METRUM
RESEARCH GROUP

A Physiologically-Based, Multi-Scale, Mathematical Model of Integrated Calcium Homeostasis and Bone Remodeling

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ACoP 2011, Session 8: Advancements and Applications of Multiscale Systems Pharmacology Modeling

Outline

- Motivation: Identifying the Need
- Initial Scope
- Getting Started
- Applications
- Model Development Timeline
- Current State and Beyond

- **M&S As A Tool**: Develop models to understand a drug and its effect on a disease
  - program, maybe TA specific

OR

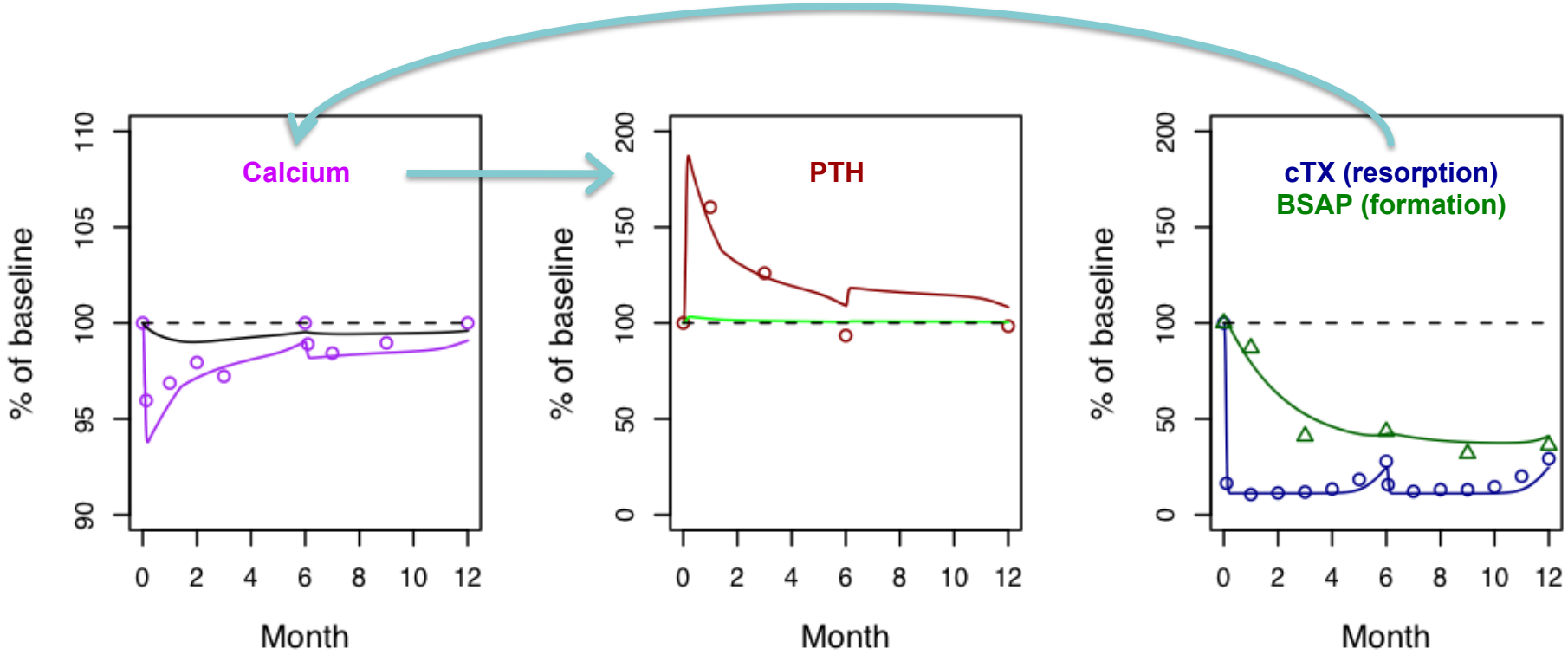
- **M&S As An Underpinning Platform**: Use drugs and diseases to understand a model system?
  - Broad applications

