Systems Pharmacology

A day in the life

May 06, 2019

Matthew Riggs, Ph.D.
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

https://gph.is/2lVWWY8
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)
“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

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!

Clinical Pharmacology / Pharmacometrics

Data Sciences

Biomarkers

ADME / Formulations

Clinical Development

Biology / Pharmacology / Toxicology

Commercial / Investors

Workshops
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

Proteomics
Network / agent - based
ODE / PDE
PK, PD, disease progression, outcomes... iPSP

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

Proteomics

From integrated proteomic subtypes to drug sensitivity prediction

Martin Frejno et al. Mol Syst Biol 2017;13:951 © as stated in the article, figure or figure legend
Model Types

Network / agent-based


Figure 1

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

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

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

PK, PD, disease progression, outcomes... iPSP

Pharmacometrics

- **Intervention**: Drug/Placebo
- **PK/PD**: in-vitro and in-vivo pharmacology (empirical direct/indirect response)
- **Physiology (empirical)**: progression models: symptomatic, disease modifying

Systems Pharmacology

- **Intervention**: Drug/Placebo
- **FAERS, omics data, pharmacology (intended and unintended pathway effects)**
- **Physiology (mechanistic)**: molecular pathways, targets, cell tissue and organ level responses

Study Simulator

- Virtual human/animal/cell populations, study designs, biomarker outcomes, safety & efficacy

Integration using parts from Pharmacometrics and SP → iPSP

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


Software Programs

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

Pro: Many options

Con: Lack of uniformity / interoperability

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

Open Source
- C++
- Python
- Julia
- R
- SBML-based
  e.g., COPASI

Commercial
- Matlab
- NONMEM
- Monolix
Biomarkers/clinical chemistry
- e.g., endocrines; cytokines; renal, hepatic function; Na/K/Po4, etc.

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

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
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.*


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

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

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

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

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

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

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

- ↓ 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

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

**Multiscale Model**

Model Development Integrate System, Disease, Drug

Chronic Kidney Disease-Mineral Bone Disorder

Long-Term Predictive Checks

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).

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

Acknowledgements

Thank you!!!