CTx (Figure 3) and BSAP (Figure 4) predicted values are within 20% of observed central median (Figure 2)
- BMD predictions within 2 percentage points at all measurement times (Figure 5)
- Model used to explore (simulate) latent and active TGF-beta, a known critical longitudinal modulator of bone remodeling [5] (Figure 6)

## Model Predictions Following RANKL Inhibition With Denosumab (Figures 3-6):

Circles (O) present observed data and model-predicted values are represented by the solid lines. A horizontal reference (dotted line) is included on Figures 3 and 4 at the baseline value of 100%. Vertical lines at 24 and 36 months indicate study extension periods (Figure 2). Observed values were reproduced from Miller et al. [2]

Figure 3: Bone resorption (osteoclast function) measured as serum CTx.

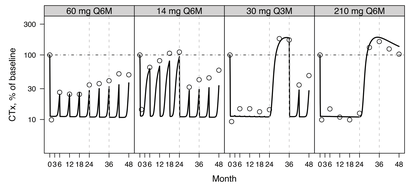



Figure 4: Bone accretion (osteoblast function) measured as serum BSAP.

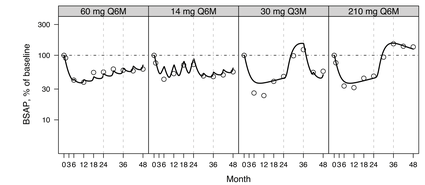



Figure 5: Clinical outcome of lumbar spine BMD.

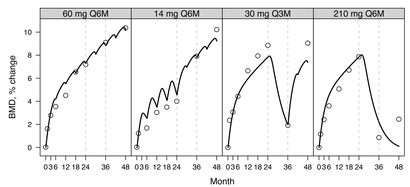
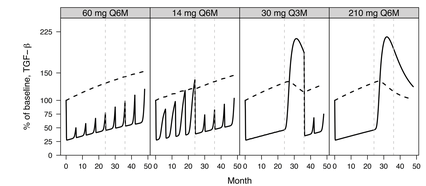



Figure 6: Bone regulation through latent (dashed) and active (solid) TGF-β.




## Summary

- A single differential equation linking longitudinal changes in bone formation and resorption markers described changes in BMD over a 4 year period of different denosumab treatment regimens
- Off-treatment and treatment-reinstitution BMD, CTx, and BSAP changes were predicted without modification of the previously existing multiscale model due to the presence ofl iterature supported mathematical feedback mechansims
- This multiscale model can now be further expanded to accommodate different treatments, diseases, and measured markers by use of scalar functions, and further generalization of the mathematically represented physiologic relationships

## References

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[3] Kearns, A.E., Khosla, S. and Kostenuik, P. Rankl and opg regulation of bone remodeling in health and disease. Endocr Rev (2007).

[4] Peterson, M., Stouch, B., Chen, D., Baughman, S., Holloway, D., Bekker, P. and Martin, S. A population pk/pd model describes the rapid, profound, and sustained suppression of urinary n-telopeptide following administration of amg 162, a fully human monoclonal antibody against rankl, to healthy postmenopausal women. The AAPS Journal 24 (2004).

[5] Quinn, J.M., Itoh, K., Udagawa, N., Hausler, K., Yasuda, H., Shima, N., Mizuno, A., Higashio, K., Takahashi, N., Suda, T., Martin, T.J. and Gillespie, M.T. Transforming growth factor beta affects osteoclast differentiation via direct and indirect actions. J Bone Miner Res 16 (2001):1787–94.

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