Argument: The latter leaves you better positioned for knowledge transfer and informed cross-talk

- Denosumab (RANK-L inhibitor)

  ↓ bone resorption = ↓Ca from bone = ↓ plasma Ca = ↑PTH

- Understand interrelations
  - Physiologic + pharmacologic
  - Quantified though a multiscale model



As reported in: M. R. McClung, E. M. Lewiecki, S. B. Cohen, M. A. Bolognese, G. C. Woodson, A. H. Moffett, M. Peacock, P. D. Miller, S. N. Lederman, C. H. Chesnut, D. Lain, A. J. Kivitz, D. L. Holloway, C. Zhang, M. C. Peterson, P. J. Bekker, and AMG 162 Bone Loss Study Group. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med, 354(8):821–31, Feb 2006.*

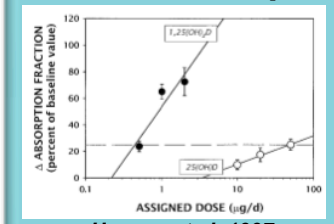
- Develop a mathematical model:
  - Represent physiology
    - Include multiscale mechanisms (signaling → organs → outcomes)
    - Incorporate relevant co-factors
      - Phosphate (PO4)
      - Parathyroid hormone (PTH)
      - Calcitriol
      - Cytokines (e.g. TGF_{beta})
      - Bone turnover markers (e.g. osteoblast/osteoclast associated)
  - Predict Ca homeostasis and bone remodeling
  - Simulate longitudinal therapeutic and disease state effects

- Reference Database
  - 200+ references
  - From 70+ sources (journals, texts, regulatory documents, etc.)
  - Publications: 1959 – present (5+ decades)

- But How to Bring It All Together?

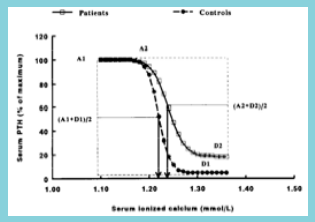
Integrating Existing Data and Models

Calcium Absorption



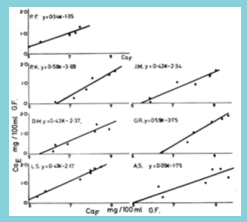
e.g., *Heaney et al. 1997*

PTH Secretion



e.g., *Ramirez et al. 1993*

Calcium Excretion



e.g., *Peacock and Nordin 1968*

Bone Therapeutics

Anabolic (*teriparatide, 2004*)

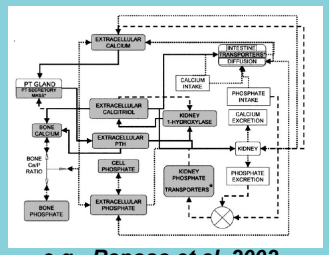
Catabolic (*denosumab, 2006*)

Disease States

Hyper- and hypo-PTH

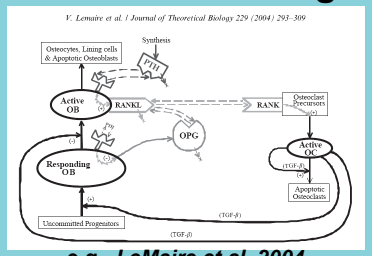
CKD-MBD (*Rix et al. 1999*)

Calcium Homeostasis



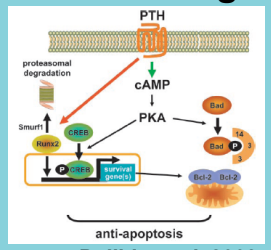
e.g., *Raposo et al. 2002*

Bone Remodeling



e.g., *LeMaire et al. 2004*

Intracellular Signaling



e.g., *Bellido et al. 2003*

- Multiscale Model:
  - *Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63.*

