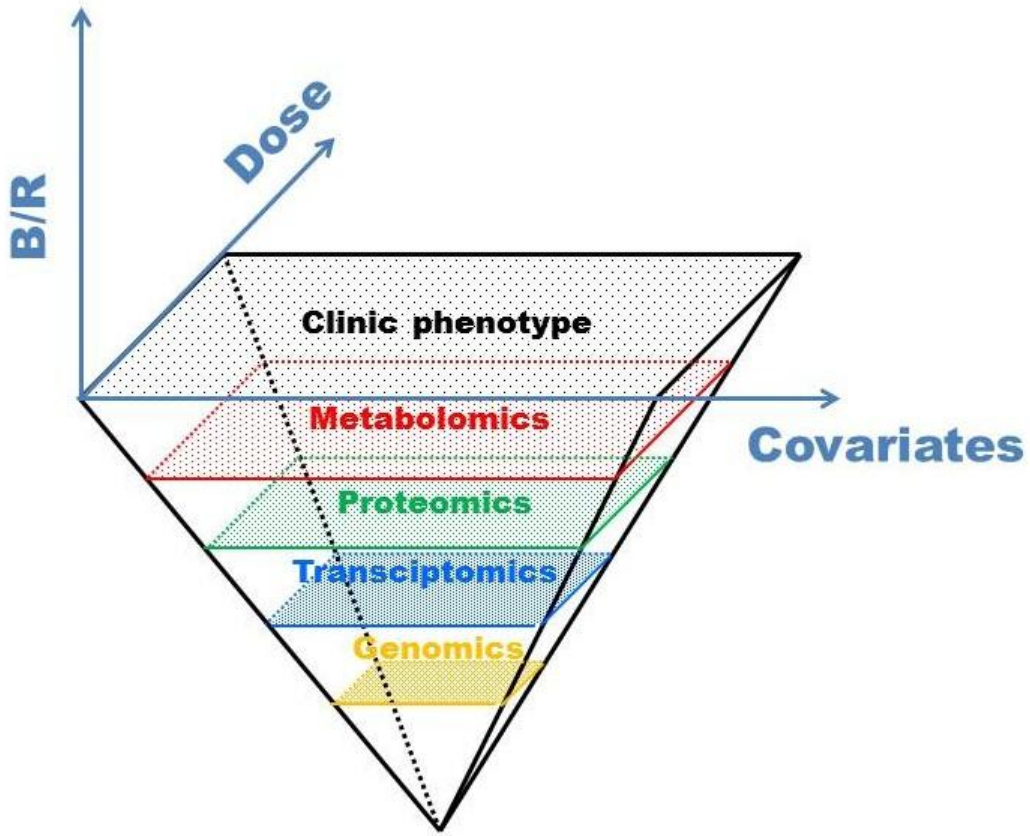
Chancen und Limitationen von PK/PD Modellen

Stephan Schmidt, Ph.D.

Center for Pharmacometrics and Systems Pharmacology (CPSP),
University of Florida, Orlando, USA

23. Jahrestagung der Pau-Ehrlich-Gesellschaft fuer Chemotherapie e.V.,
Dresden, 12. Oktober 2012

Observation Levels in Pharmacology



Pharmacometric Models

⇩

Mechanism-Based Models

⇧

System Pharmacology Models

*Adapted from: Post et al. (2005) Pharm Res **22**:1038-1049.*

*Lesko and Schmidt (2012) Clin Pharmacol Ther **92**: 458-466.*

Population PK(/PD) Analysis

- Determine PK model structure for the population
- Estimate typical (mean) population PK parameters and inter-individual variability
- Estimate individual PK parameters
- Estimate residual variability
- Identify measurable sources of variability in PK and describe their relationship to PK parameters
- http://team.inria.fr/popix/files/2011/11/PopulationApproach.swf

Population vs. Traditional Approaches for PK(/PD) Data

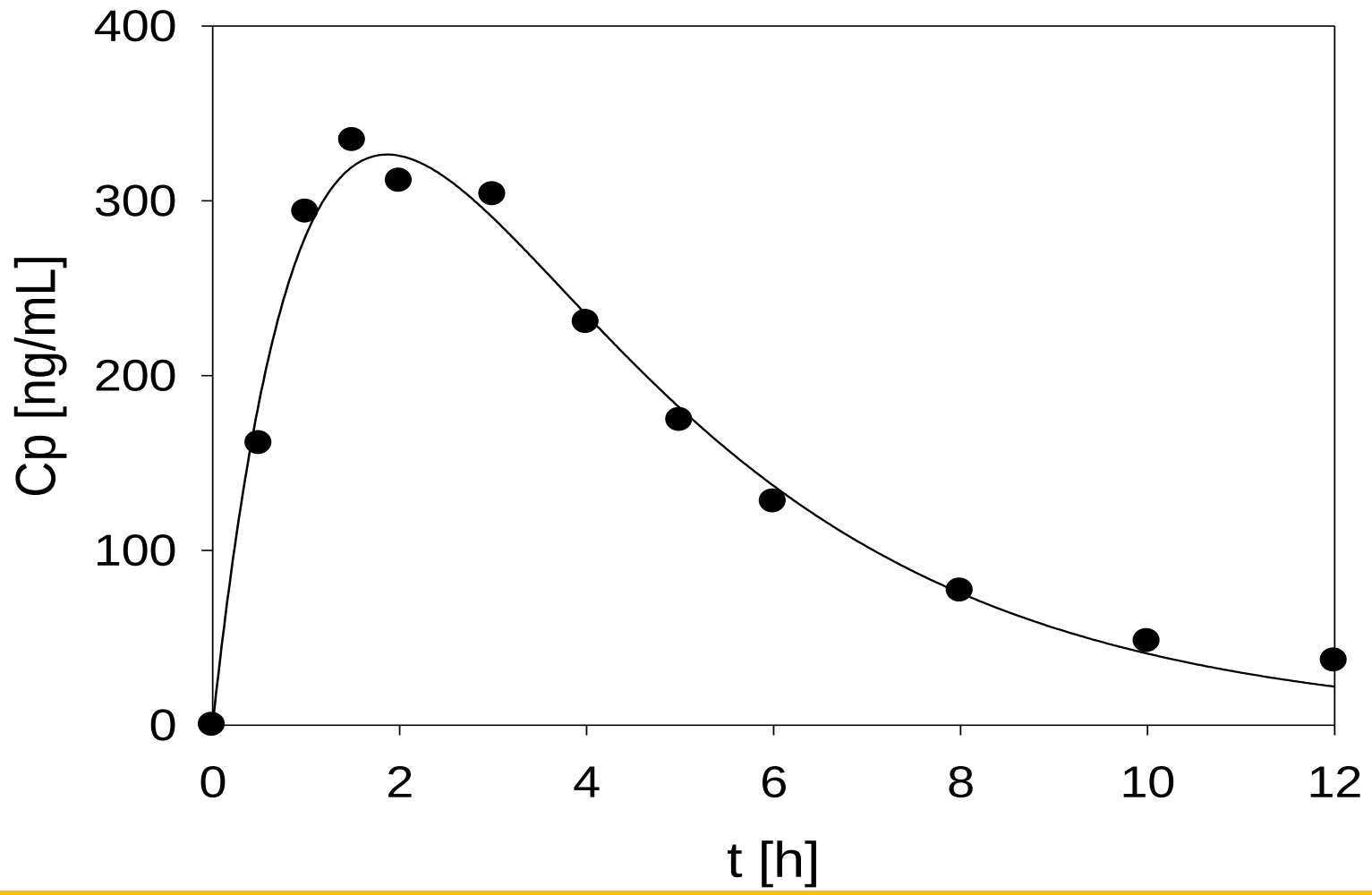
Population PK(/PD)

