Systems Pharmacology

A day in the life

May 06, 2019

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METRUM
RESEARCH GROUP

Session Description and Objectives

- Description: Six pharmaceutical predictive modelers will share the day-to-day methods, challenges, teams, and applications specific to their respective disciplines.

- Introduce and foster an appreciation of what Predictive Modelers in other disciplines contribute to pharmaceutical R&D;
- Develop an understanding of common and unique approaches across PM disciplines; comparisons and contrasts will be carried into the following breakout sessions

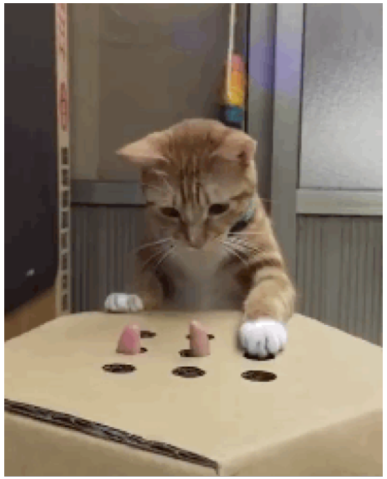
What is Systems Pharmacology?

Tagline

If I push this button (i.e. – block this pathway), why does THAT happen?

What it feels like sometimes

Whack-a-mole



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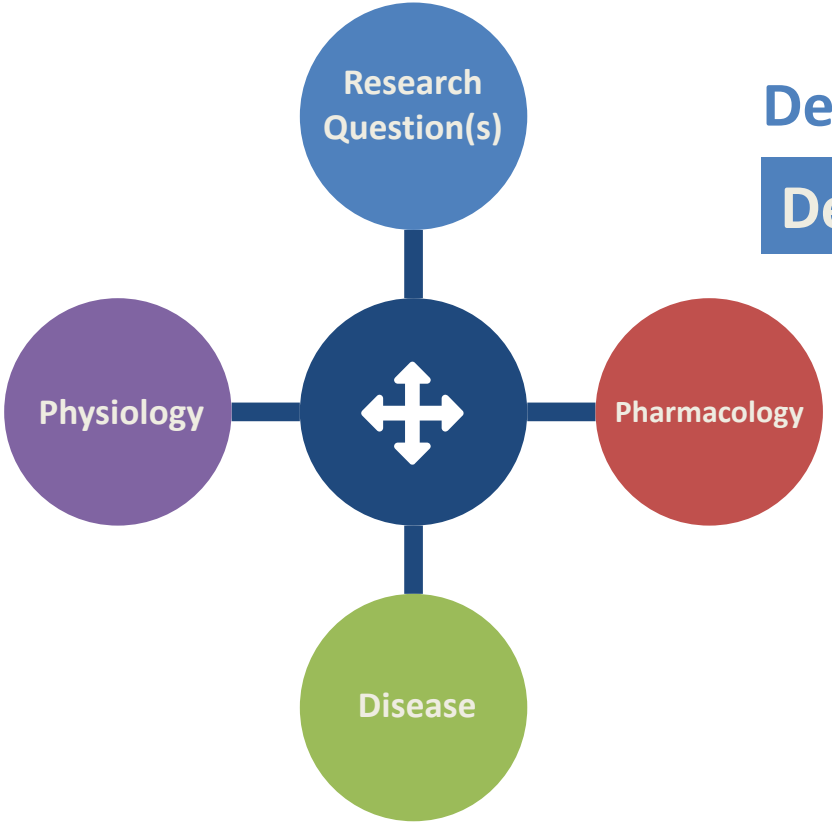
What is Systems Pharmacology?



Developing a Multiscale Model

Define Needs: Time, Space, Precision

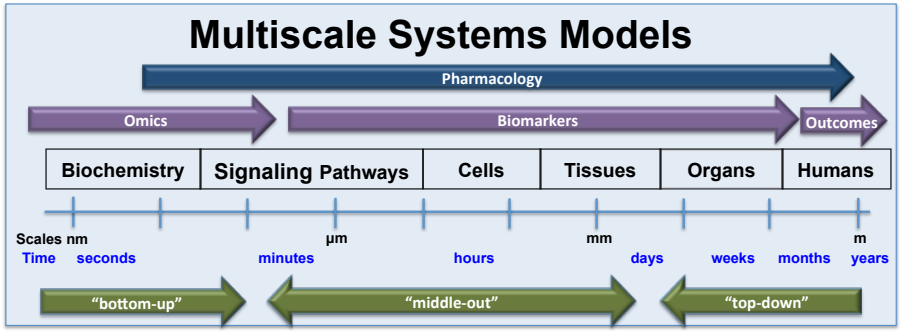
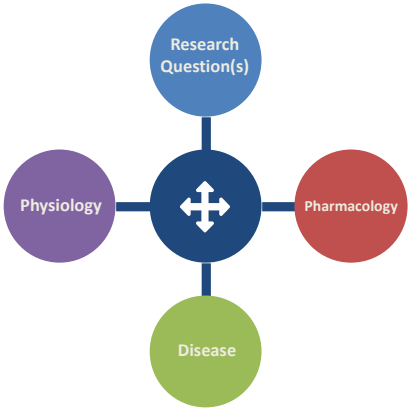


Figure 1 of Riggs M. Multiscale Systems Models as a Knowledge Bridge Between Biology, Physiology and Pharmacology. *AAPS Newsmagazine (December, 2011)*

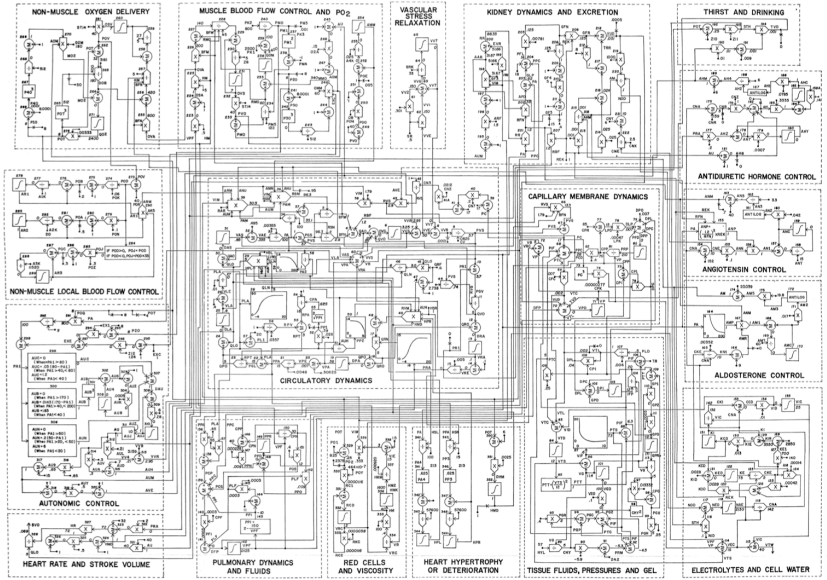
Example of a Systems Model

"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

2. Guyton AC, Coleman TG. Quantitative analysis of the pathophysiology of hypertension. Circ. Res. 1969, 24 (Suppl I): I1-I19.



