2010 AAPS CPTR OPEN FORUM

Development of Mechanistic / Multiscale / Systems Biology Models in Clinical Pharmacology and Translational Research:

Do the Challenges Outweigh the Potential Benefits?

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METRUM RESEARCH GROUP

Introductions

- Moderator

- Matthew Riggs, Ph.D. ; Metrum Research Group LLC

- Speaker

- Matthew Onsum, Ph.D. ; Merrimack Pharmaceuticals

- Panelists

- Don Mager, Ph.D. ; SUNY – Buffalo
- Tristan Maurer, Pharm. D., Ph.D. ; Pfizer Inc.

- Sponsors

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Objectives

- **A Viewpoint**
- **Review Definitions and Proceedings**
- **Define the Vision**: What are the benefits?
- **Focus on Reality**: How we face the challenges?
- **Demonstrate Value**: By examples.

Viewpoint

- **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

Definitions

- **Systems biology**: quantifying interactions between biological components
  - Emphasis on how interactions control system kinetics and dynamics (e.g., enzymes and metabolites in a metabolic pathway, or cytokines in an intracellular signaling cascade).
  - Developed "top down" or "bottom up"
  - Recent extensions to organ level functions (e.g., Bassingthwaighte J, Hunter P and Noble D (2009) The Cardiac Physiome: perspectives for the future. Exp Physiol 94:597-605.)

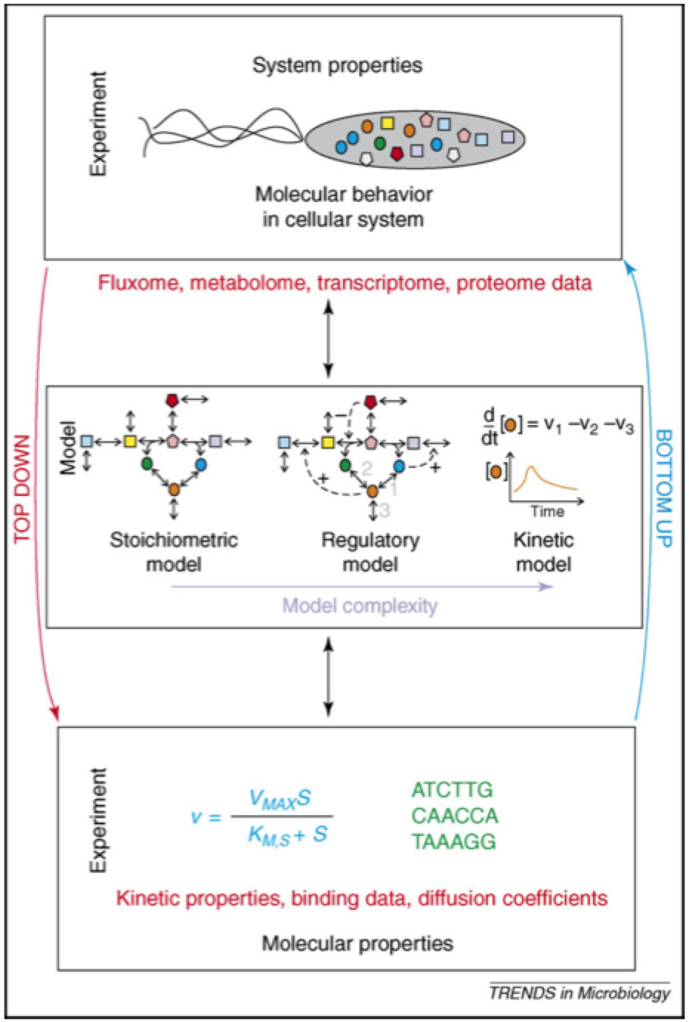


Figure 1 of Bruggeman FJ and Westerhoff HV (2007) The nature of systems biology. Trends Microbiol 15:45-50.