- Sparse sampling
- Single large study or data pooled from different studies
- Heterogeneous population
- Allows studying several factors
- Complex data analysis
- Exploratory

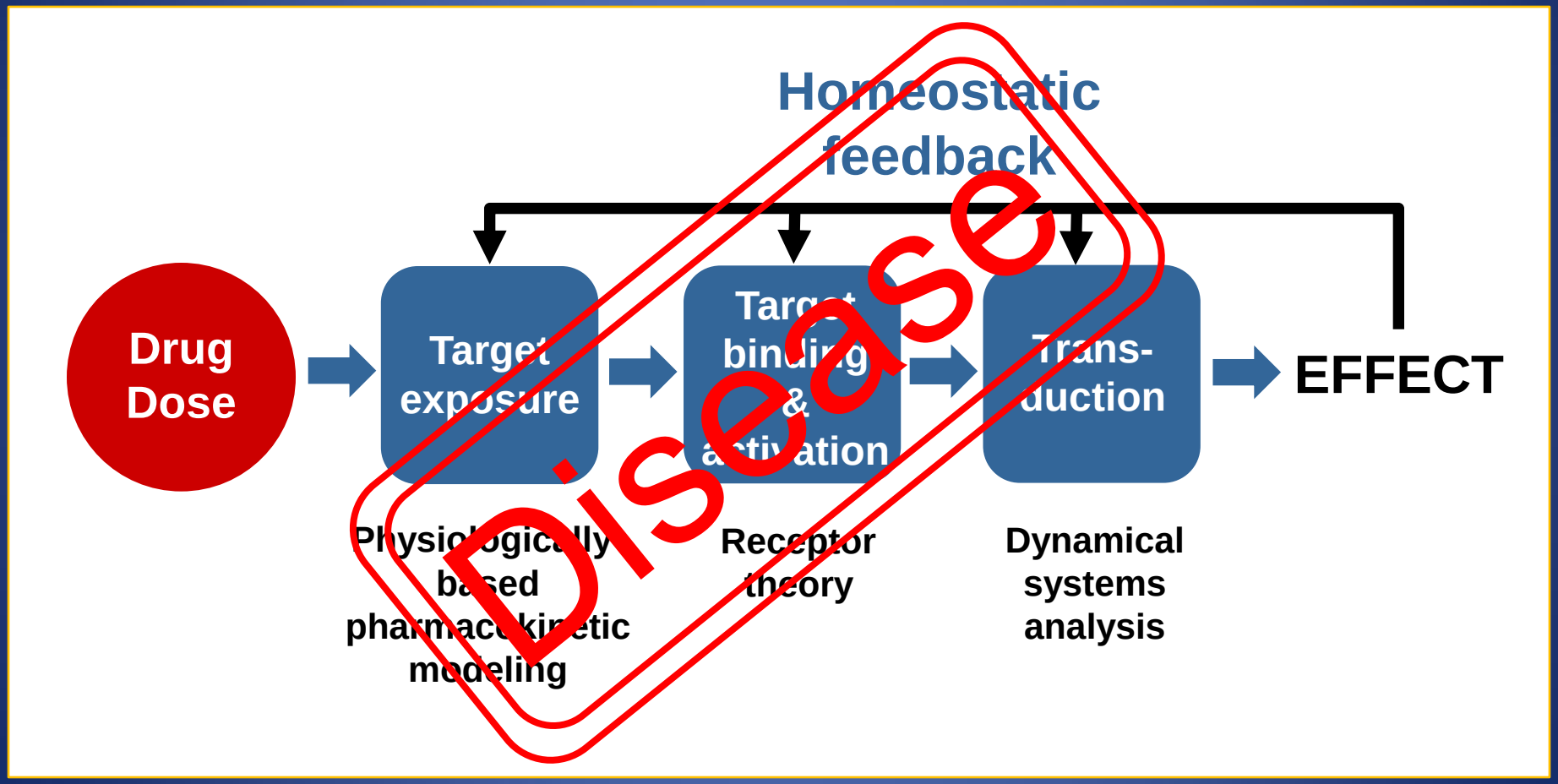
Traditional PK(/PD)

- Extensive sampling
- Single small study
- Homogeneous population
- Single factor per study
- Non-compartmental data analysis
- Confirmatory