Guyton AC, Coleman TG, Granger HJ 1972. Circulation: overall regulation. Annu Rev Physiol 34:13-46.



Types of questions our models inform

Efficient Impact on Critical Decisions

Identification

Viable target/pathways involved in disease for drug or combination of therapies? Effects of perturbing one or more, simultaneously or timed-for purpose

Dosing support

Patient responder identification, biomarker identification and development, study design (what to measure when in whom)

Knowledge / Assumption Testing

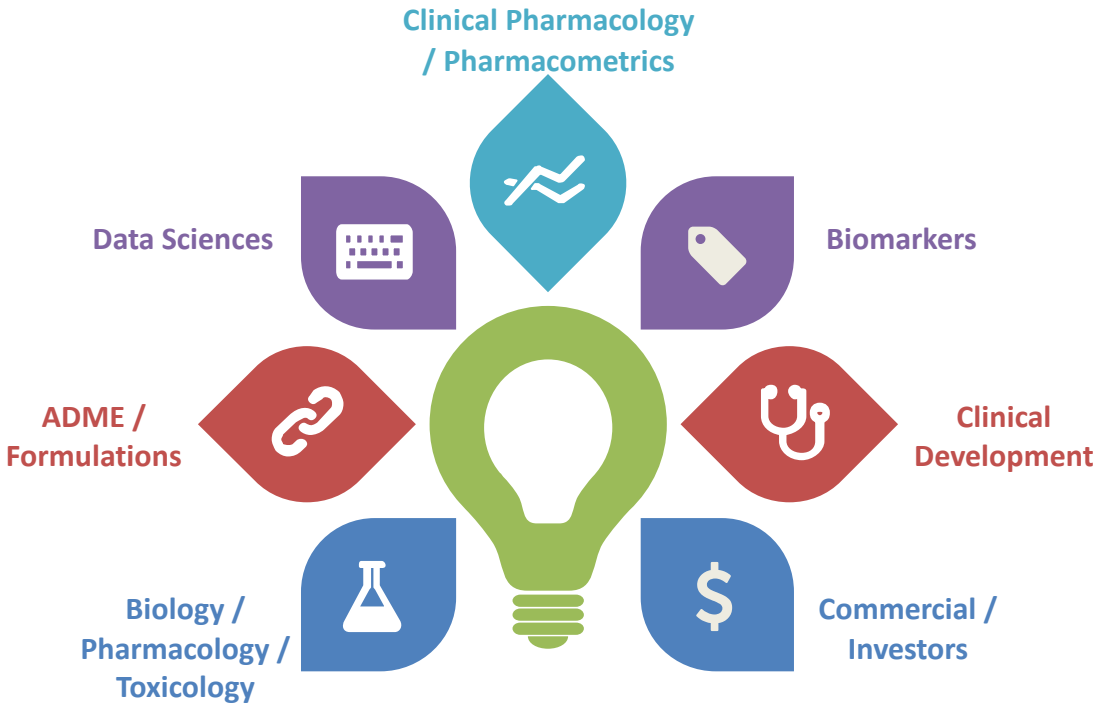
What is the interplay Pharmacology - Biology - Pathophysiology -- where are the gaps, how much do those gaps affect predictability

Expand / Understand

How can one drug, disease, and/or mechanism inform another?

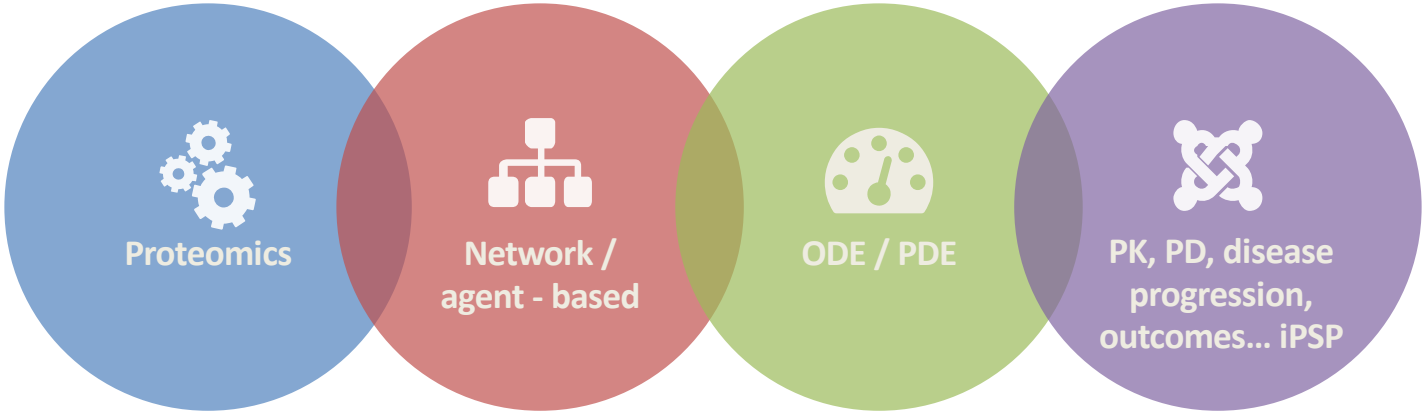
Teams/partners interface

How does it work… teamwork!



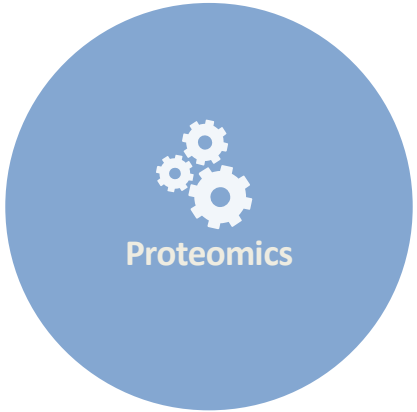
Model Types

You must remember this. An ODE is just an ode, a sine is just a sign. The fundamental things apply. Louis Armstrong, paraphrase