Software

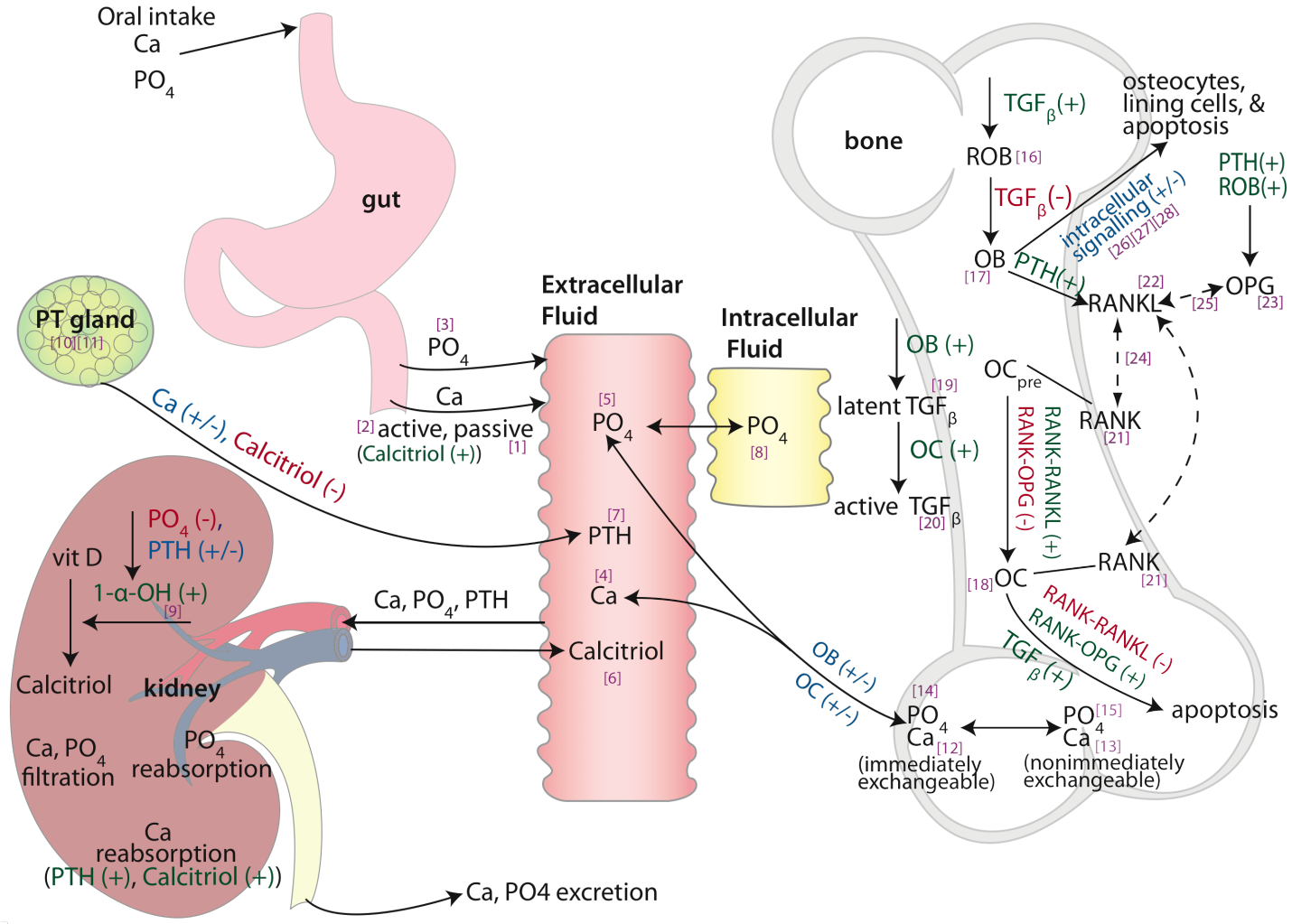
-Original Development

- Berkeley-Madonna

-Additional Development

- WinBUGS
- R (www.opendiseasemodels.org)

