Comparison of NLME and Mechanistic Physiological Modeling Methods Using Examples in Drug Discovery and Development.

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Objectives

To compare and contrast NLME modeling and mechanistic physiological (PhysioPD™) modeling in these dimensions:

(1) What questions can be addressed?

(2) What data are needed?

(3) How are hypotheses used and tested?

(4) How is confidence built in each kind of model?

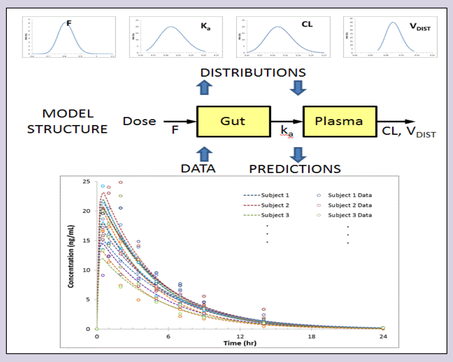


Figure 1. Select components of a NLME model.

Background

Both statistical (e.g., NLME) and mechanistic, physiological (systems biology ODE models based on physical laws and physiological knowledge, PhysioPD in the Rosa & Co practice) modeling methods can be used to support decision-making in drug discovery and development. There is a lack of clarity in the field about which method is appropriate under what conditions. The authors systematically reviewed ten examples from their modeling disciplines in similar therapeutic areas to address the research questions.

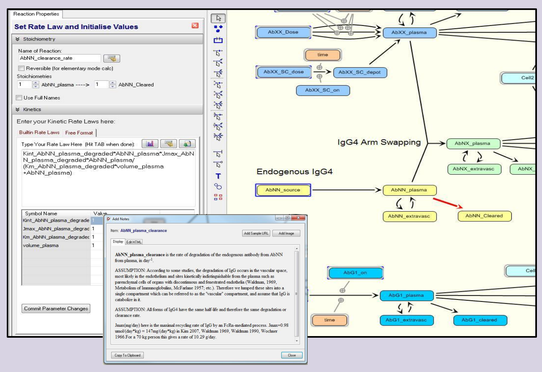


Figure 2. Select components of a PhysioPD model (disguised) investigating antibody dynamics.

Results

(1) Goals / questions addressed: NLME modeling is best suited to quantify and illuminate drug-related PK/PD processes and to separate/quantify different sources of variability in clinical and post-clinical stages. PhysioPD modeling is ideal for exploring mechanistic connections between pathophysiology, therapeutic PK and PD, and outcomes at any stage of discovery and development.

(2) Data: NLME models require clinical or pre-clinical data sets and are fully inferred from the data, with most model parameters being estimated; the model complexity is mainly determined by the data. Physiological knowledge is utilized to inform model structure. PhysioPD models start with knowledge and hypotheses of biological processes and do not require detailed data sets for the drug of interest. Many types of data are used to inform and parameterize the models, which tend to be more complex as mechanisms are combined and their interactions explored.

(3) Hypotheses: The NLME modeling process is guided throughout by the hypotheses to be tested: for model building, addition of mechanistic components, covariate relationships etc. In PhysioPD models, scope is guided by the decision to be made, modeling uncovers knowledge gaps, and the models facilitate investigation of the systemic implications of alternative hypotheses.

(4) Confidence: For NLME models, many tools are available to evaluate models internally and externally and assess goodness of fit. For physiological models, comparison to data is critical, with an emphasis on choosing data from many different data sets at the clinical and sub-system levels. Additional criteria must be met to ensure that the model is relevant and adequately addresses uncertainty and variability (see Model Qualification Method, Fig. 3).

Conclusions

NLME and PhysioPD modeling methods are both used to illuminate relationships and test hypotheses. NLME methods require data sets specific to the research question at the individual subject or population level, while PhysioPD models draw from a variety of data sources to construct representations of biology informed by data and knowledge. Consequently, PhysioPD methods can be used earlier in discovery and development and tend to have more complex representations of mechanisms.

Based on our exercise, we conclude that the methods are complementary. Additional work is under way to crisply define hand-off points and optimize overall use of modeling in drug discovery and development.