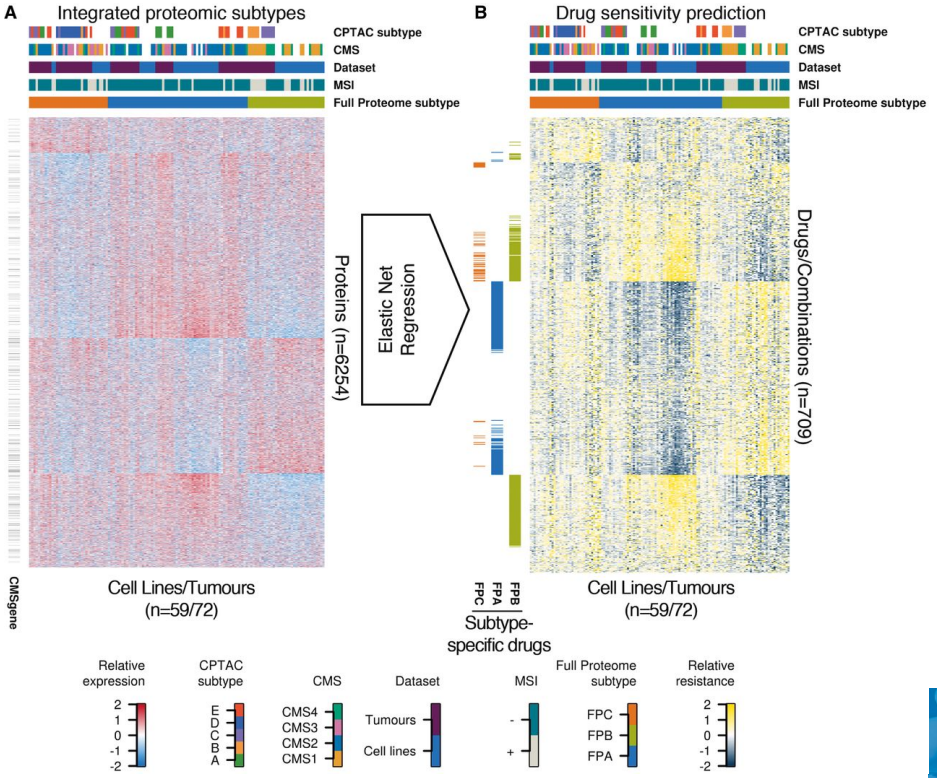


to describe pathways, cytokines, tissues, organ functions (and structure)

Model Types



From integrated proteomic subtypes to drug sensitivity prediction



Martin Frejno et al. Mol Syst Biol 2017;13:951

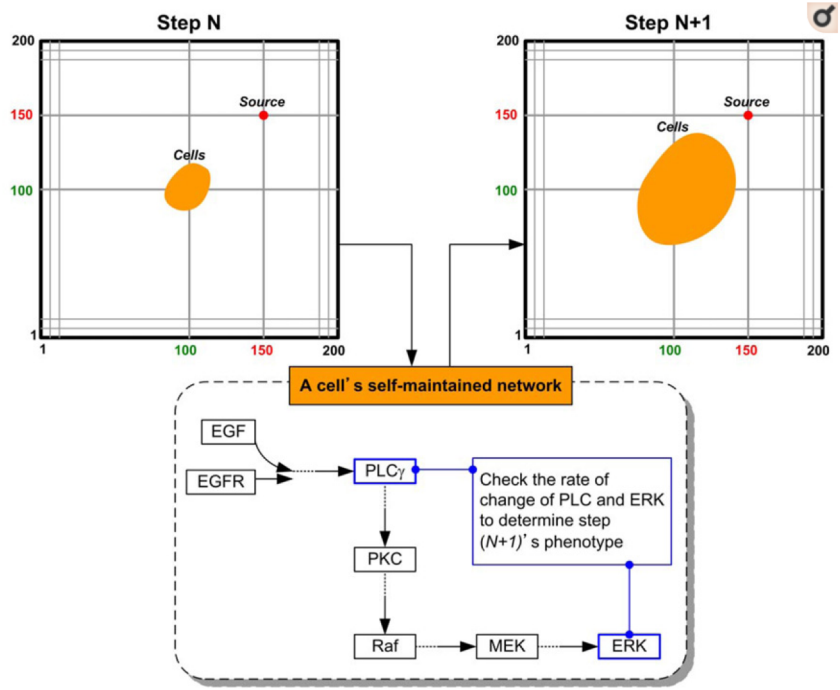
Model Types

Network / agent - based

Wang, Z., Birch, C. M., & Deisboeck, T. S. (2008). Cross-scale sensitivity analysis of a non-small cell lung cancer model: linking molecular signaling properties to cellular behavior. *Bio Systems*, *92*(3), 249–258.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2430419/figure/F1/?report=objectonly

Figure 1



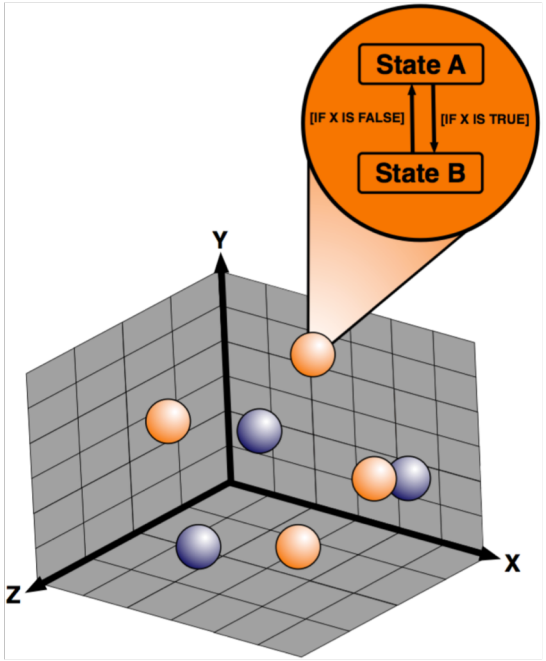
Phenotypic decision process for a cancer cell between two time steps.

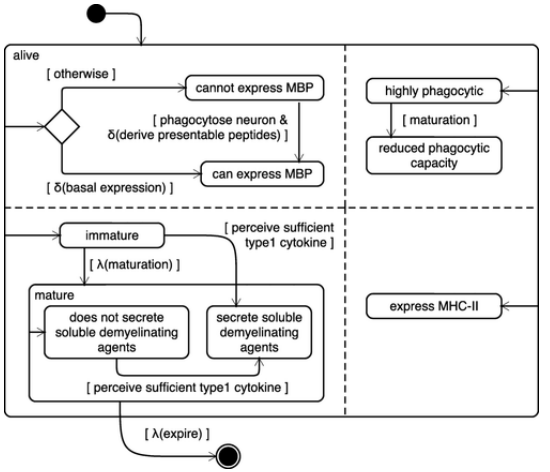
Model Types

Cosgrove, J., Butler, J., Alden, K., Read, M., Kumar, V., Cucurull-Sanchez, L., … Coles, M. (2015). Agent-Based Modeling in Systems Pharmacology. *CPT: Pharmacometrics & Systems Pharmacology*, *4*(11), 615–629.