Multiscale Model Schematic

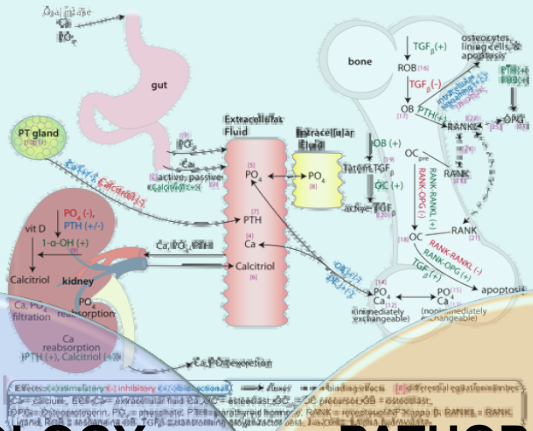


Effects: (+) stimulatory (-) inhibitory (+/-) bidirectional → fluxes - - - binding effects [#] differential equation number

Ca = calcium, ECF Ca = extracellular fluid Ca, OC = osteoclast, OC_{pre} = OC precursor, OB = osteoblast, OPG = Osteoprotegerin, PO_4 = phosphate, PTH = parathyroid hormone, RANK = receptor of NF-Kappa B, RANKL = RANK Ligand, ROB = responding OB, TGFβ = transforming growth factor beta, 1-α-OH = 1 alpha hydroxylase

Schematic of physiologic system model to describe calcium homeostasis and bone remodeling (reprinted from Figure 1 of *(Peterson and Riggs, 2010)*)

PHYSIOLOGY



PHARMACOLOGY

RANK-L inhibition (denosumab)

Intermittent PTH (teriparatide)

GnRH receptor modulation

PATHOPHYSIOLOGY (Disease Progression)

Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD)

Primary Hyper- and Hypo-parathyroidism

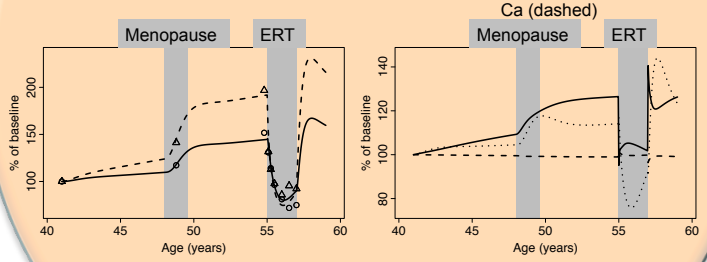
Age + Menopause Effects on Estrogen

AGE + MENOPAUSE

Includes longitudinal estrogen loss
Predicts Ca & bone estrogen-related effects

Bone Markers
Resorption (dashed)
Formation (solid)

Maintain Ca Balance
PTH (solid)
Active TGF-beta (dotted)
Ca (dashed)



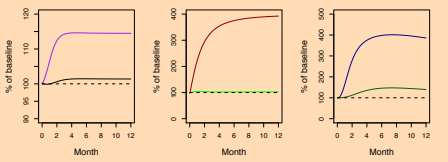
Riggs MM, Gillespie WR, Gastonguay MR, Peterson MC. NIGMS Quantitative Systems Pharmacology Workshop II: September 9, 2010.

DISEASE PROGRESSION

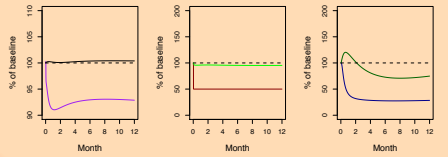
1^0 HYPER- & HYPO-PARATHYROIDISM

Predicts Ca and bone effects

Calcium Increases ← PTH increases → Osteoclasts increase



Calcium Decreases ← PTH decreases → Osteoclasts decrease

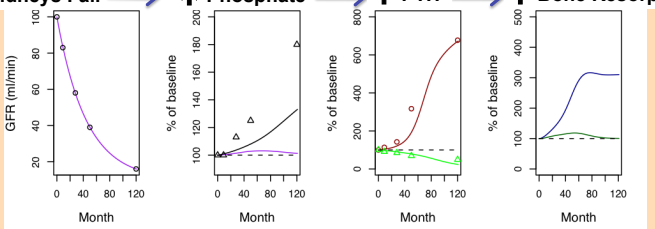


Peterson and Riggs (2010)
Bone 46:49-63 (Fig 5 & 7)

