Modeling and Simulation as Applied to Drug Development and Regulatory Decision Making

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Mission: To advance drug development and regulatory science through innovative translational research, education and scientific multidisciplinary collaborations with industry, FDA, NIH, academia, foundations and other public entities, with a focus on quantitative clinical pharmacology.
Overall Trend in R&D Efficiency

Quantitative Pharmacology (M&S)

Visser et al. (2014) CPT Pharmaco Sys Pharmacol
Keys to Successful Use of M&S For Strategy and Decision-Making in Drug Development

- Who is the patient?
- Define the shape of D/R or PK/PD curves
- Identify the right target
- Understand pathophysiology
- Disease biomarkers
3 Key Questions that Define the Context for M&S

✓ What do we want to know?
✓ How certain do we need to be?
✓ What are we willing to assume?

ALL MODELS ARE BUILT “FIT FOR PURPOSE”
What Do We Want to Know?
What Do Clinicians Need to Know?

- What is a reasonable initial dosage regimen?
- How to adjust for intrinsic and extrinsic factors?
- When will effect be seen?
- When will effect plateau?
- How to know when to change dose?
- What happens when dose is skipped?
How Certain Do we Need to Be?
What Are We Willing to Assume?
Integration of Available Knowledge: Clinical Trial Simulations

Drug-Disease Models

Uncertainty

Variability

Trial Execution
- Enrollment rate
- Drop out
- Compliance

Statistical Analysis Models

Decision Criteria
- Stopping rules
- Allocation
- Power

Simulations

Uncertainty in Dose response
- Most likely
- Optimistic
- Pessimistic

Change in HbA1c (%)

Dose (mg)

Probability

Dose (mg)

Protocol Designs
- Visits
- Treatment arms
- Dosing regimen
- Trial duration
- Allocation
- Sample size
- Patient baseline characteristics (age, sex, BMI, HbA1c, FBG)

Adapted from: Garhyan et al. In: Applied Pharmacometrics (2014) 139-159
What Impact Does This Have on Regulatory Decision Making?

Critical Part of Regulatory Decision-Making

In theory, any and all clinical situations where physicians need information about dosing can be tested during drug development.

However, ethical and practical limit the number of studies that a sponsor can conduct.

CONDUCT → LEARN → CONFIRM → PREDICT → WAIVE
Actually, There is a Fourth Question: Who Is Going to Pay for it?

Challenge: Relating Knowledge & Data
Challenge: Different Time Scales for PK&PD

PK

Dose → Exposure

PD (clinical endpoint/surrogate)

Fast Biomarker

Slow Biomarker

Outcome

<table>
<thead>
<tr>
<th>HOURS</th>
<th>MINUTES TO HOURS</th>
<th>WEEKS TO MONTHS</th>
<th>YEARS</th>
</tr>
</thead>
</table>

- **PK**
- **PD** (clinical endpoint/surrogate)
- **Outcome**

**Graphs:**
- Plasma concentration over time (h)
- Glucose (mg/dL) over time (hrs)
- HbA1c (%) over years
- Progression of CKD (Years)
“Reverse Engineering” Strategy in Drug-Disease Modeling

OUTCOME (YEARS)

PHARMACODYNAMICS

Fast biomarker(s) (MINUTES to HOURS)

PHARMACOKINETICS

DOSE (PK) (MINUTES to HOURS)
Drug-Disease Model Setup

Pharmacokinetics (PK)

Drug

Drug Conc.