Network / agent - based

Agent-Based Modeling in Systems Pharmacology





CPT: Pharmacometrics & Systems Pharmacology, Volume: 4, Issue: 11, Pages: 615-629, First published: 12 August 2015, DOI: (10.1002/psp4.12018)

Model Types

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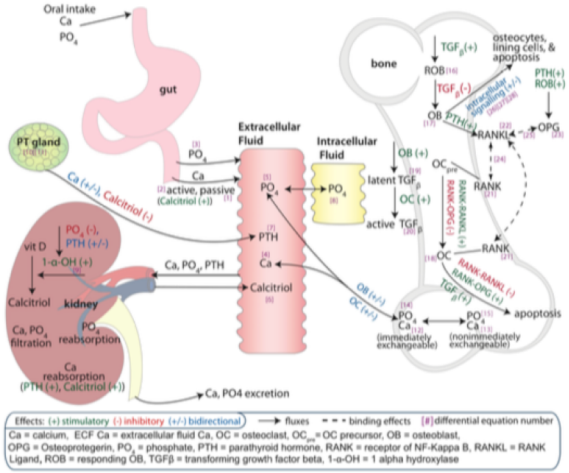
Cross-Functionality is Captured Mathematically



Peterson MC, Riggs MM. A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone, 46:49-63, Jan 2010

Model Types

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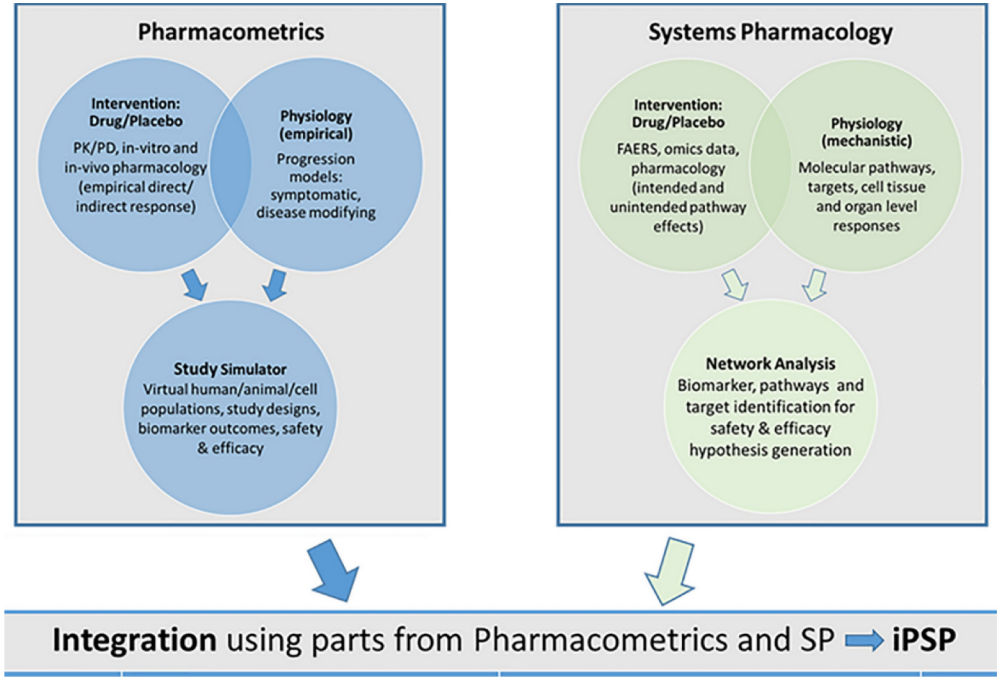
PK, PD, disease progression, outcomes… iPSP



Trame, M. N., Riggs, M., Biliouris, K., Marathe, D., Mettetal, J., Post, T. M., … Musante, C. J. (2018). A Perspective on the State of Pharmacometrics and Systems Pharmacology Integration. *CPT: Pharmacometrics & Systems Pharmacology*. https://doi.org/10.1002/psp4.12313

Methods behind our models

What makes them tick?

Persistence over Parsimony

Models to describe the "system" often contain many, many, many parameters: fix, tune or estimate

Parameter Values

Sensitivity analysis, likelihood profiling, optimization algorithms, verification and validation

"Virtual" Patients

With this method, in reality, we don't differentiate lack of identifiability from real variability in these "patients"

One Lump or Two?

Scale reduction techniques: linearization

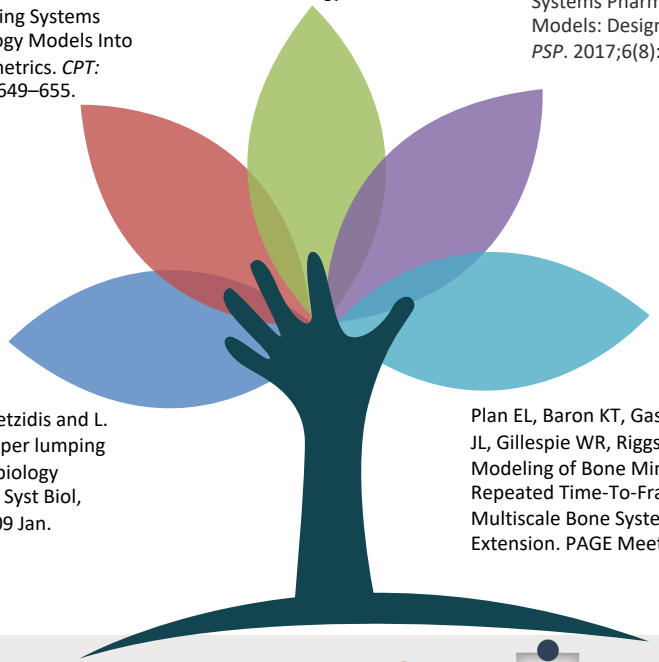
Bayesian Estimation

Balance known/unknown, existing info with incoming information, understand variability accordingly

Duffull, S. B. (2016). A Philosophical Framework for Integrating Systems Pharmacology Models Into Pharmacometrics. *CPT: PSP*, *5*(12), 649–655.

Rieger et al. (2018). Improving the generation and selection of virtual populations in quantitative systems pharmacology models. *Progress in Biophysics and Molecular Biology*, *139*, 15–22.