CKD-MBD

Predicts Secondary hyperPTH
Predicts increased bone turnover

Kidneys Fail → ↑ Phosphate → ↑ PTH → ↑ Bone Resorption

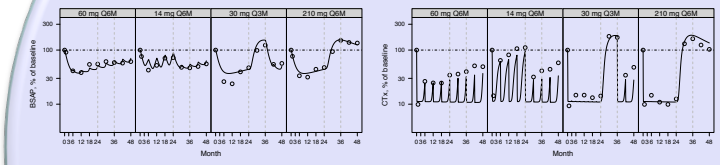


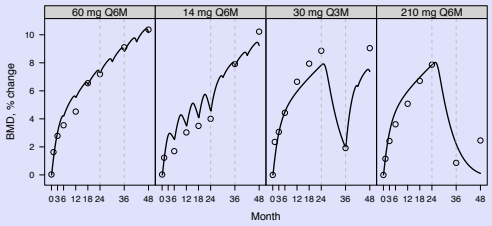
Riggs MM, Gastonguay MR, Peterson MC. AAPS Annual Meeting 2010; Poster # W4403

PHARMACOLOGY

DENOSUMAB

Rebound in bone metabolism is predictable.
BMD can be modeled as a function of bone markers

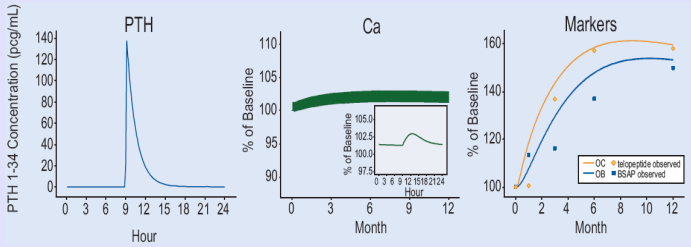




Peterson MC and Riggs MM.. AAPS-NBC: May 2010.

TERIPARATIDE

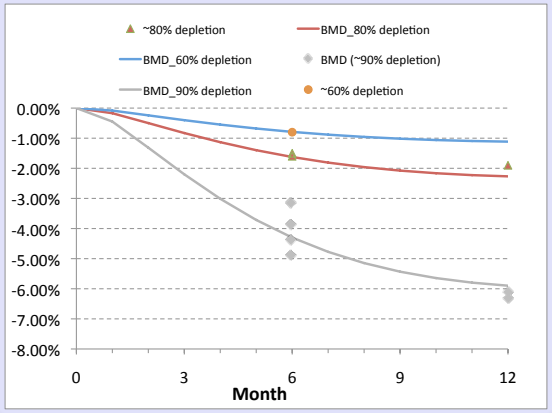
Bone anabolics are predictable.
Effects on Ca / other physiology can be evaluated