Data Requirements



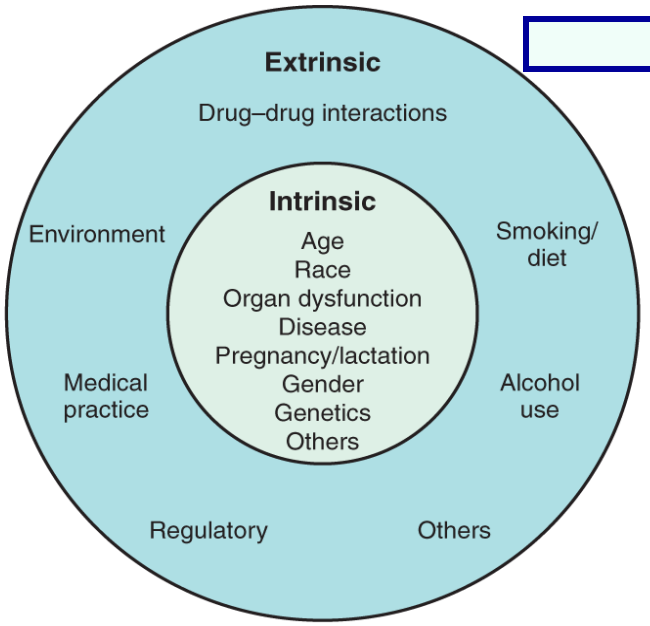
Mechanism-Based Models



Modified from: Danhof et al. (2007) Annu. Rev. Pharmacol. Toxicol. ***47****:357-400.*

Physiology-Based Modeling

Intrinsic/extrinsic Factors



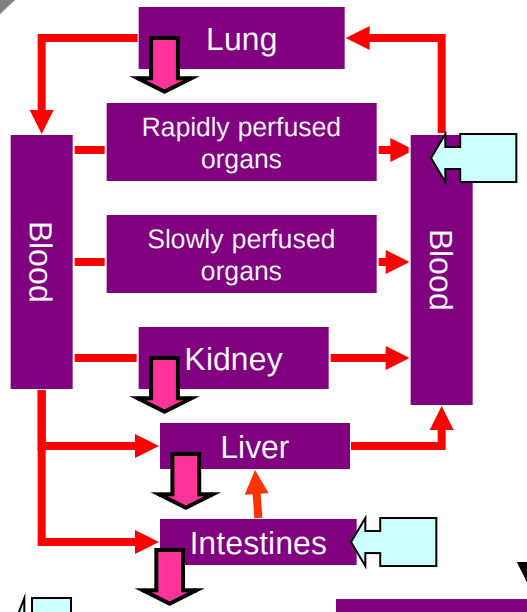
Huang and Temple, 2008

Individual or combined effects on human physiology

PBPK Model components

System component (drug-independent)

Drug-dependent component



ADME, PK, PD and MOA

Metabolism
Active transport
Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding

Dosing

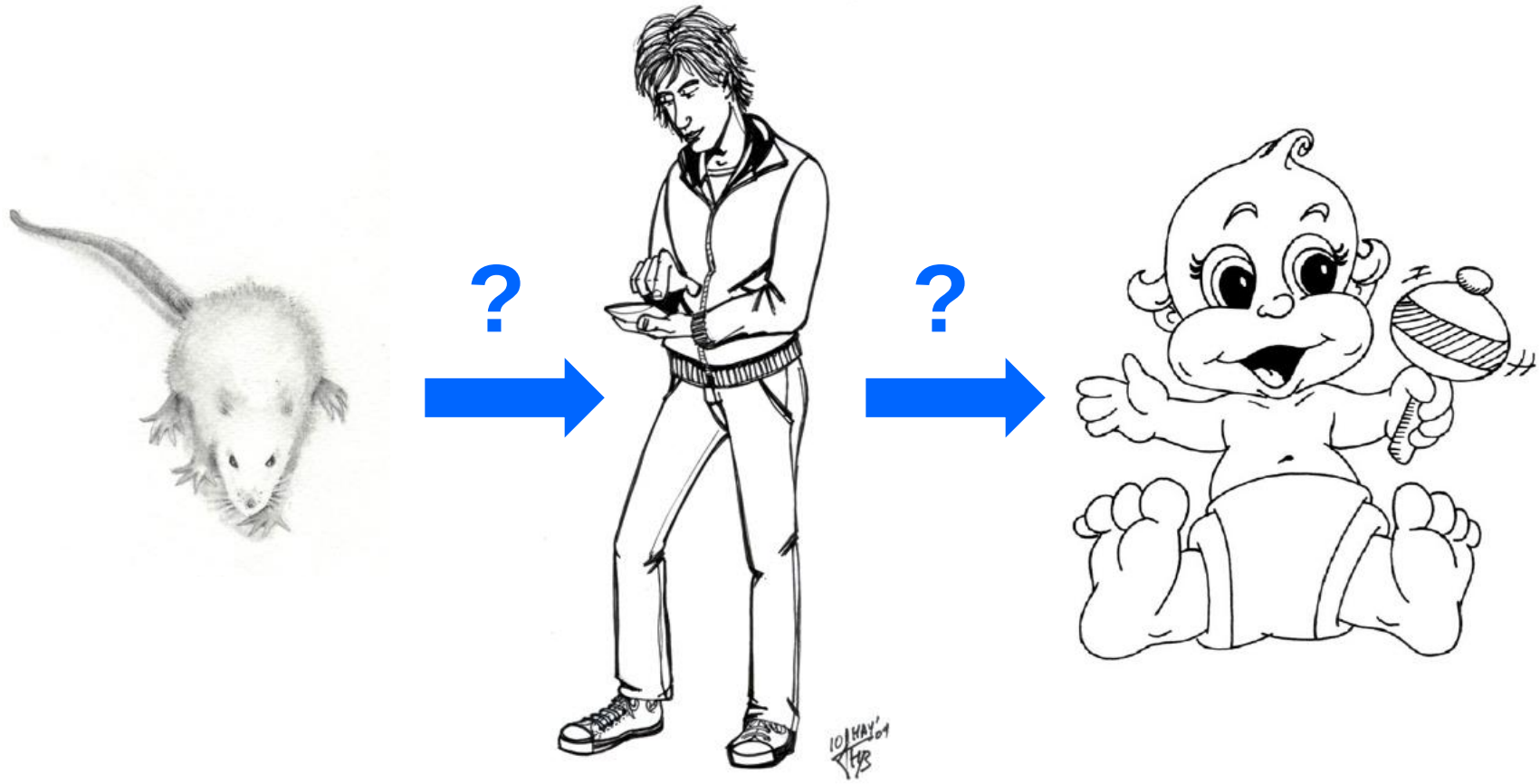
Elimination

PBPK Model

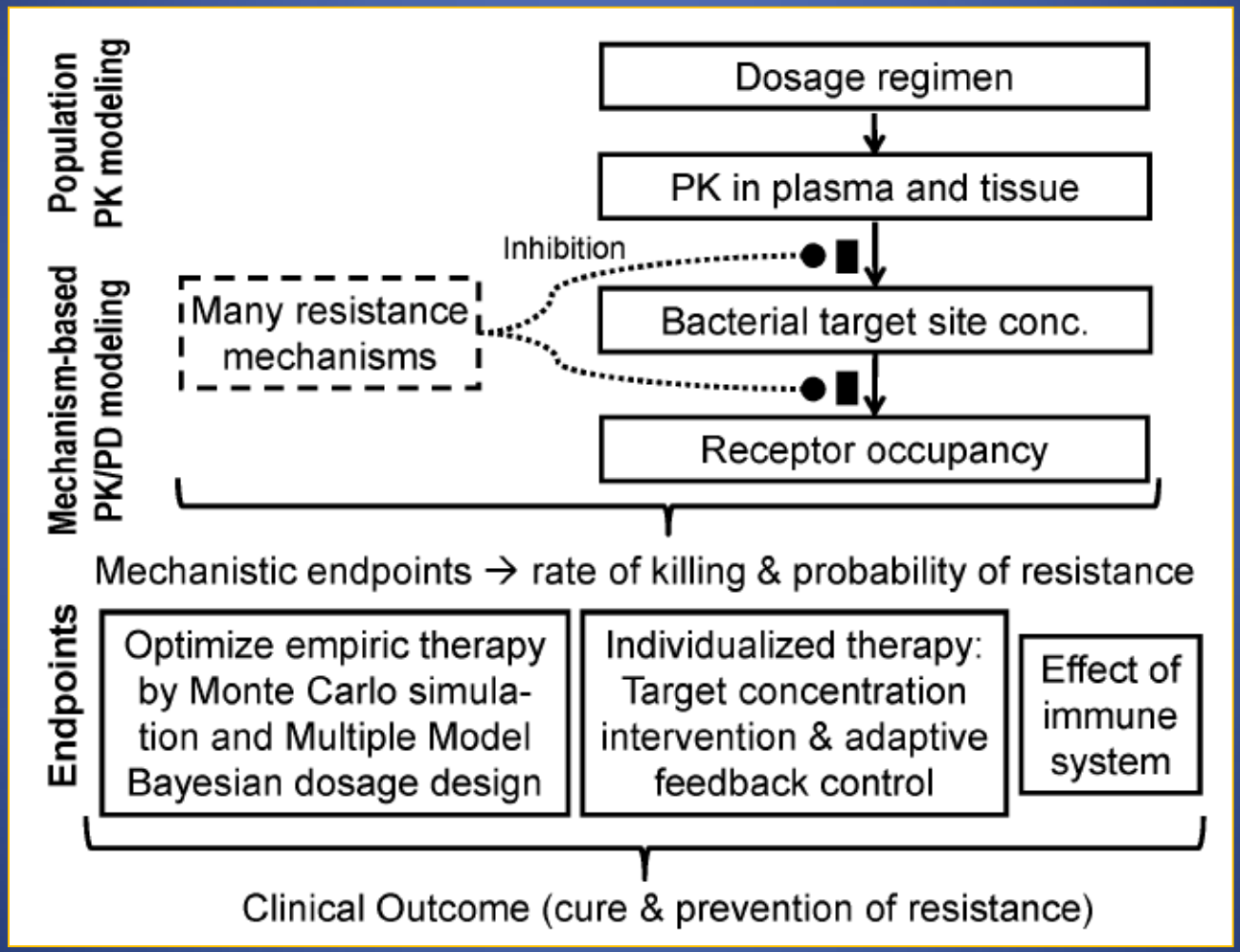
Predict, Learn, Confirm, Apply

Zhao P, et al Clin Pharmacol Ther 2011