Ribba B, Grimm HP, Agoram B, et al. Methodologies for Quantitative Systems Pharmacology (QSP) Models: Design and Estimation. *CPT PSP*. 2017;6(8):496–498

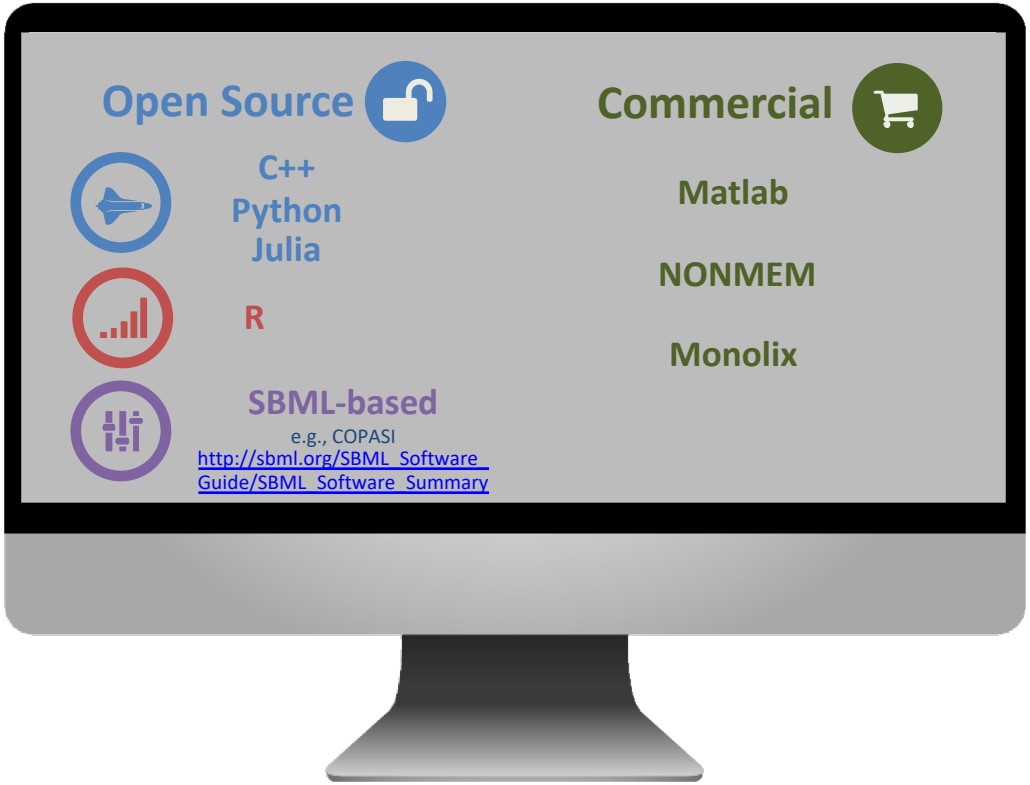


A. Dokoumetzidis and L. Aarons. Proper lumping in systems biology models. IET Syst Biol, 3(1):40, 2009 Jan.

Plan EL, Baron KT, Gastonguay MR, French JL, Gillespie WR, Riggs MM. Bayesian Joint Modeling of Bone Mineral Density And Repeated Time-To-Fracture Event For Multiscale Bone Systems Model Extension. PAGE Meeting. 2012.

Software Programs

Pro: many options / Con: Lack of uniformity / tranferability in our tools



Pro: Many options

Con: Lack of uniformity / interoperability

Trade-offs: Speed, versatility (complexity, code) vs ease of use (GUI, visual)

Data Sources

Literature vs Internal vs 3rd Party

.

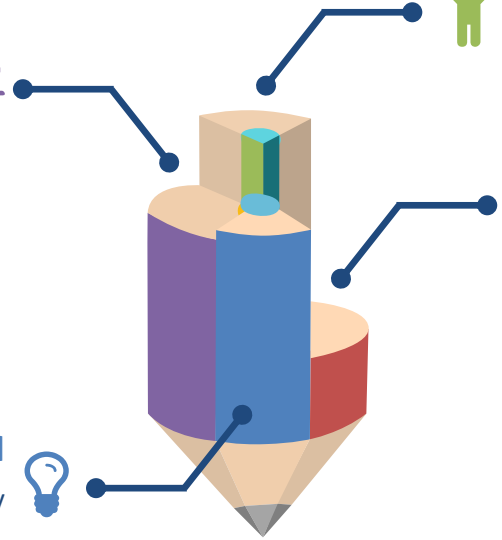
Experimental

Nonclinical: In vitro / in vivo / ex vivo

Wells, cells, organelles.
Inter-species experiments.

Hypothetical

Assess sensitivity



Clinical

Biomarkers/clinical chemistry

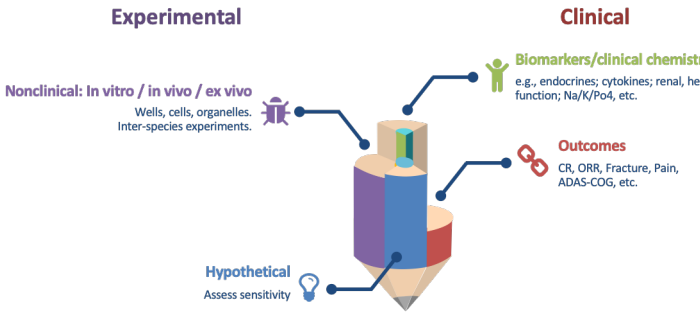
e.g., endocrines; cytokines; renal, hepatic function; Na/K/Po4, etc.

Outcomes

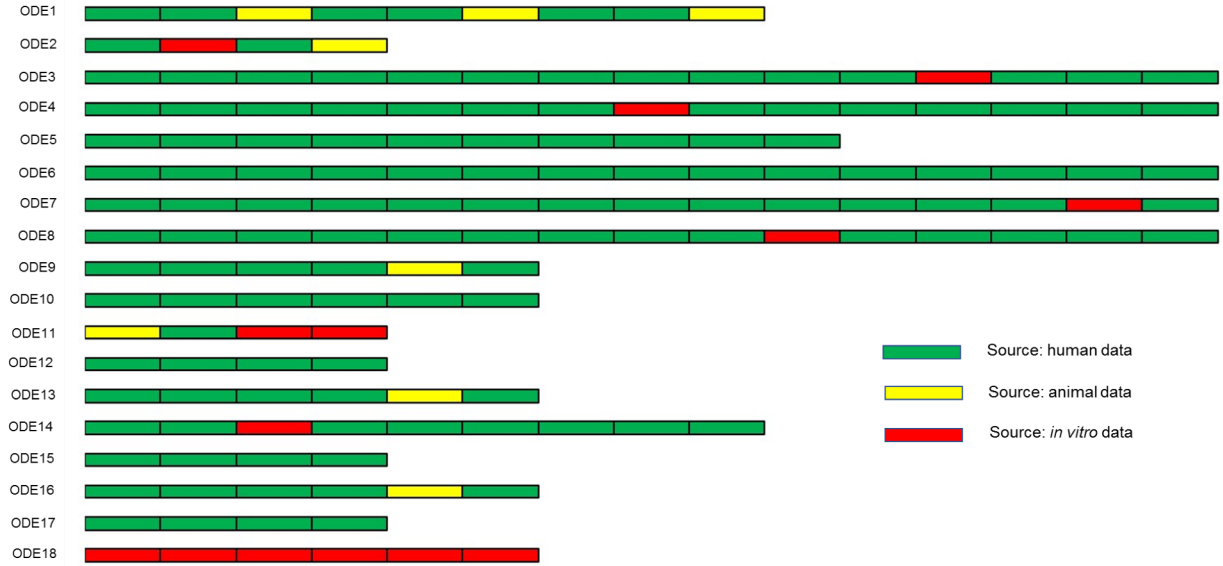
CR, ORR, Fracture, Pain, ADAS-COG, etc.