Peterson MC and Riggs MM. Bone 46:49-63: 2010

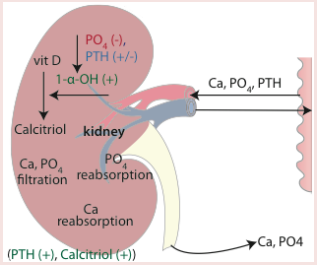
GnRH RECEPTOR

Estrogen-BMD relationship is predictable.
Degree of GnRH modulation targeted



ACoP 2011

CKD-MBD



Chronic Renal Failure

Decreased GFR = Decreased Phosphate Clearance

↓

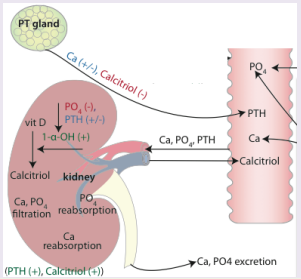
Increased Plasma Phosphate

↓

Decreased 1-α-hydroxylase

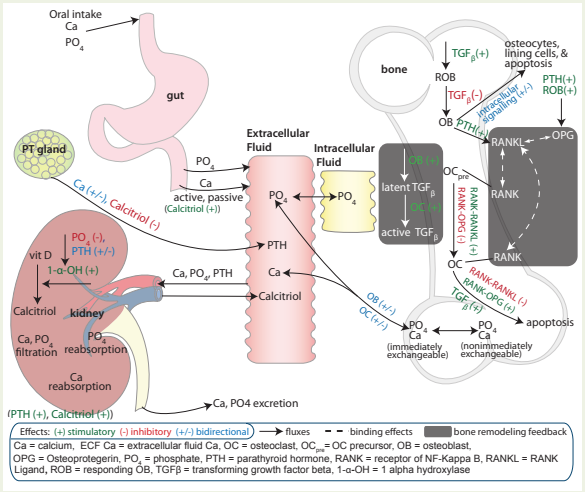
↓

Decreased Calcitriol (active Vitamin D)