Extrapolation (Scaling) of PK/PD by Function Rather Than Size

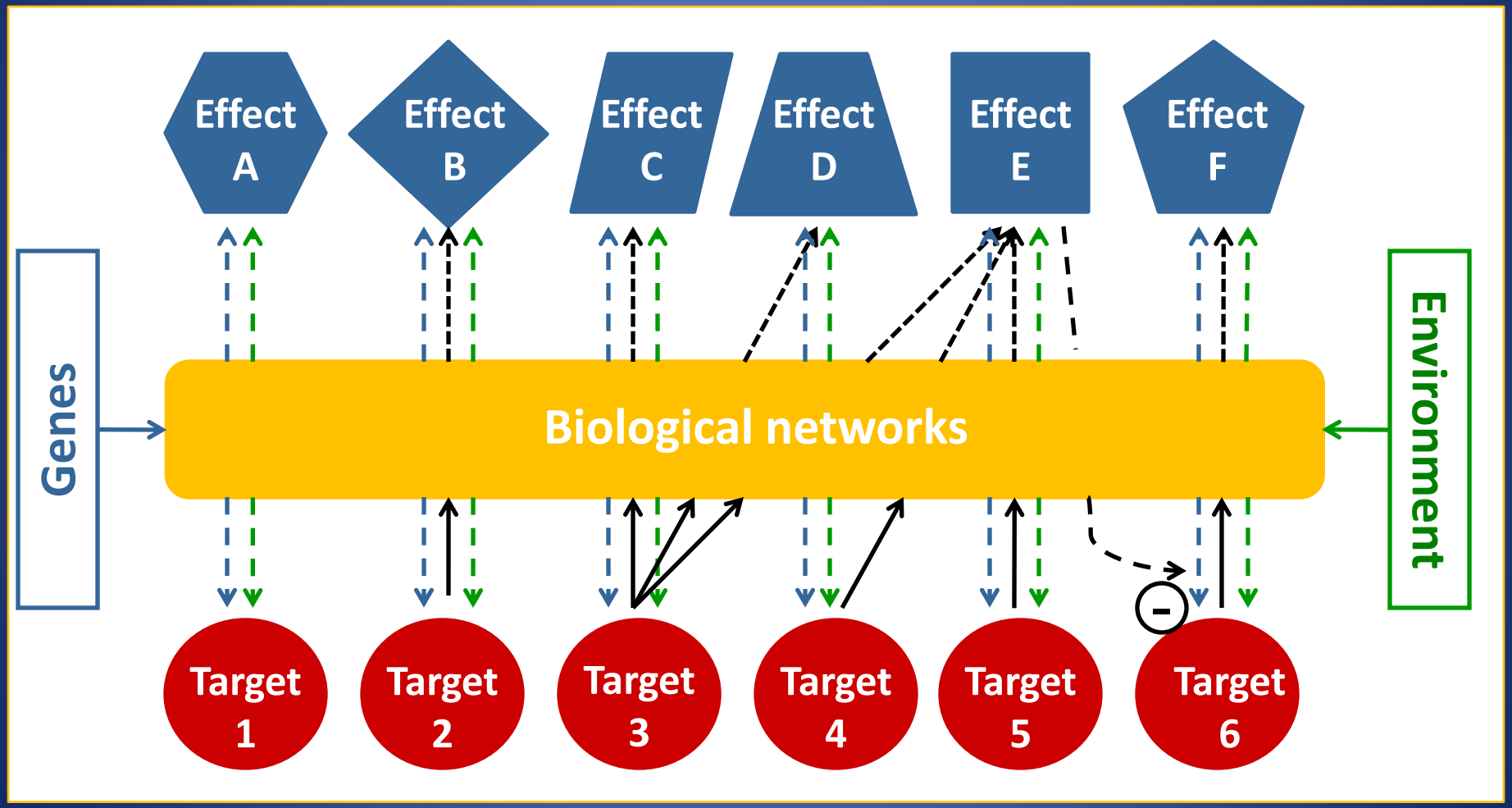


Mechanism-Based PK/PD Models



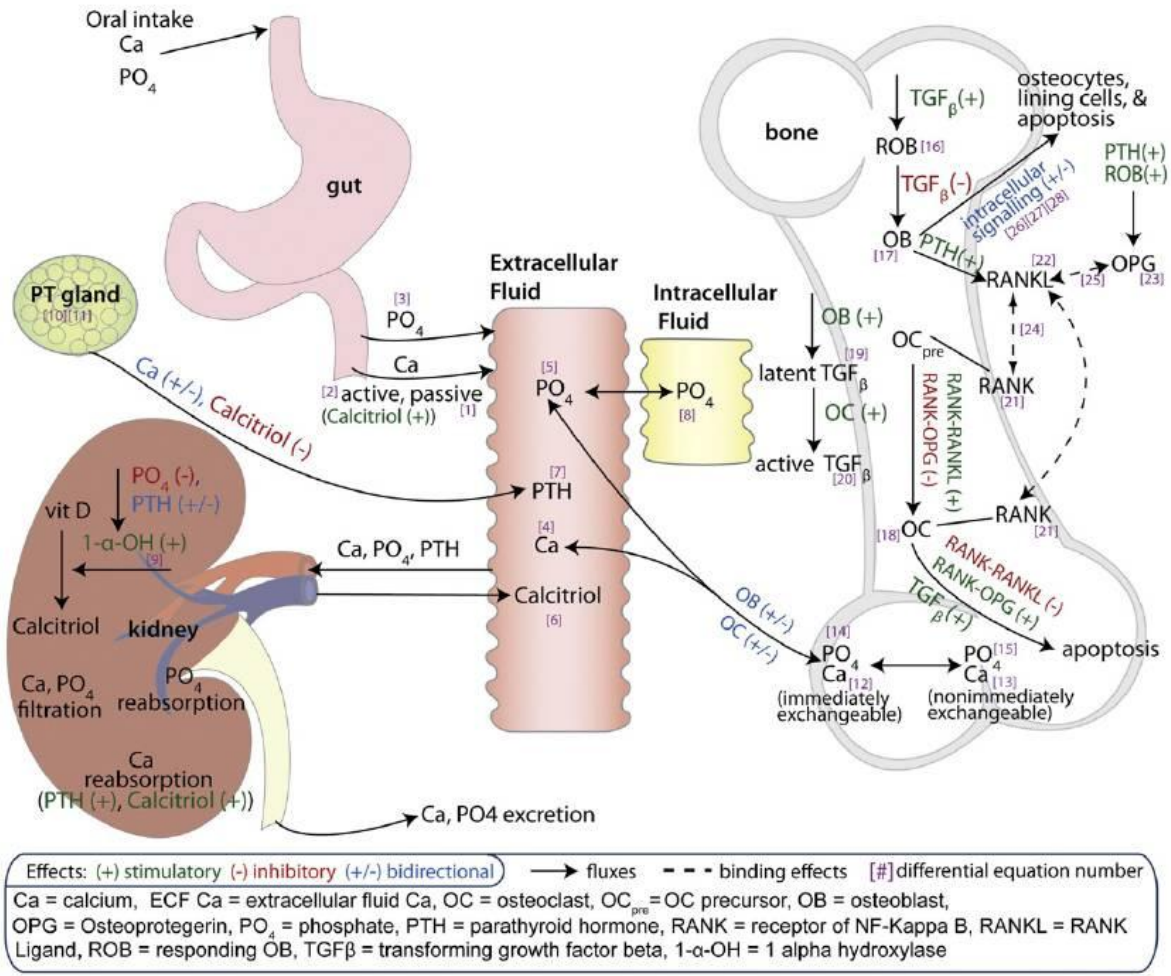
*Bulitta et al. (2011) Curr Pharm Biotechnol. **12**:2044-61.*