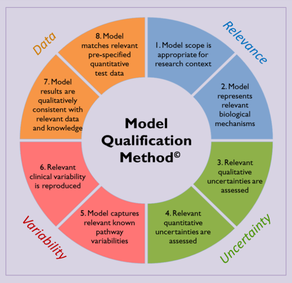
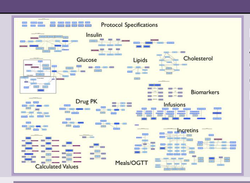
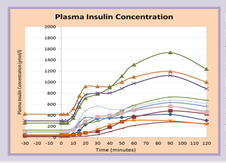
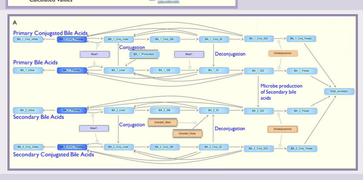
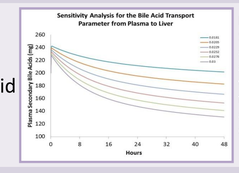
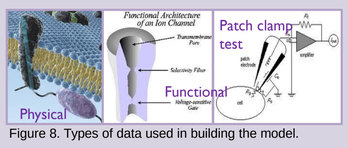
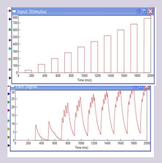
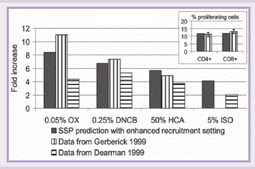
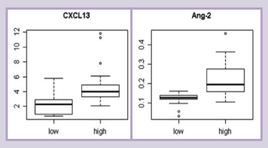
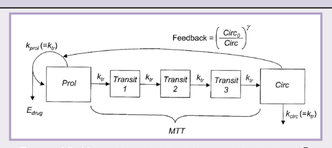
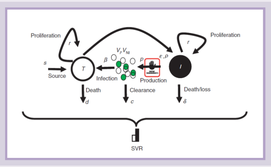
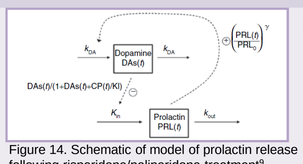
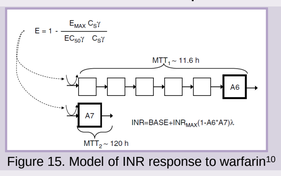
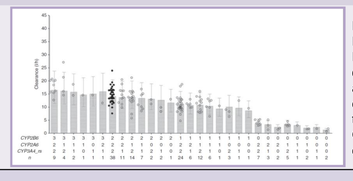


Figure 3. Rosa & Co.'s Model Qualification Method ensures that PhysioPD models are fit for purpose.

PhysioPD modeling

Case	Goal / Questions Addressed	Data Used	Hypotheses Used and Tested	Confidence Built By…
Diabetes project supporting compound development at preclinical / early clin. stage.[1]  Figure 4. A version of the diabetes PhysioPD platform.	• Will MoA of drug class be efficacious? • What compound properties to optimize? • How does rat translate to human?	• Physiological knowledge of diabetes • Understanding of target role in diabetes • Public literature and summary clinical data on other diabetes drugs • In vitro binding and preclinical data for new compound	• Virtual patients constructed to represent disease pathophysiology hypotheses • Hypotheses about how drug-induced signal combines with endogenous used to test effects on predicted outcomes  Figure 5. Selected virtual patients display two-phase insulin secretion as appropriate for disease severity.	• Following Model Qualification Method[2] • Conservation of mass (here: nutrients) • Qualitative data – virtual patients behaved well under many protocols • Matched data for related compounds
Understanding ursodiol dosing in the treatment of cholestasis in neonates. Early to late clinical.[3]  Figure 6. Bile Acid PhysioPD model includes four types of bile acids and their metabolism	• What accounts for clearance variability?	• Public literature on bile acid metabolism • Metabolomic data of all bile acid species Ursodiol (drug) concentration in plasma	 Figure 7. Sensitivity analysis shows that varying transporter affects clearance. • Sensitivity analysis revealed pathways that could cause clearance variability • Literature confirmed polymorphisms consistent with clearance hypothesis	• Following Model Qualification Method • Mechanistic representation predicted ursodiol concentration profile • SNPS evidence supports conclusions
Understanding and improving in- vitro tests to be more predictive for neuropathic pain. Discovery.	• Why do current in vitro models fail to predict neuropathic pain? • How could models be improved?  Figure 8. Types of data used in building the model.	• Public data on ion channels, neurotransmitters, channel blockers, pain response, electrophysiology of other drugs • Proprietary electrophysiology data	• Standard assumptions about nocioception, transmission, and modulation were tested – some not correct • Novel hypotheses about drug action and physiology were confirmed or rejected  Figure 9. Comparison to data with implementation of enhanced recruitment hypothesis.[5]	• Reproduced and explained current assay's failure modes • Modeling lead to biological insight that scientists bought into
Prediction of skin sensitization potential for novel chemicals. Preclinical safety assessment.[4]	• What are the key biological pathways driving sensitization? • What assays predict human response?	• Public data on sensitization mechanisms • Known chemicals tested using local lymph node assay (LLNA) in mouse	• Virtual chemicals to explore implications of unmeasurable compound properties • Predictive assays must be robust to these uncertainties  Figure 10. Comparison to data with implementation of enhanced recruitment hypothesis.[5]	• Model represented known biology • Matched sub-system and whole system data • Reproduced and explained LLNA data • Led to novel biological insights[5] • Dealt explicitly with uncertainty
Identification of new serologic markers for rheumatoid arthritis (RA) severity using an in silico model of the rheumatic joint.[6] Late clinical.	• What novel serologic marker can give insight into disease severity?	• For model, public data about RA joint biology and patho-physiologies • For markers, serum samples from two populations  Figure 11. Simulated synovial concentrations (in ng/ml) of two possible markers in 120 distinct virtual patients. Patients with erosion scores in lowest quartile (low) were compared with patients with erosion scores in highest quartile (high).[6]	• 120 virtual patients with different pathophysiologies • Biomarker hypotheses tested empirically	• Model represented known biology • Matched data at sub-system and whole system level • Virtual patients matched data for marketed therapies and had appropriate qualitative behaviors • Biological rationale for biomarker was scientifically sound and confirmed experimentally