PT Gland Feedback

Increased PTH production



Secondary Hyperparathyroidism

Increased RANK-L expression

↓

Increased Osteoclast Activation
Decreased Osteoclast Apoptosis

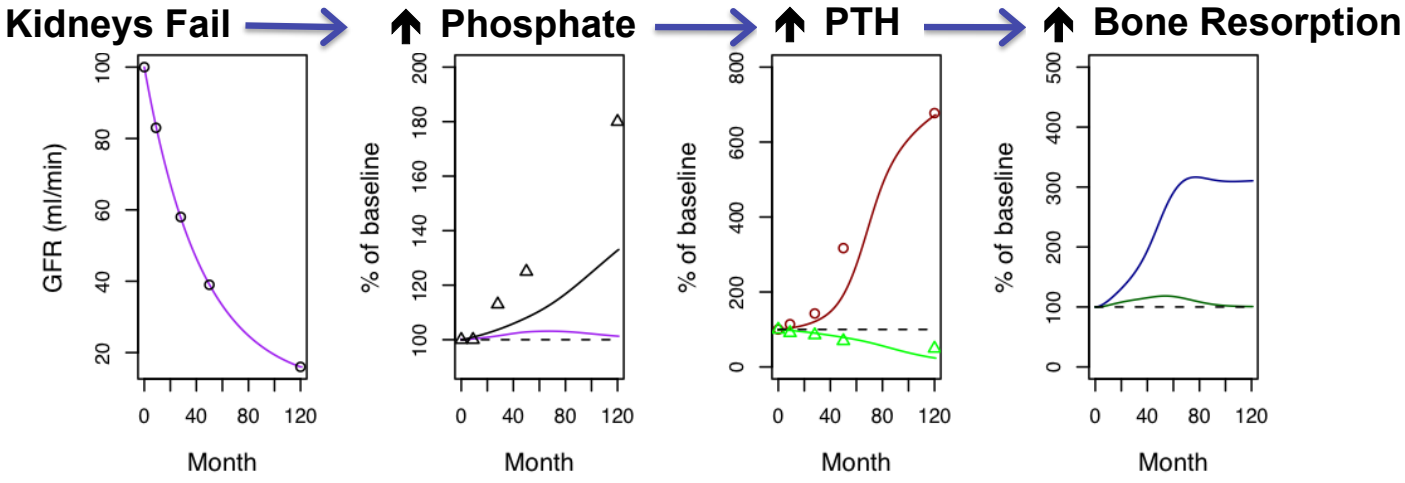
↓

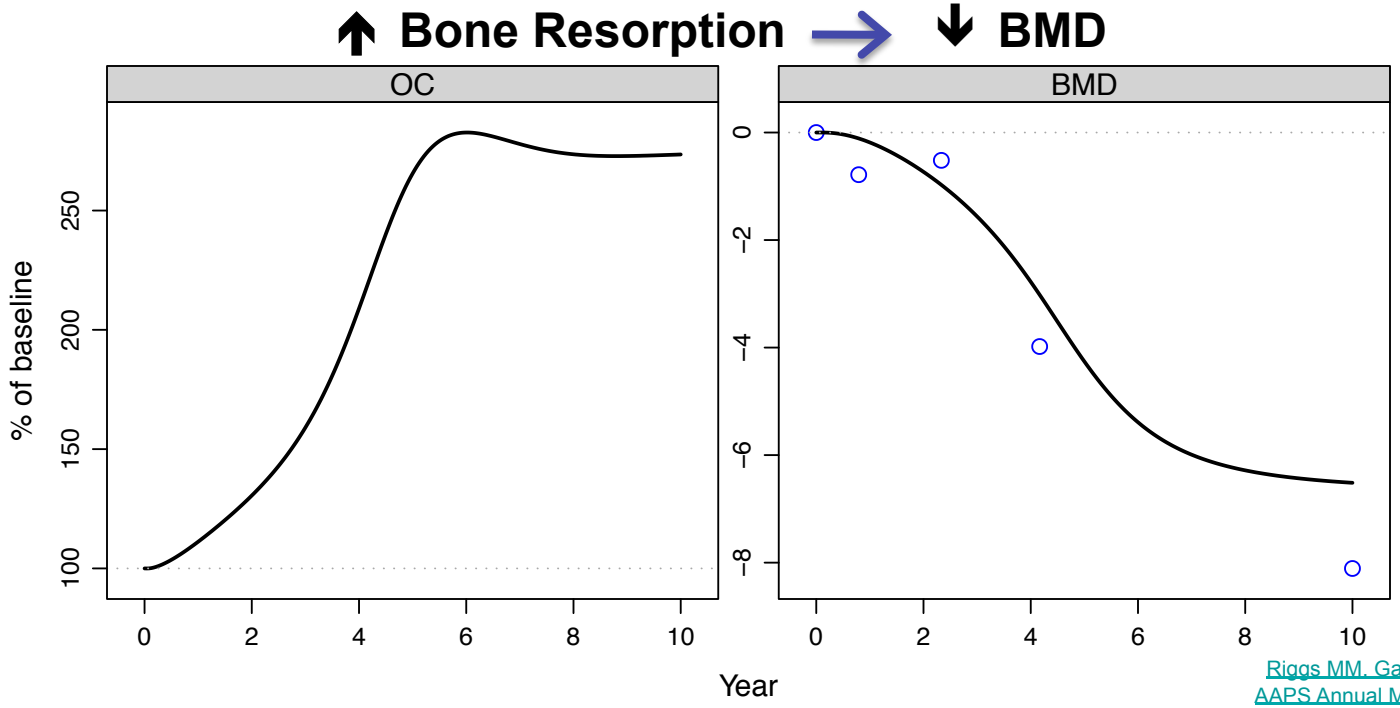
Increased Bone Resorption

↓

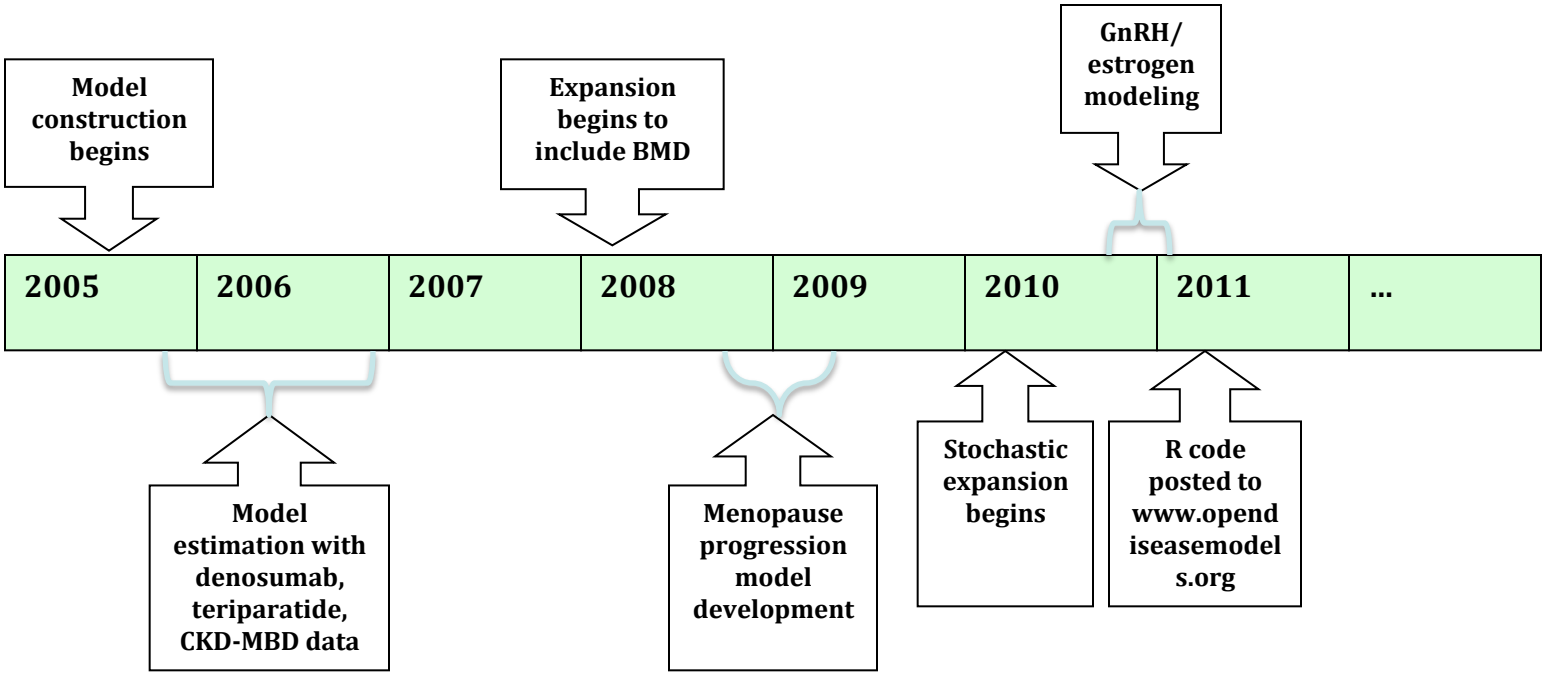
Decreased BMD

CKD-MBD





Riggs MM, Gastonguay MR, Peterson MC. AAPS Annual Meeting 2010; Poster # W4403


Model construction begins
Expansion begins to include BMD
GnRH/ estrogen modeling
2005
2006
2007
2008
2009
2010
2011
...
Model estimation with denosumab, teriparatide, CKD-MBD data
Menopause progression model development
Stochastic expansion begins
R code posted to www.opendiseasemodels.org

Done…

✓ Estrogen-related effects
✓ CKD-MBD
✓ PTH disease & treatment
✓ Denosumab treatment
✓ Link bone markers with BMD

Doing…

➢ Parameter Sensitivity Analysis
➢ Osteo Database: METAMODL™ (www.metamodl.com)

To do…

❑ Marker reconciliation (e.g. NTx/CTx, BSAP/P1NP)
❑ Bone quality / fracture probability
❑ Combination therapies
❑ Therapy switching
❑ Sclerostin
❑ Wnt signalling
❑ Metalloproteases
❑ FGF-23
❑ Additional disease states (Vitamin D, Calcium deficiency)
❑ Etc…

Questions / Comments / Suggestions…

Special thanks to:
ACoP/ASoP
Metrum Colleagues
Mark Peterson / Wojciech Krzyzanski