Data Sources

With so many sources, how / when is it appropriate to integrate.



Assessing and Weighting the Quality



Gulati A and Tannenbaum S. Using Visualization to Address the Reliability of Sources of Initial Parameter Values in a Quantitative Systems Pharmacology (QSP) Model. AAPS PharmSci 360 2018.

Model Verification and Validation

Reproducible research

Data Definitions

Clearly outline data to be used for validation. If literature, consider PRISMA guidelines

Predictive Check

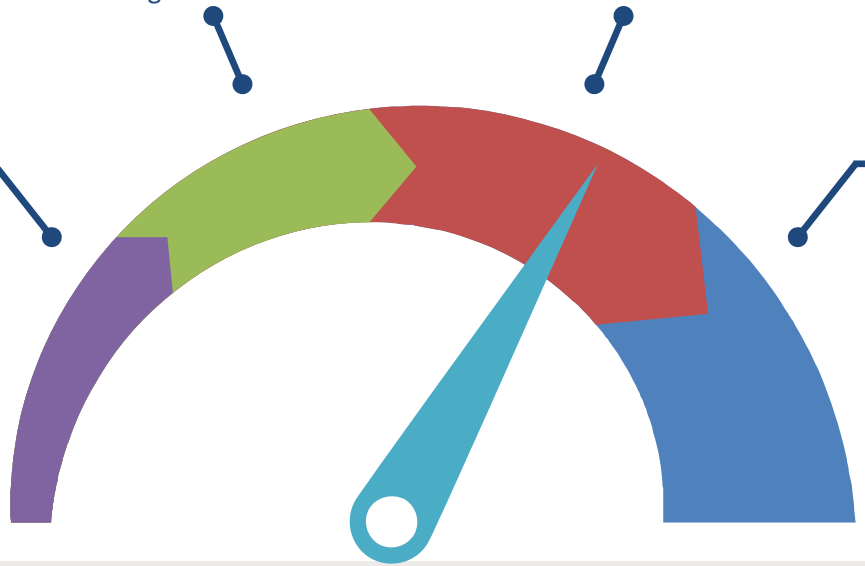
e.g., visual overlay of observed and simulated data

Code Verification

Unit analysis, code reproducibility, initial conditions, assumptions testing …

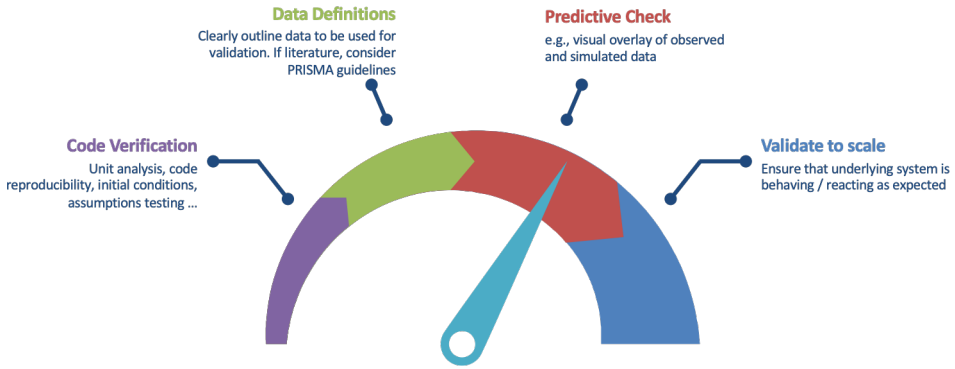
Validate to scale

Ensure that underlying system is behaving / reacting as expected



Model Verification and Validation

Reproducible research



Cucurull-Sanchez et al. (2019). Best Practices to Maximize the Use and Reuse of Quantitative and Systems Pharmacology Models: Recommendations From the UK Q&SP Network. *CPT: PSP*.

Kirouac, D. C. (2018). How Do We "Validate" a QSP Model? *CPT: PSP*, *7*(9), 547–548.

Friedrich, C. M. (2016). A model qualification method for mechanistic physiological QSP models to support model-informed drug development. *CPT: PSP*, *5*(2), 43–53.

Agoram, B. (2014). Evaluating systems pharmacology models is different from evaluating standard pharmacokinetic-pharmacodynamic models. *CPT: PSP*, *3*, e101.

Kirouac, D. C., Cicali, B., & Schmidt, S. (2019). Reproducibility of Quantitative Systems Pharmacology Models: Current Challenges and Future Opportunities. *CPT: PSP*, *8*(4), 205–210.

Challenges Faced

Don't cry to give up, cry to keep going. … Get a reward from it E. Thomas

Model Complexity
Balance descriptiveness against identifiability, parsimony; V&V … AND communicating it all

Technology vs Training vs Standard of Care
What we CAN do may exceed what the community as a whole is capable of doing, and accepts as appropriate to do

Data
Getting the right data from the right patient (experiment) at the right time(s)

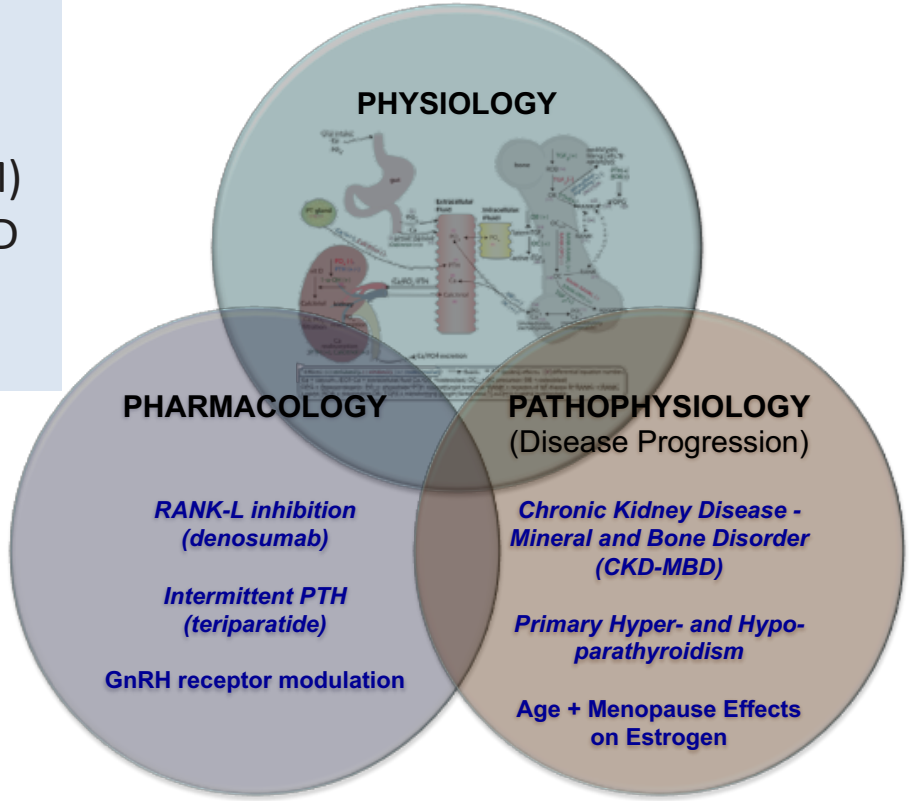
Infrastructure
Academic, regulatory and industry: internal and external alignment, resourcing and timing

