Systematic Extension of a Physiologic Model of Bone and Calcium Homeostasis

Matthew M. Riggs, Ph.D.
Principal Scientist II
Group Leader, Systems Biology M&S
mattr@metrumrg.com

May 22, 2012
Multiscale Modeling

- Introduction
  - Define ‘Scales’
  - Examples:
    - Guyton’s Cardiovascular Model
    - A Calcium/Bone Model

- Extensions of the Calcium/Bone Model
  - Disease Response (example: Chronic Kidney Disease)
  - Therapeutic Response
  - Ongoing R&D

- In Summary
  - Concept: A Research Platform
  - Parting Thoughts
INTRODUCTION

- What is a Multiscale Systems Model?

From Figure 1 of Riggs M. Multiscale Systems Models as a Knowledge Bridge Between Biology, Physiology and Pharmacology. AAPS Newsmagazine (December, 2011)
- Why Multiscale?

**PHYSIOLOGY**

- 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 Hypoparathyroidism
- Age + Menopause Effects on Estrogen

**INTRODUCTION** - Why Multiscale?
INTRODUCTION

Schematic of Cardiovascular Model

“When he first presented his mathematical model of cardiovascular function … in 1968… responses … (2)… reflected a tone of disbelief and even sarcasm. Dr. Guyton’s systems analysis had predicted a dominant role for the renal pressure natriuresis mechanism in long-term blood pressure regulation, a concept that seemed heretical to most investigators at that time.”


http://www.the-aps.org/membership/obituaries/arthur_guyton.htm
“When he first presented his mathematical model of cardiovascular function … in 1968 … responses … (2)… reflected disbelief or ridicule from some quarters. But Dr. Guyton’s systems analysis had predicted a dominant role for the renal pressure natriuresis mechanism in long-term blood pressure regulation, a concept that seemed heretical to most investigators at that time.”


http://www.the-aps.org/membership/obituaries/arthur_guyton.htm
Multiscale Model of Calcium and Bone

- Original Motivation: Denosumab (RANK-L inhibitor)

\[ \downarrow \text{bone resorption} = \downarrow \text{Ca from bone} = \downarrow \text{plasma Ca} = \uparrow \text{PTH} \]

INTRODUCTION

Multiscale Model of Calcium and Bone

- Intentions
  - Represent physiology
    - Include multiscale mechanisms (signaling $\rightarrow$ organs $\rightarrow$ outcomes)
    - Incorporate relevant co-factors
      » Phosphate (PO4)
      » Parathyroid hormone (PTH)
      » Calcitriol
      » Cytokines (e.g. TGF$_b$)
      » Cell Signaling
      » Bone turnover markers (e.g. osteoblast/osteoclast associated)
  - Predict Ca homeostasis and bone remodeling
  - Provide a platform for evaluating longitudinal therapeutic and disease state effects
INTRODUCTION

Multiscale Model of Calcium and Bone

- Existing Research / Data
  - 200+ references
  - From 70+ sources (journals, texts, regulatory documents, etc.)
  - Publications: 1959 – present (5+ decades)

- But How to Bring It All Together?
**INTRODUCTION**

**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:**

INTRODUCTION

Multiscale Model of Calcium and Bone

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

Effects: (+) stimulatory (-) inhibitory (+/-) bidirectional

- Ca = calcium, ECF Ca = extracellular fluid Ca, OC = osteoclast, OCp = OC precursor, OB = osteoblast
- OPG = Osteoprotegerin, PO4 = 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

©2012 Metrum Research Group LLC

AAPS NBC 2012: Advancements and Applications of MSP Modeling 12
Chronic Kidney Disease-Mineral Bone Disorder

**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

Fig. 1; Riggs MM, Peterson MC, Gastonguay MR. Multiscale Physiology-Based Modeling of Mineral Bone Disorder in Patients With Impaired Kidney Function. J Clin Pharmacol. In press.
EXTENSIONS: Disease Response

Chronic Kidney Disease-Mineral Bone Disorder

Kidneys Fail → Phosphate → PTH → Bone Resorption

Kidney Failure → Phosphate Level → Parathormone Level → Bone Resorption

Bone Resorption → BMD

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

Chronic Kidney Disease-Mineral Bone Disorder

Simulated Effects of CaSR agonism

Fig.4; Riggs MM, Peterson MC, Gastonguay MR. Multiscale physiology-based modeling of mineral bone disorder in patients with impaired kidney function. J Clin Pharmacol, 52(1 Suppl):45S–53S, Jan 2012.

black solid = no intervention; gray dot = 0.33 mmolar Ca Eq; black longdash = 0.67 mmolar Ca Eq; gray dotdash = 1.0 mmolar Ca Eq
EXTENSIONS: Disease Response

Chronic Kidney Disease-Mineral Bone Disorder

Simulated Effects of Calcitriol Infusion

Fig.5; Riggs MM, Peterson MC, Gastonguay MR. Multiscale Physiology-Based Modeling of Mineral Bone Disorder in Patients With Impaired Kidney Function. J Clin Pharmacol. In press.
EXTENSIONS: Disease Response