Pharmacodynamics (PD)

Bio-marker

Disease

PK/PD Models

Effect
Example: Diabetes Mellitus

- Is a chronic progressive disease
- One of the top 10 leading causes of death
- Type 2 is the most common form
- To date, >8% of the global adult population (>380 million people) are affected (T2DM)
- Expected rise to ~600 million people worldwide by 2035
- Cost: 11% of the global healthcare budget in 2013 ($US 548 billion)
Biomarkers are generally defined as:

“Characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”

Fasting Plasma Glucose
- Biomarker for diabetes
- Normal level 4.0 – 6.0 mmol/L
- $t_{1/2}$ dependent on insulin concentrations

Fasting Serum Insulin
- Biomarker for diabetes and insulin tolerance
- Normal level < 11 mU/L
- $t_{1/2} \approx 4 – 6$ min

HbA1c
- Biomarker for sustained glycemic control
- Non-enzymatic glycation of hemoglobin
- Normal level 3.6 – 5.4%
- $t_{1/2} \approx 100 – 120$ days (cf. RBCs)

Pharmacometric (Drug-Centric) Models

Study in 624 Type 2 Diabetes Mellitus patients evaluating the long-term effect of modified release gliclazide on fasting plasma glucose (FPG) levels

\[ FPG(t) = FPG_0 + \alpha \cdot t - f(T) \]

\( \alpha \) is a hybrid constant that does not provide any information about the underlying physiological parameters and may also change over time.

Application of Pharmacometric Models

- Pharmacometric models are currently used to:
  1) Quantify treatment response (Δ from placebo)
  2) Support dose selection
  3) Inform clinical trial design

- However, they face limitations with characterizing:
  1) Complex, multilevel (disease) processes
  2) The impact of the patient’s disease status on treatment response

Need for more mechanistic modeling approaches to explain the dynamic interaction between drug, biological system and underlying disease processes
Mechanism-Centric Models

Drug exposure

Target binding & activation

Transduction

Disease

PK

PD

Homesostatic feedback

Physiologically-based pharmacokinetic modeling

Receptor theory

Dynamical systems analysis

Link to Biomarkers

Identification of Clinically Relevant Covariate Relationships


Physiological Response to Food Intake

GLP-1
*Glucagon-like peptide 1*
- Stimulates insulin
- Inhibits glucagon, somatostatin, gastric emptying and food-intake
  - Serum conc. $\approx 6 \text{ ng/mL}$
  - $t_{1/2} \approx 2 \text{ min}$

GIP
*Gastric inhibitory polypeptide*
- Stimulates insulin and fat storage
- Inhibits somatostatin
  - Serum conc. $\approx 16 \text{ ng/mL}$
  - $t_{1/2} \approx 7 \text{ min}$
Integrated Incretin-Glucose-Insulin Model

Application of Mechanism-Centric Models

• Mechanism-centric models are currently used to:
  1) Characterize the dynamic interaction between drug, biological system and disease at multiple (biomarker) levels
  2) Evaluate the effect of combination therapy
  3) Distinguish between treatment effects (given an appropriate study design)

• However, they face limitations with characterizing:
  1) Multiple (disease) pathways contributing to the clinical condition
  2) T2DM patients are treated as a homogeneous patient population
  3) Primarily focused on evaluation of efficacy

Network-centric models may be needed to sufficiently characterize on- as well as off-target effects
Systems Pharmacology (Network-Centric) Models

Application of Network-Centric Models

• **Network-centric models are currently used to:**
  1) **Characterize** the pertinent physiology that comprise the *key pathways* or *targets* of interest
  2) **Quantitatively integrate** relevant biology across systems
  3) **Explore** the impact of (novel) therapeutic interventions on the system

• **However, they face limitations with characterizing:**
  1) **Clinical data** due to the inherent complexity of the model
  2) Parameter values obtained from the *literature* for informing these models can be *highly variable* between settings
  3) Link to *long-term* clinical outcome is frequently missing

→ **Simplified version of these network-centric models may have to be developed that conserve key dynamic properties**
Wait a Second!

 Aren’t physiologically-based pharmacokinetic (PBPK) models using information on metabolic and transporter networks?

 Yes.

 So could one call them network-centric (Systems Pharmacology) models?