Definitions

- **Clinical Pharmacology / Translational Research**: Aim = provide 'bench to bedside' continuum
  - Integrate data through PK-PD models:

    preclinical → clinical biomarkers → clinical outcomes
  - Model complexity increasing with:
    - Expanded understanding of the biology & pathophysiology
      - » "Mechanistic" models are now incorporating cellular mechanisms and organ level functions = 'top-down' expansion
    - Integration of epidemiologic and evidence-based information
      - » Decision analyses = 'bottom-up' expansion

Definitions

- **Multiscale Modeling:** the natural 'confluence' of systems biology, clinical pharmacology and translational research
  - uses mathematics and computation to represent and simulate a physiological system at more than one biological scale.
    - Biological scales include atomic, molecular, molecular complexes, sub-cellular, cellular, multi-cell systems, tissue, organ, multi-organ systems, organism, population, and behavior.
      http://grants.nih.gov/grants/guide/pa-files/PAR-08-023.html

Proceedings

- NIGMS Quantitative and Systems Pharmacology Workshops

- Workshop I (September 25-26, 2008) Breakout Sessions
  - Horizontal systems integration
  - Vertical systems integration
  - Quantitative biology and pharmacology
  - Education and training
  - Data management
  - Meeting summary: http://www.nigms.nih.gov/News/Reports/PharmacologyConference20080925.htm
- Workshop II (September 9-10, 2010)
  - http://meetings.nigms.nih.gov/index.cfm?event=agenda&ID=8316

Proceedings

- **FDA Cooperative Research and Development Agreements (CRADAs)**
  - **Office of Clinical Pharmacology / Division of Pharmacometrics**
    - **Alzheimer's Disease Model**
    - **FDA Pharmacometrics 2020 Strategic Goals**
  - **Division of Applied Pharmacology Research** (Thomas J. Colatsky, Ph. D., Director)
    - **Drug induced liver injury**
    - **Cardiovascular risk**

Potential Benefits: Defining the Vision

- Model applicable across development programs and therapeutic areas… allow for rapid information sharing, review and sharing of new model developments
  - External (training, registration, research)
  - Internal (cross functional: discovery through evidence-based outcomes and back again)

Potential Benefits: Defining the Vision

- Integrate known with unknown (e.g., Bayesian methods)
  - Scale past, present and future data (internal & external)
  - Understand model limitations
    - Sensitivity analyses
    - Incorporate parameter uncertainties
  - Quantify inter- and intra-patient variability

Potential Benefits: Defining the Vision

- Facilitate translational research efforts by allowing for early exploratory development *in silico*
  - Pathway identification
  - Combination treatment evaluation
  - Kinetic & chrono effect exploration
  - Susceptible / resistant genotype identification (patient selection)