**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)

**DISEASE PROGRESSION**

**1\(^0\) HYPER- & HYPO-PARATHYROIDISM**
Predicts Ca and bone effects

*Calcium Increases* → *PTH increases* → *Osteoclasts increase*

*Calcium Decreases* → *PTH decreases* → *Osteoclasts decrease*

**CKD-MBD**
Predicts Secondary hyperPTH
Predicts increased bone turnover

Kidneys Fail → Phosphate → PTH → Bone Resorption

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

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

**Riggs MM, Gastonguay MR, Peterson MC. AAPS Annual Meeting 2010; Poster # W4403**
DENOSUMAB
Rebound in bone metabolism is predictable. BMD can be modeled as a function of bone markers

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

PHARMACOLOGY

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

Peterson MC and Riggs MM. AAPS-NBC; May 2010.
Peterson MC and Riggs MM. Bone 46:49-63; 2010
ACoP 2011
- **Ongoing Extensions**
  - Bone markers → Bone Mineral Density → Fracture Risk
  - Vitamin D kinetics and biotransformation

- **Future Plans**
  - WNT/SOST/DKK-1 pathways
  - FGF-23
  - Oncology
  - Glucocorticoid-induced bone loss
- Bayesian Joint Modeling of Bone Mineral Density and Repeated Time-To-Fracture Event for Multiscale Bone Systems Model Extension.

- Vitamin D input: diet and sun
- Biotransformation: involves liver and kidney
- Pharmacology: active Vit D = calcitriol
- Applications: disease states & trial design

Figure 3-1 of Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary Reference Intakes for Calcium and Vitamin D. National Academies Press, 500 Fifth Street, N.W. Washington, DC 20001, 2011.
- **Public Source**
  - Opendiseasemodels.org
  - Extensions available from individual papers and posters: see [www.metrumrg.com/publications](http://www.metrumrg.com/publications)

- **METAOMODL™**
  - Subscription-Based, Therapeutic Area Model and Data Repository
  - Incorporates All Current Ca-Bone Model Extensions
- Multiscale Models as a Knowledge Platform

- A repository of known mechanisms, hypotheses (theory), and assumptions

- Include supporting data

- Input emerging research
  - New data = learn/confirm hypotheses and assumptions
  - Information becomes knowledge (translational, model-based R&D)

- Sharing within and across R&D teams
  - Portable across drug and disease states
  - Expandable to new drug and disease states
- Multiscale Models as a Knowledge Platform
  
  ➢ A repository of known mechanisms, hypotheses (theory), and assumptions
- Why Multiscale?

- Physiology/biology, drugs and diseases inform one another

**PHYSIOLOGY**

- RANK-L inhibition (denosumab)
- Intermittent PTH (teriparatide)
- GnRH receptor modulation

**PHARMACOLOGY**

**PATHOPHYSIOLOGY**

- Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD)
- Primary Hyper- and Hypoparathyroidism
- Age + Menopause Effects on Estrogen
Model construction begins

Model estimation with denosumab, teriparatide, CKD-MBD data

Expansion begins to include BMD

Menopause progression model development

Stochastic expansion begins

GnRH/estrogen modeling

Fracture Risk and Vit D modeling

R code posted to www.opendiseasemodels.org

Implementation in METAMODL™

TIMELINE

2005

2006

2007

2008

2009

2010

2011

2012

...
- Parting Thoughts

- The scales do not need to be all inclusive…
  - but should match the question(s) at hand

- Model validation/evaluation?
  - Consider model validation at different scales

- Team ownership: biologists, pharmacologists, clinicians
  - Shared consensus on assumptions
  - Appropriate representations
    - the known
    - the unknown
    - the ‘to be determined’

- These models are complicated, but…
  - biology, pathphysiology and pharmacology are even more complicated
- Acknowledgements

- Metrum RG
  - Kyle Baron, Ph.D.
  - Marc Gastonguay, Ph.D.
  - Alanna Ocampo, M.S., Ph.D. Student
  - Elodie Plan, Ph.D.

- Mark Peterson, Ph.D., Pfizer (formerly Amgen)

- Pfizer (GnRH modulation modeling)
  - Steve Martin, Ph.D.
  - Piet van der Graaf, Ph.D.
- **Benefits: What’s to be Gained?**

  - selection of therapeutic modality
  - hypothesis driven experimentation
  - holistic drug design
  - selection of target pathways and patient populations
  - dose / regimen selection
  - broad scale understanding of intended (and unintended) effects associated with disease, genetic variants and drug intervention,
  - trial (experiment) simulation/optimization
  - simultaneous predictions of all involved co-factors -- potential for biomarker identification
  - can serve as repository of known, suspected, and assumed effects with supporting data ... information sharing within and across R&D teams
  - …
- Challenges/Barriers: What's holding us back?

- differing role(s) on R&D teams
- sufficient resources (time, people and/or $)
- training -- broad skill set required
- leadership investment in defining opportunities for real impact
- intellectual inertia (differing discipline nomenclatures, perspectives, and motivations to develop models),
- data (formatting, availability, quality)
- …