 Yes. They provide the pharmacokinetic front-end to systems pharmacology models.
Physiologically-Based Pharmacokinetic Models

Intrinsic/extrinsic Factors

- **Extrinsic**
  - Drug–drug interactions

- **Intrinsic**
  - Age
  - Race
  - Organ dysfunction
  - Disease
  - Pregnancy/lactation
  - Gender
  - Genetics
  - Others

Huang and Temple, 2008

Individual or combined effects on human physiology

PBPK Model components

- System component (drug-independent)
  - Lung
  - Rapidly perfused organs

- Blood
  - Slowly perfused organs
  - Kidney
  - Liver
  - Intestines

Drug-dependent component

ADME, PK, PD and MOA
- Metabolism
- Active transport
- Passive diffusion
- Protein binding
- Drug–drug interactions
- Receptor binding

PBPK Model components

Predict, Learn, Confirm, Apply

How is PBPK Being Utilized by Sponsors?

- Increased use of PBPK by drug developers
- Majority of the cases were related to drug-drug interactions (~ 60%); pediatrics ranks the second

*Huang et al, J Pharm Sci, 2013*

*Pan, ASCPT Annual Meeting, 2014, Atlanta, GA*
Extension to a PBPK/PD Model for Diabetes Mellitus

Case Study 1:

How Informative Are Drug-Drug Interactions (DDIs) of Gene-Drug Interactions (GDIs)?
Background

• Clinical pharmacology studies of drug-drug interactions (DDIs) and pharmacogenomics (PGx) are interrelated for substrates of polymorphic cytochrome P450 (CYP) enzymes because both change the intrinsic clearance of an enzyme substrate

• Therefore, FDA recommendations for managing polymorphic CYP-mediated DDIs and gene-drug interactions (GDIs) are typically similar.
Research Question

• **Research Question**: Can DDIs be used to reliably **predict** GDIs for CYP2D6, CYP2C9 and CYP2C19 using prototypical victim drugs?

• **Research Approach**:
  
  ➢ Systematically compare **changes in exposure due to DDIs and GDIs** across different prototypical CYP2D6, CYP2C9 and CYP2C19 substrates
  
  ➢ Determine the overlap in exposure between DDIs and GDIs using:
    
    - **Descriptive** convergence analysis
    - **PBPK-based** convergence analysis

Methods – Selection of Enzymes, Substrates & Inhibitors

- **CYP2D6, CYP2C9 and CYP2C19** were selected as polymorphic pathways with clinically different phenotypes

- **Prototypical substrate drugs** (preferably fraction metabolized>0.8 via single CYP pathway) were selected for **CYP2D6** (*metoprolol, dextromethorphan, atomoxetine, vortioxetine*), **CYP2C9** (*warfarin, flurbiprofen, celecoxib*) and **CYP2C19** (*omeprazole, clopidogrel*)

- **Strong inhibitors** (preferably selective) for single CYP pathways were selected for **CYP2D6** (*paroxetine, fluoxetine, quinidine, bupropion*), **CYP2C9** (*fluconazole*) and **CYP2C19** (*fluconazole, fluoxetine, omeprazole*)

Descriptive Convergence Analysis

- PK exposure (AUC) data was collected from the literature sources for:
  - **Poor metabolizers** (PM’s) for GDIs
  - **Strong inhibitor** studies for DDIs

- Substrate drug **AUC ratios** in the presence of: i) DDIs and ii) GDIs using extensive metabolizers (EM’s) as a reference point were calculated

- DDI-GDI convergence was declared if the computed AUC ratio was within the 90% confidence interval limits (80-125%)