Challenges: Getting Realistic

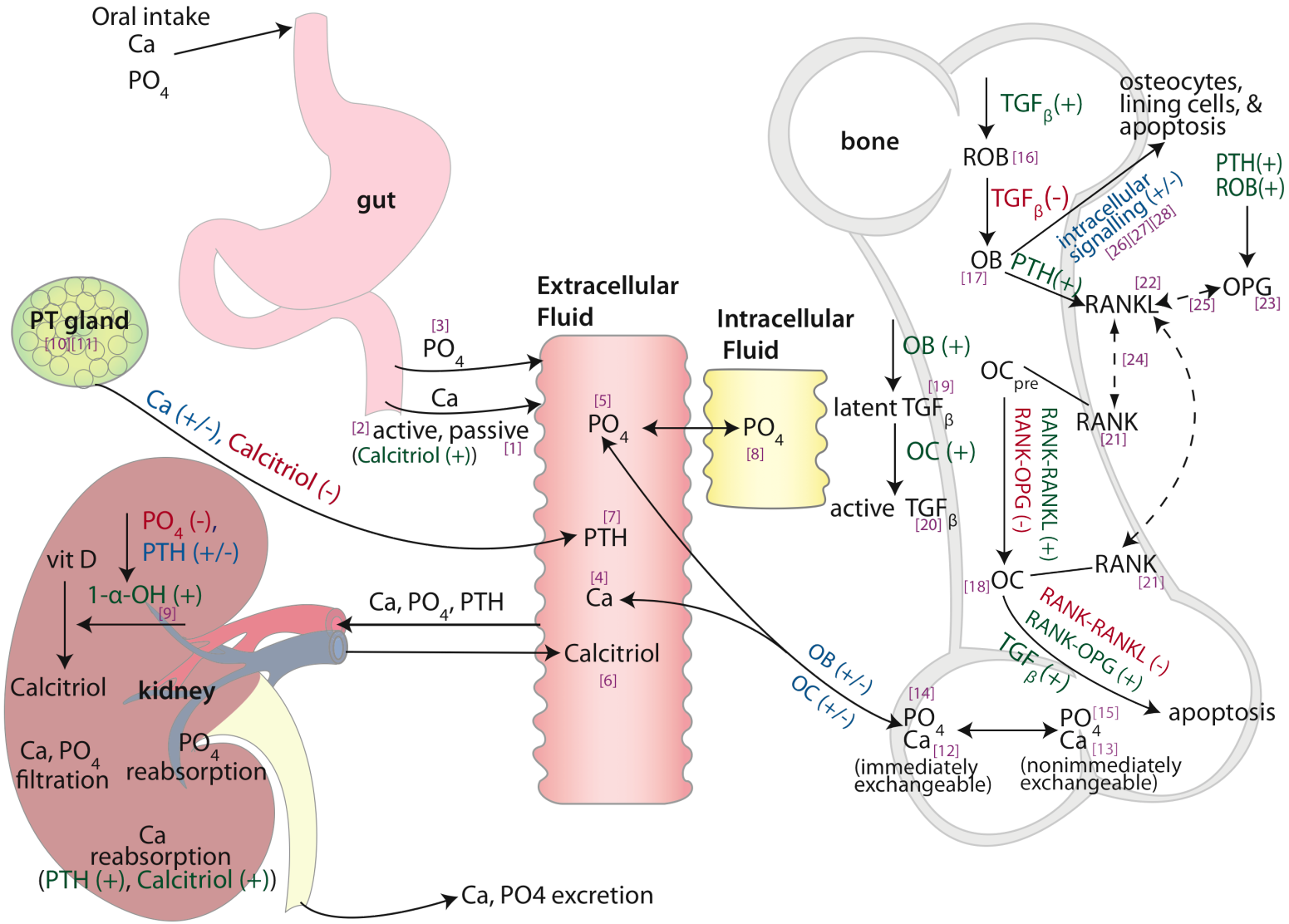
- Motivation
  - Convince decision makers
    - Information gain worth time & cost
    - How? By example…
  - Convince ourselves to share
    - Pre-competitive data and models
    - Across academic/industrial modeling and simulation communities
    - How?
      - Common language(s)
      - Software with sufficient capabilities (e.g., stochastic ODEs)
      - Consortiums & well managed collaborations

Challenges: Getting Realistic

- What and how to share?
  - Collecting existing experimental data in a centralized database, and conducting additional experimentation as necessary
  - Code and, as importantly, what it does and doesn't do
- Why? Transition and translation of multilevel models to clinical applications
- What else is missing?
  - Significant need to expand current educational programs in quantitative pharmacology and pharmacometrics

The Value of Multiscale Models

- Example: Calcium / Bone Multiscale Model
  - Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63.
  - A physiologically-based, multiscale model used to predict progressive bone mineral density loss due to chronic renal disease.
    - Poster #: W4403
    - Session Date: Wednesday, November 17, 2010
    - Session Time: 08:00 am-12:00 pm
    - Location: Exhibit Hall B1



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

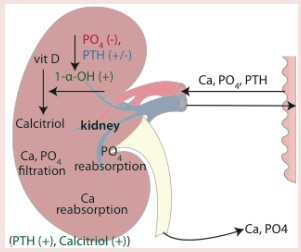
Ca = calcium, ECF Ca = extracellular fluid Ca, OC = osteoclast, OC_{pre} = OC precursor, OB = osteoblast, OPG = Osteoprotegerin, PO_4 = phosphate, PTH = parathyroid hormone, RANK = receptor of NF-Kappa B, RANKL = RANK Ligand, ROB = responding OB, TGFβ = transforming growth factor beta, 1-α-OH = 1 alpha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