NLME modeling

Case	Goal / Questions Addressed	Data Used	Hypotheses Used and Tested	Confidence Built By…
Hematological toxicity model.[7] Post-clinical.  Figure 12. Hematological toxicity model structure.[7]	• Develop mechanistic model to describe chemotherapy-induced myelosuppression • Separate system- and drug-related parameters	• Clinical data containing neutrophils and PK information for 6 different cancer drugs • Physiological knowledge on neutrophils life cycle	• System parameters are consistent across different drugs • Their estimates resemble physiological values • Model mechanisms mimic physiology • Drug effect parameters are robust	• Formal statistical tests • Goodness of fit graphical diagnostics • Estimated parameters are physiologically plausible • Predictive checks • Parameter uncertainty
Hepatitis C Viral Kinetic Model.[8] Late / post-clinical.  Figure 13. Hepatitis C viral kinetic model schematic.[8]	• Develop mechanistic model to describe interplay between HCV virus, host and tx • Implement cure/viral eradication boundary	• Clinical data from 2100 patients (one phase 2 and three phase 3 studies) • Physiological knowledge on HCV dynamics and infection	• Complex mechanistic interplay between HCV virus, host and drug effect • Viral eradication/cure boundary is essential to describe different virus dynamics/profiles • Importance of left censored data implementation	• Formal statistical tests • Goodness of fit graphical diagnostics • Estimated parameters are physiologically plausible • Predictive checks • Parameter uncertainty • External validation to predict clinical outcome (SVR)
Prolactin Release Model following Risperidone and Paliperidone Treatment.[9] Early to post-clinical.	• Develop mechanistic model to describe interplay between prolactin, dopamine and risperidon/paliperidone in schizophrenic and healthy subjects • Compare prolactin increasing effect of risperidon and paliperidone  Figure 14. Schematic of model of prolactin release following risperidone/paliperidone treatment[9]	• Clinical data from 1462 subjects (five phase 1 and four phase 3 studies) • Dopamine and prolactin physiology	• Diurnal rhythm of prolactin • Dopamine production rate controlled by prolactin feedback • Competitive agonist-antagonist interaction model describes drugs vs. dopamine competition for D2 receptors • Different mechanisms for describing relationships of interest • Covariate effects of demographic and genetic covariates	• Formal statistical tests • Goodness of fit graphical diagnostics • Estimated parameters are physiologically plausible • Predictive checks • Parameter uncertainty • External validation to predict new dataset
Individualization of Warfarin tx by pharmacogenetics and age using a PKPD model.[10] Late / post-clinical.  Figure 15. Model of INR response to warfarin[10]	• Quantify relationship between warfarin concentration & INR response • What are important predictors for dose individualization?	• Clinical data from 140 patients containing PK, PD, pharmacogenetic and demographic information • Knowledge on warfarin PK and pharmacogenetic influence • Physiology of coagulation mechanism	• CYP2C and VKORC1 genotype plays important role in warfarin CL • VKORC1 genotype plays important role in INR response • Demographic covariates (Age) affect warfarin CL • Time delay between warfarin dosing and INR response	• Formal statistical tests • Goodness of fit graphical diagnostics • Estimated parameters are physiologically plausible • Predictive checks • Parameter uncertainty
Pharmacogenetic – Pharmacokinetic analysis of efavirenz in HIV-1 infected patients[11] Late / post-clinical.	• What is the effect of multiple functional alleles on EFV CL? • Which gene-gene interaction is important for EFV elimination?  Figure 16. Predicted EFV CL for different allelic combinations of CYP enzymes.[11]	• Clinical data from 169 patients (PK, pharmcogenetics, demog.) • Knowledge on EFV PK, pharmacogenetic and toxicity	• Demographic covariates (Age, BW, ethnicity, sex, height) affect EFV CL • CYP2B6, CYP2A6, CYP3A54, CYP3A5 pharmacogenetics affects EFV CL • Gene-gene interaction plays a role in EFV CL • Choice of gene interaction model is important	• Formal statistical tests • Goodness of fit graphical diagnostics • Estimated parameters are physiologically plausible • Parameter uncertainty • Predictive checks

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