Methods Con’t…

PBPK-Based Convergence Analysis

Results: Descriptive Convergence Analysis

<table>
<thead>
<tr>
<th>Polymorphic Pathway</th>
<th>Candidate Drug</th>
<th>Statistical DDI-GDI Convergence (Inhibitor Drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Metoprolol</td>
<td>Yes (Paroxetine)</td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan</td>
<td>Yes (Quinidine)</td>
</tr>
<tr>
<td></td>
<td>Atomoxetine</td>
<td>Yes (Paroxetine &amp; Fluoxetine)</td>
</tr>
<tr>
<td></td>
<td>Vortioxetine</td>
<td>Yes (Bupropion)</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Warfarin</td>
<td>No (Fluconazole)</td>
</tr>
<tr>
<td></td>
<td>Flurbiprofen</td>
<td>No (Fluconazole - Low Dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes (Fluconazole - High Dose)</td>
</tr>
<tr>
<td></td>
<td>Celecoxib</td>
<td>No (Fluconazole - Low Dose)</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Omeprazole</td>
<td>No (Fluconazole)</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>Yes (Omeprazole)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (Other proton pump inhibitors – lansoprazole, pantoprazole, dextlansporazole)</td>
</tr>
</tbody>
</table>

Results: PBPK-based Convergence Analysis

![GDI Simulation](image1)

ATM Dose: 20-mg B.I.D.  PXT Dose: 20-mg Q.D.

![DDI Simulation](image2)

ATM Dose: 20-mg B.I.D.  PXT Dose: 20-mg Q.D.

**Atomoxetine**


**Venlafaxine**
Results:
PBPK-based Convergence Analysis

CYP2C9: Celecoxib

CXB Dose: 200-mg Q.D.
FCZ Dose: 200-mg Q.D.

CXB Dose: 200-mg Q.D.
FCZ Dose: 400-mg Q.D.

Key Messages

• Both descriptive and PBPK-based convergence analysis showed that **DDIs for CYP2D6 substrates using strong CYP2D6 inhibitors** can be used to inform respective GDIs.

• The situation is more complex for CYP2C9 and CYP2C19 substrates.
  
  ➢ **Potency and dose of the inhibitor** for DDIs as well as **remaining enzyme activity** for loss-of-function allele carriers for GDIs needs to be considered.

• The approach presents a valuable alternative for:
  
  ➢ studying both DDIs and GDIs clinically
  
  ➢ saving time and development costs.

Case Study 2: Acetaminophen

- Acetaminophen is present in >100 products.
- It is the most common drug associated with intentional and unintentional poisoning.
- Acetaminophen toxicity occurs in some but not in all patients.
- Toxicity is caused by NAPQI, a reactive metabolite.
- Risk factors include age, co-medication and alcohol intake.

**Question:** Is the current dosing regimen for children (based on adult data) safe and effective?

**Approach:** Development of a PBPK model that accounts for maturational changes in metabolic pathways from birth.
Physiologically-Based PK Model

Figure adapted from Barrett JS, et al. (2012).
Scheme of UGT and CYP enzyme ontogeny profiles adapted from Simcyp training handouts (2012).
Acetaminophen PBPK Model in Healthy Adults

A. 5 mg/kg (2 hr i.v. infusion)

B. 20 mg/kg (2 hr i.v. infusion)

C. 20 mg/kg (0.2 hr i.v. infusion)

D. 1000 mg (solution)

E. 1000 mg (tablet)

F. 975 mg (syrup/elixir)

Acetaminophen PBPK Model in Children

So where do we stand?
Center Faculty and Their Research Areas
Lawrence J. Lesko, Ph.D., F.C.P.
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Positions:
2011-present  Director and Professor CPSP
1995-2011    Director, Office of Clinical Pharmacology (OCP), Center for Drug Evaluation and Research (CDER), Food and Drug Administration, Rockville Maryland
1992-1995    Associate Director of Research, Office of Generic Drugs (OGD), CDER, FDA, Rockville, Maryland
1988-1992    Chief Scientific Officer and Vice-President, PharmaKinetics Laboratories, Baltimore Maryland
1981-1988    Associate Professor of Pharmaceutics and Director, Clinical Pharmacokinetics Laboratory, University of Baltimore, Maryland

Research Interest:
- Drug Development and Regulatory Science
- Personalized Medicine
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Current Research Group:
6 Post-docs
5 Ph.D. students
4 International scholars