Open vs Proprietary Models / Technology
Rewarding innovation vs pushing past redundancies

Training
Scientific and management personnel: building the right models for the right questions

Example of a Systems Model

"In 2004, denosumab was under development for treating osteoporosis, … Questions existed that could not be practically addressed with clinical studies due to the protracted dosing interval (q6M) and required trial duration, nor by traditional PKPD models. … " Peterson and Riggs. CPT:PSP, 4(3), 2015.

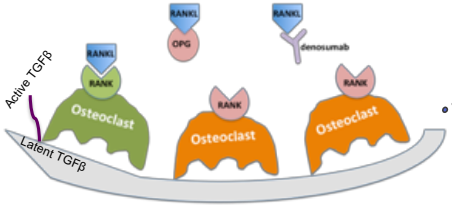


What is Systems Pharmacology?

Tagline

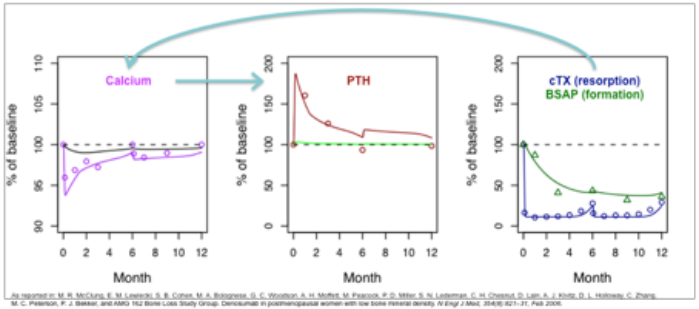
If I push this button (i.e. – block this pathway), why does THAT happen?

Denosumab: RANKL inhibition



- ↓ available RANKL
- ↓ RANK--RANKL interaction
- ↓ Osteoclast activity (sCTx)
- ↓ Activation of TGF-β
- ↓ Osteoblast activity (BSAP)
- ↑ bone mineral density (BMD)

- ↓ Calcium release from bone
- ↓ Serum calcium
- ↓ Ca sensing in PT gland
- ↑ PTH release (calcium-sparing)

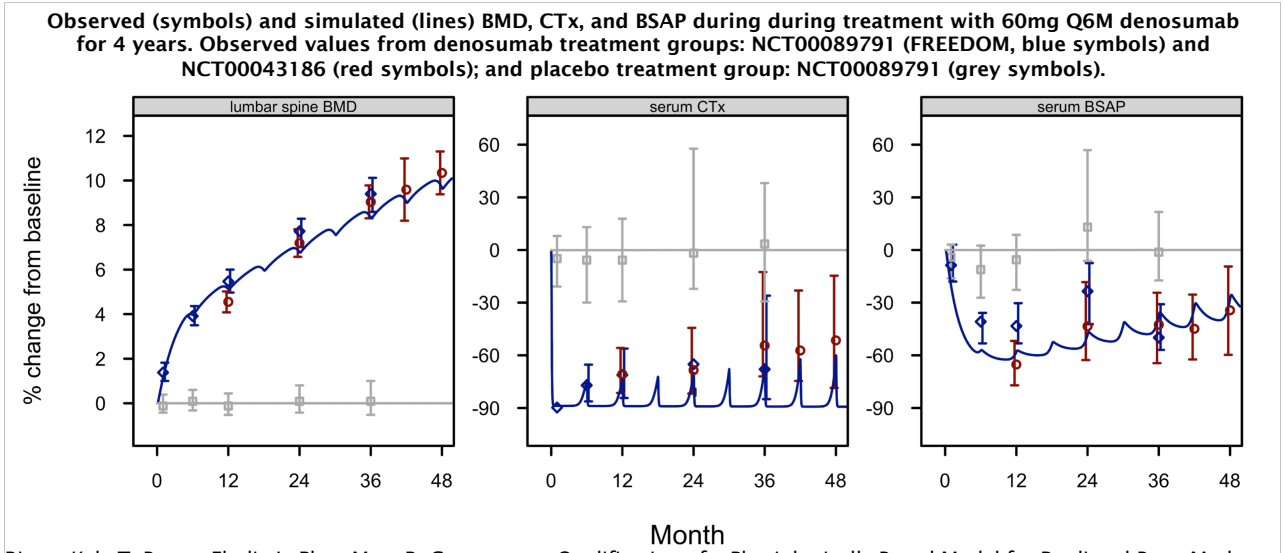


What is Systems Pharmacology?

Tagline

If I push this button (i.e. – block this pathway), why does THAT happen?

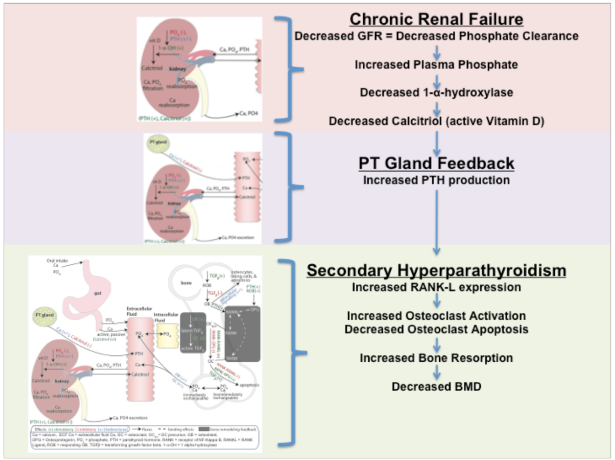
Denosumab: RANKL inhibition → Bone Markers → BMD Change