Systems Pharmacology Models: Network Analysis



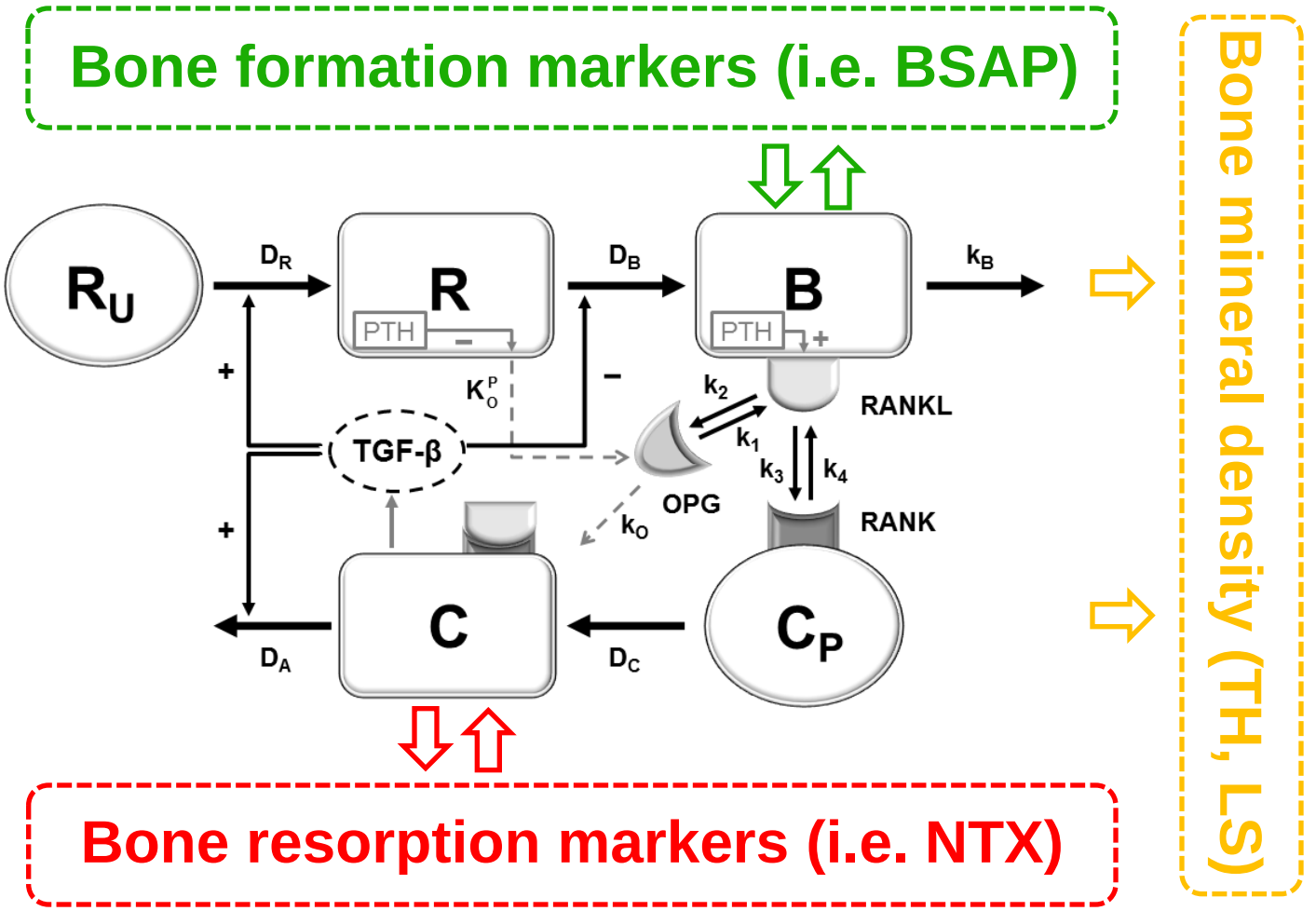
Modified from: Kohl et al. (2010) Clin Pharmacol Ther. 88: 25-33.

What Are the Challenges?



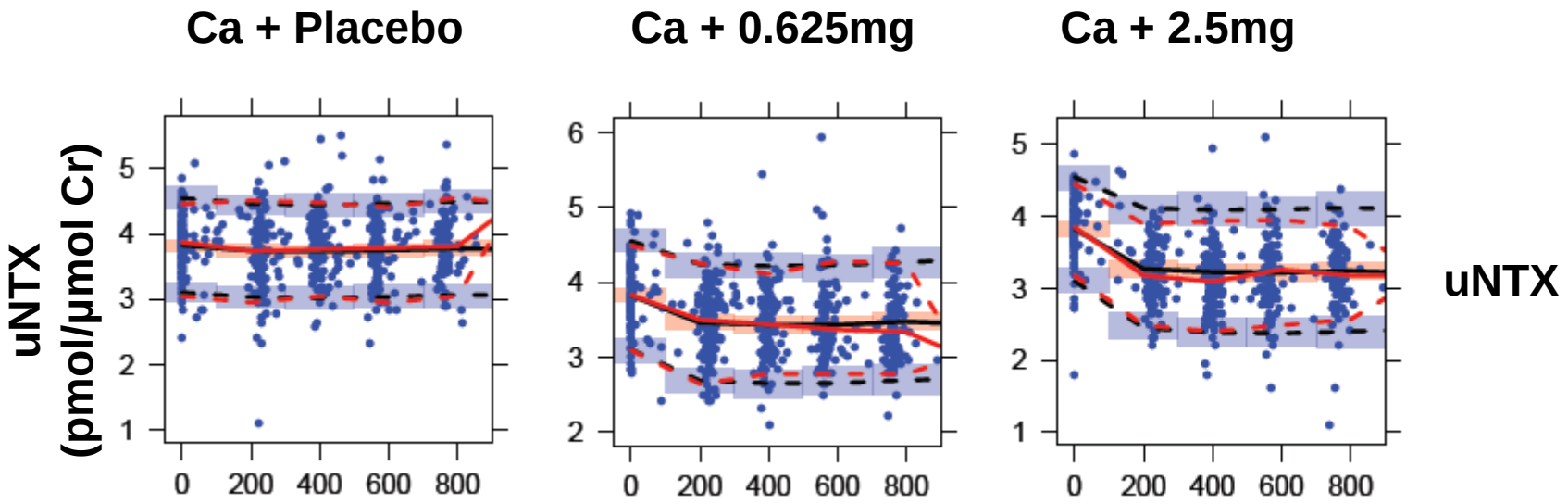
*Peterson and Riggs (2010) Bone **46**:49-63.*