Education:
1999-2003 B.S. Pharmacy, Erlangen, Germany
2004-2008 Ph.D. Pharmacy, UFL, USA
2009-2011 Post-doctoral fellowship, Leiden, The Netherlands

Research Interest:
Application of pharmacometric & systems pharmacology tools to answer clinically relevant questions with particular focus on:

- **Physiologically-based PK/PD** models for pediatrics, geriatrics & drug safety
- **Mechanism-based drug-disease models** for Type 2 Diabetes Mellitus & (post-menopausal) osteoporosis

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Research Group:
4 Post-docs
4 Ph.D. students
3 Research technicians
2 International scholars

Education:
1999-2003  B.S. & M.Sc. in Chemistry, Erlangen, Germany
2006-2009  Post-doctoral fellowship, SUNY at Buffalo, Buffalo, NY

Research Interests & Goals:
Develop and rationally optimize clinically relevant dosage regimens with a focus on:

➢ **Discovery of new antibiotics** based on mechanistic biological insights and developing **innovative combination dosing strategies** to combat multidrug-resistant ‘superbugs’.

➢ Optimizing therapy for **anti-cancer**, anti-infective, cardiovascular and other drugs.

➢ **Translational systems pharmacology via** mechanistic population modeling.


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Current Research Group:
7 Post-docs
1 Ph.D. students
4 International scholars

Education:
2001-2007  B.S. in Pharmaceutical Sciences, Münster, Germany
2007-2010  Pharm.D., UFL, USA
2008-2011  Ph.D. in Clinical Pharmacy/Pharmacometrics, Münster, Germany
2011-2013  Post-doctoral fellowship in Pharmacometrics, Uppsala University, Sweden

Research Interest:
Application of quantitative analysis tools (pharmacometrics and systems pharmacology) to address clinically relevant research questions in the area of diabetes, obesity, energy expenditure modeling in different diseases, antithrombotic therapy, neurodegenerative diseases, rare diseases, drug induced nephrotoxicity, pediatrics, cardiovascular and drug safety, cystic fibrosis, and translational research
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Education:
2001-2002  M.S. Immunology, Paris, France
2006-2007  M.S. Pharmacokin and biopharmacy, Paris, France
2006-2007  Pharm.D., School of Pharmacy, Paris, France
2007-2010  Ph.D. in pharmacometrics, SUNY Buffalo, NY, USA
2010-2011  Post-doctoral associate, SUNY Buffalo, NY, USA
2011-2015  Research Assistant Professor, SUNY Buffalo, NY, USA

Research Interest:
- Translational systems PK/PD in oncology: experimental and computational analyses
  - Quantitative systems pharmacology (QSP) approaches to guide the development of new therapies and the identification of promising combination therapies and novel biomarkers.
  - Bringing QSP with PK/PD models to advance drug discovery and development, and leverage the understanding of drugs action (efficacy and toxicity).
- Optimization of sequential combination of targeted chemo- and immuno-therapeutics
- Large molecule therapeutics (proteins, monoclonal antibodies, ADCs, bispecific Ab), targeted small molecules, nanoparticles delivery systems

Research goals & a 5-years vision of my laboratory:
- -omics: established in vitro/in vivo identification of drug/cancer biomarkers (proteomics, transcriptomics, metabolomics)
- Multiscale translational systems modeling platforms for targeted therapeutics and combinations
- Training of graduate students (master, PhD), postdocs, and interns
Summary Thoughts

• If you want to go fast, go alone. If you want to go far, go together!
  ➔ cross-talk between disciplines is critical!

• Try to understand the dynamics of your system. That fact that you have data does NOT mean that it is informative for what you are trying to accomplish!
  ➔ make sure that parameters are physiologically meaningful (where applicable)!

• No single model can answer all questions! Make sure you understand/formulate your question clearly and let the question drive the complexity of your model, NOT the other way around!
  ➔ models should be fit for purpose!