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

Breadth of Applications

- **Work completed / in progress**
  - Renal insufficiency
  - Vitamin D deficiency
  - Estrogen (menopause effects, HRT therapy)
  - Calcium receptor sensitivities (agonism, antagonism)
  - PTH treatment/abnormalities
  - Denosumab treatment
  - Drug/Disease → Bone Markers → BMD
- **Work envisioned**
  - Marker reconciliation (e.g. NTx/CTx, BSAP/TRAP)
  - Bone quality/fracture probability
  - Combination / switching therapies
  - Emerging pathways: sclerostin, wnt, cathepsin K, metalloproteases, FGF-23
- **Adaptation can occur relatively quickly**

Disease Progression: Chronic Renal Failure



Chronic Renal Failure

Decreased GFR = Decreased Phosphate Clearance

↓

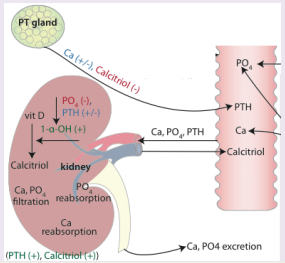
Increased Plasma Phosphate

↓

Decreased 1-α-hydroxylase

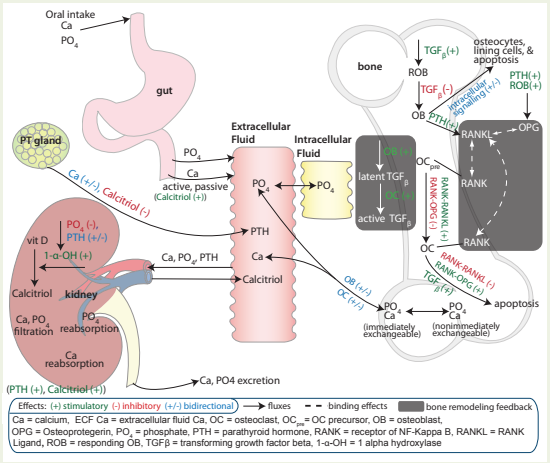
↓

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

Disease Progression: Chronic Renal Failure

Kidneys fail → Phosphate increase → PTH increases → Osteoclasts increase

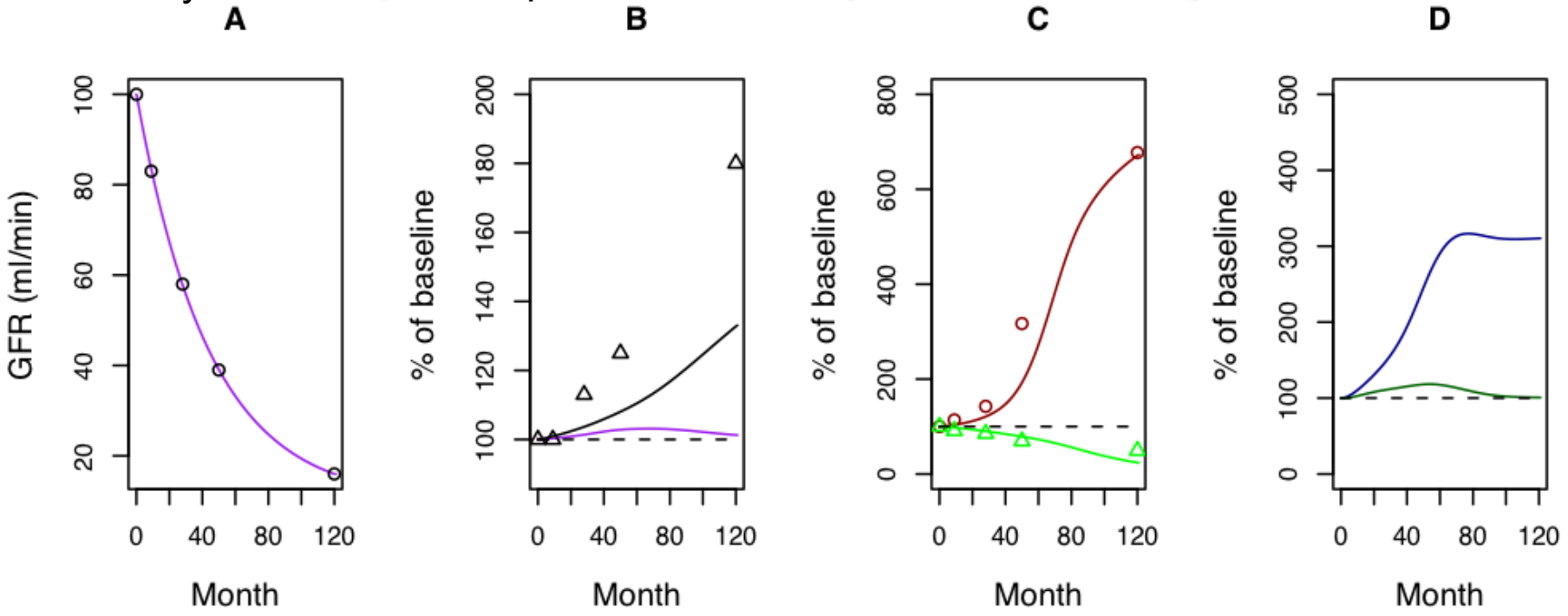
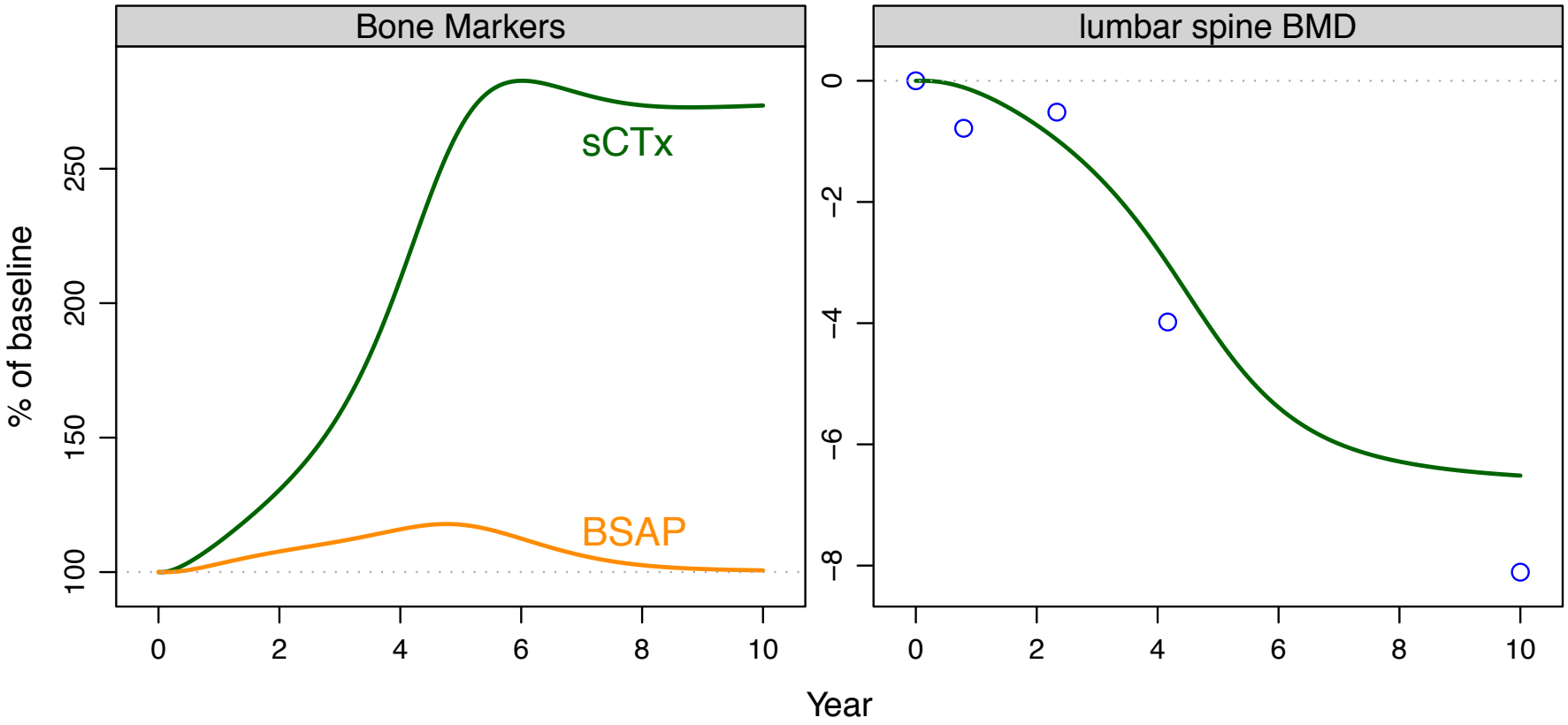