System Pharmacology Models

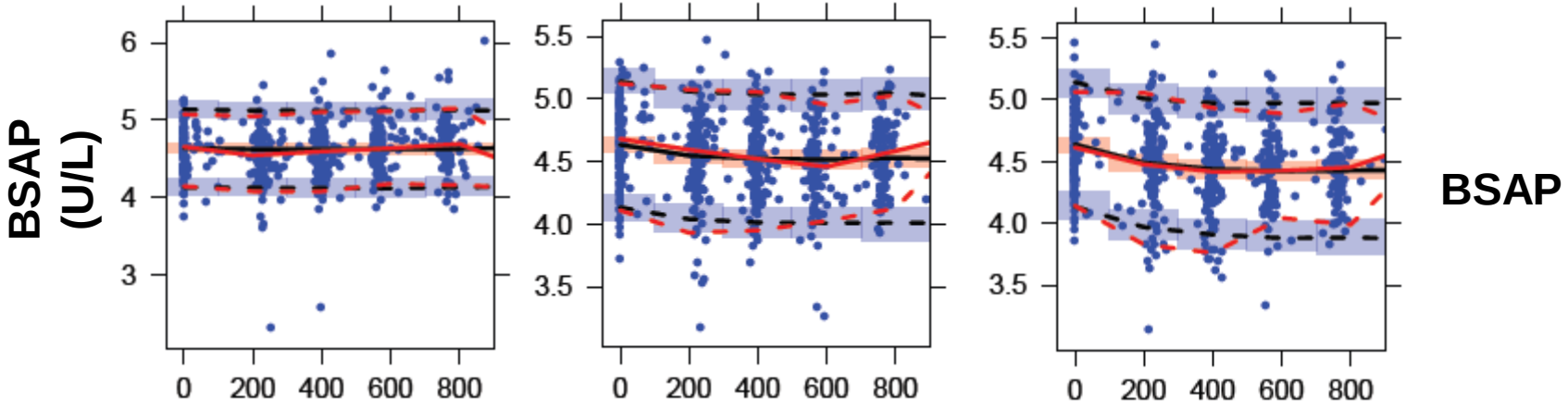


Post et al. currently under submission with J Pharmacokinet Pharmacodyn

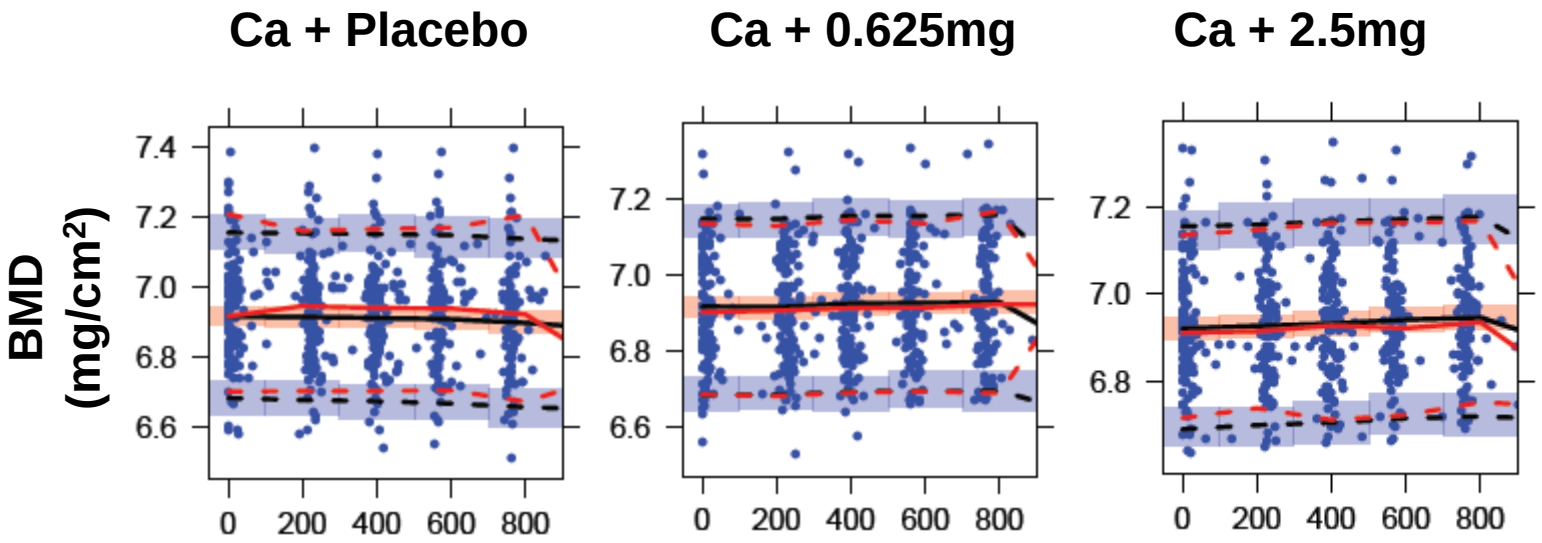
Bone Removal



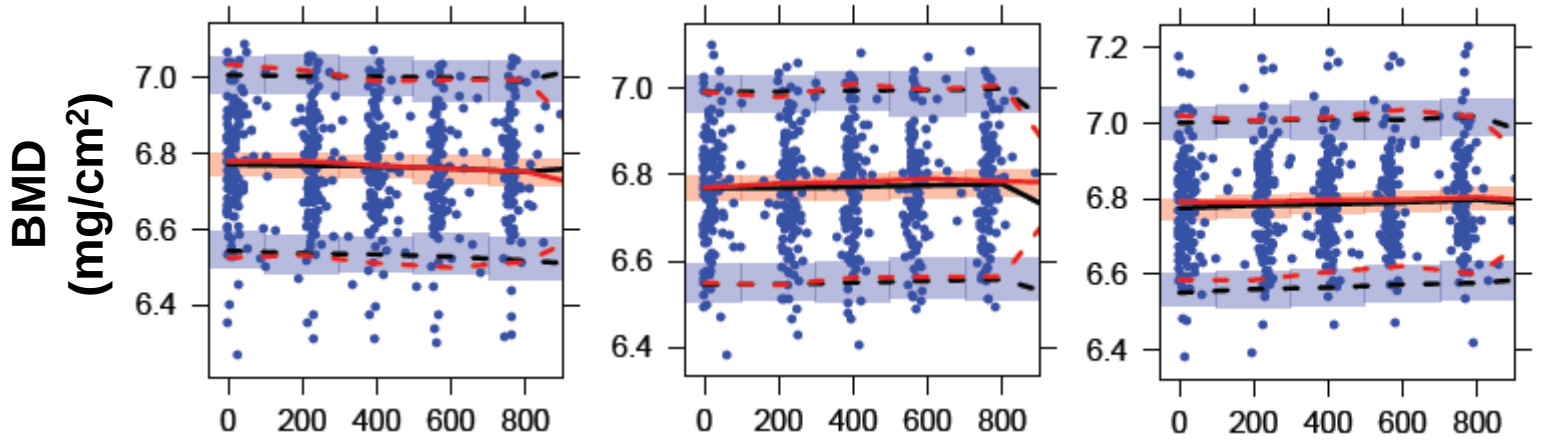
Bone Formation



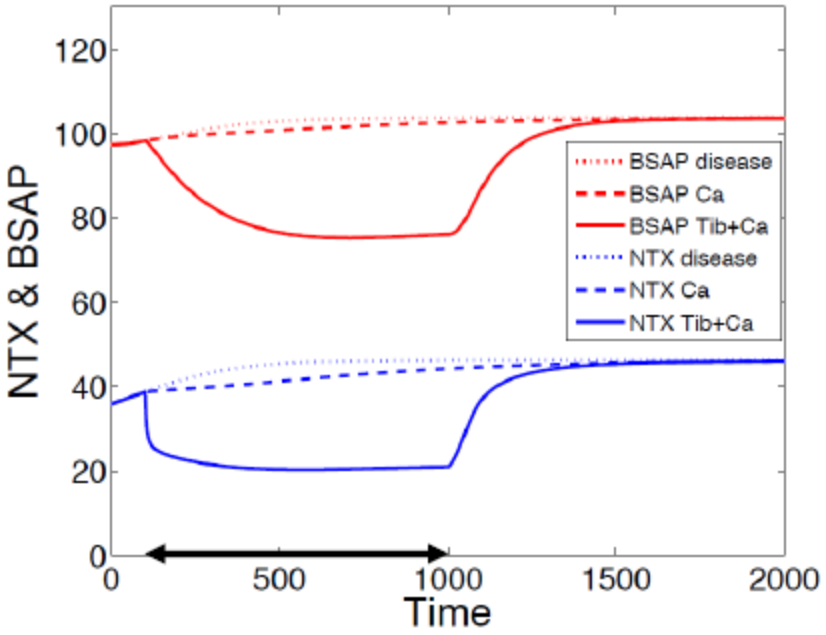
Bone Mineral Density (Lumbar Spine)



Bone Mineral Density (Total Hip)

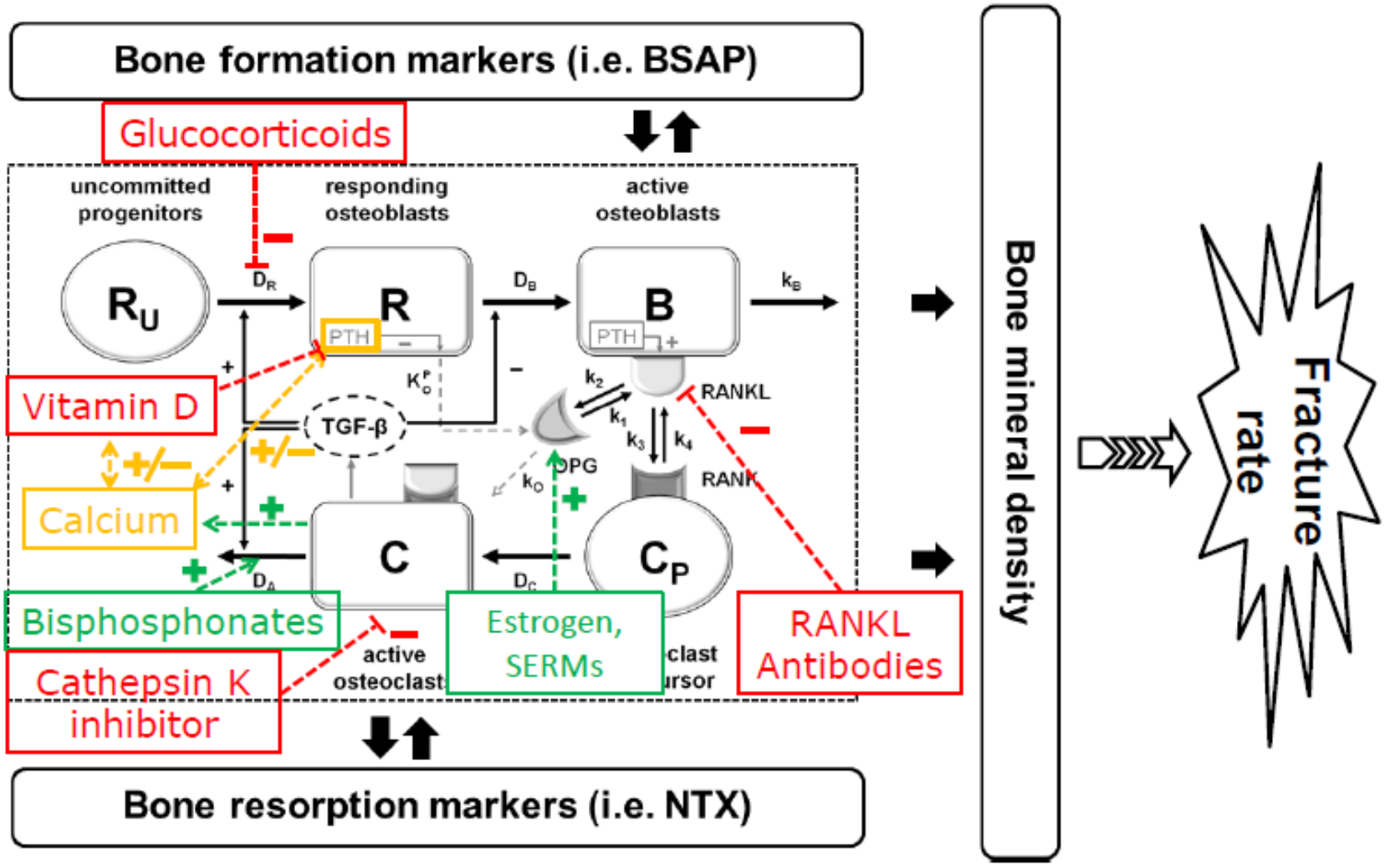


Impact on Study Design



Left panel: change of ***BSAP*** and ***NTX*** over time due to disease (dotted), placebo (dashed) and tibolone (solid) treatment.

Opportunities for Evaluating On/Off-Target Effects



Challenges

- Availability of freely-accessible data
- Availability of easy-to-use software for computing and graphing
- Genetic and non-genetic data (covariates) to explain interindividual differences in treatment response
- Training of students and working professionals in multidisciplinary teams
- Crosstalk between disciplines


FLORIDA