Matthew M. Riggs, Kyle T. Baron, Elodie L. Plan, Marc R. Gastonguay. Qualification of a Physiologically-Based Model for Predicted Bone Marker and Bone Mineral Density Changes Associated with Denosumab Treatment. Presented at American Society of Bone Mineral Research (ASBMR) Annual Meeting, Minneapolis, MN; October 14, 2012 (Abstract# SU0363). Available at: http://metrumrg.com/index.php/publications

Model Development Integrate System, Disease, Drug

Chronic Kidney Disease-Mineral Bone Disorder



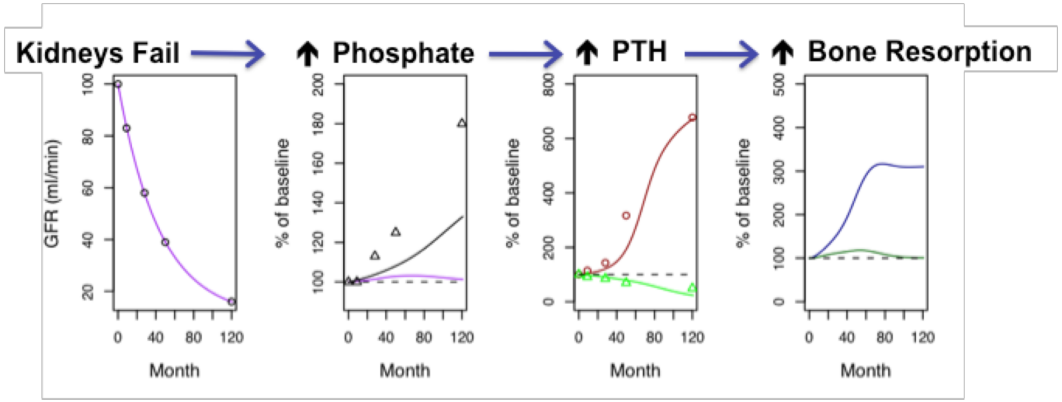


Fig. 1, 2; M. M. Riggs, M. C. Peterson, and M. R. Gastonguay. Multiscale physiology-based modeling of mineral bone disorder in patients with impaired kidney function. J Clin Pharmacol, 52(1 Suppl):45S–53S, Jan 2012.

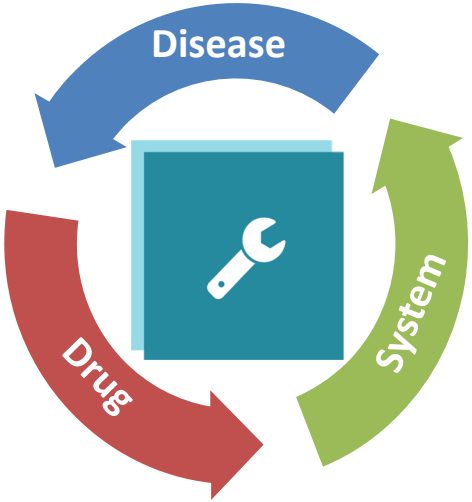
- Can these effects be used to describe PTH and Ca response following long-term etalcalcetide treatment?

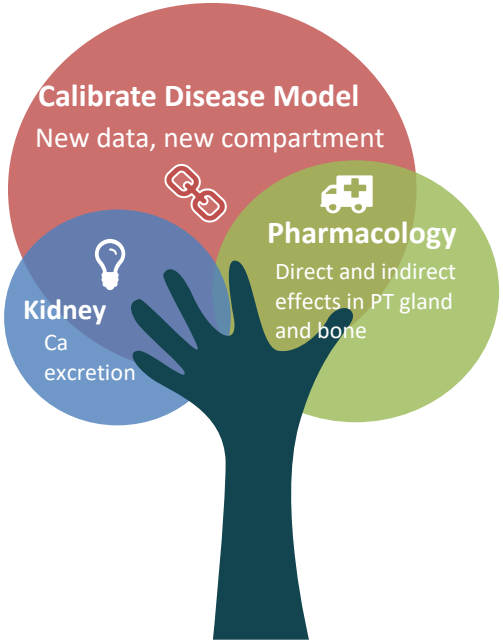
Multiscale Model

Riggs MM, Baron KT, Melhem M (2018) Multiscale physiology-based modeling of mineral bone disorder in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis: application to etelcalcetide treatment effects on calcium homeostasis. ACoP9 Abstract #T-078.

Model Development Integrate System, Disease, Drug

Chronic Kidney Disease-Mineral Bone Disorder





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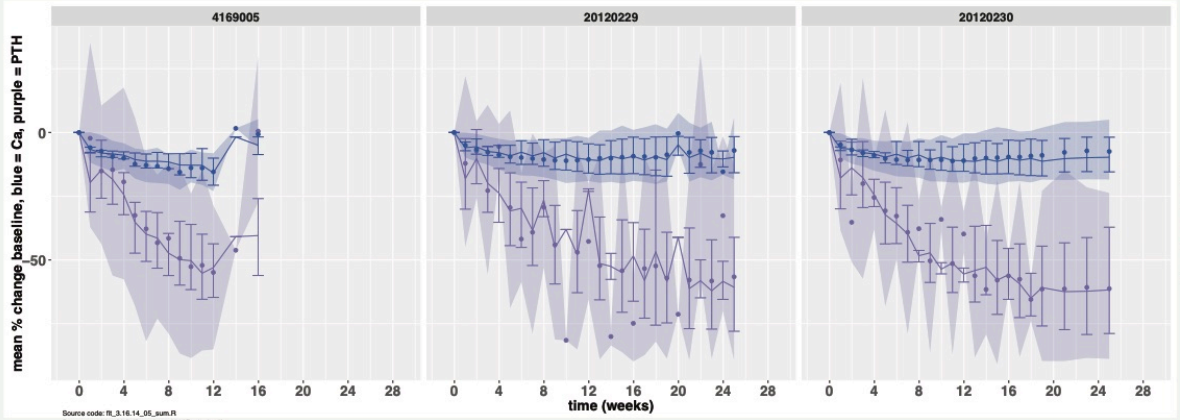
Model Development Integrate System, Disease, Drug

Chronic Kidney Disease-Mineral Bone Disorder

Long-Term Predictive Checks



Despite continued decline in PTH (e.g., beyond weeks 4-6), feedback controls lead to leveling and partial rebound in Ca.

Figure 2: *Predictive check: change from baseline (percentage) for serum calcium (blue) and PTH (purple)*

Phase 3 Study 20120229 was included as external validation. Observed data: solid circle (mean) and 10th - 90th percentile range (shaded region); Simulated data: mean (solid line) and 10th - 90th percentile range (error bars).

Riggs MM, Baron KT, Melhelm M (2018) Multiscale physiology-based modeling of mineral bone disorder in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis: application to etelcalcetide treatment effects on calcium homeostasis. ACoP9 Abstract #T-078.

Acknowledgements