Figure 6 of *Peterson and Riggs (2010) Bone 46:49-63*

Original Data Source*: Rix et al. (1999) Kidney Int 56:1084-93*

Disease Progression: Chronic Renal Failure

Osteoclasts increase → **BMD decreases**



Circles = Lumbar spine BMD scaled from *Rix et al. (1999) Kidney Int 56:1084-93*

The Value of Multiscale Models

Examples

1. Disease progression
   - Known mechanism, data available, evaluate therapeutic interventions
     - Chronic Renal Failure
   - Known mechanism, little or no controlled, longitudinal data
     - Primary Hyper- and Hypo-parathyroidism
   - Several possible mechanisms, available data, evaluate for 'control' longitudinal effects
     - Effects of age and menopause on estrogen, Ca and bone
2. Therapy discontinuation
   - Denosumab treatment interruption

Summary

- Multiscale models represent an opportunity
  - The benefits, the vision is clear
  - The challenges are not new and are not insurmountable

- Discussion Points
  - Benefits
  - Challenges

Survey

1. Models developed to simultaneously understand biochemistry, physiology, pathophysiology and pharmacology are:
(a) on our future path to successful therapeutic development (8)
(b) too complicated to be of any real use (5)
(c) nice to have, but not necessary
(d) not something I know enough about to comment on (1)

2. I have used, or been on a team that has used, a "mechanistic" PK-PD model to support drug development
(a) on several occasions (6)
(b) Once (3)
(c) not yet (5)

3. My institution has an integrated system for translating models developed using nonclinical data into clinical programs:
(a) yes, with operational success (2)
(b) yes, in theory only (3)
(c) somewhat, but not well defined (6)
(d) not defined (3)

4. Systems biology, or multiscale, models can be use to:
(a) understand and quantify the complexities of biology and disease (2)
(b) identify target pathways involved in disease propagation for new therapies (2)
(c) identify patient specific characteristics (e.g., genomics differences) that may render them more or less responsive to a given therapy (1)
(d) all of the above (9)
(e) none of the above

5. "Top down", "bottom up" or "middle out" strategies for building mechanistic / multiscale / systems models are useful for describing:
(a) molecular and sub-cellular mechanisms (1)
(b) cellular, tissue and organ systems
(c) multi-organ systems, organism, population, and behavior (1)
(d) all of the above (8)
(e) I'm not familiar with these types of modeling strategies (4)

6. If your company has applied multilevel systems models to development programs, how has the work been resourced?
(a) internal dedicated systems modeling group or individual (5)
(b) combination of internal and outsourced efforts (5)
(c) ad-hoc internal efforts (2)
(d) outsourced project (1)
no answer (1)

"***Systems pharmacology*** is helping us put the 'pharmacology' back into pharmacology"

Paraphrased from participant, NIGMS QSP Workshop II, September 9, 2010