PROGRAM PAGE 2010

Tuesday June 8

16:00-20:00	**Registration**	
18:00-20:00	**Welcome reception**	

Wednesday June 9

08:00-08:45	**Registration**	
08:45-09:00	**Welcome and Introduction**	
09:00-10:20	**Physiology based modelling**	*chair: Charlotte Kloft*
09:00-09:40	***Wilhelm Huisinga***	Physiologically-based pharmacokinetic/pharmacodynamic modelling, mathematical model reduction and a mechanistic interpretation of simple empirical models
09:40-10:00	*Emilie Hénin*	Semi-physiological modeling of absorption kinetics: application to diclofenac
10:00-10:20	*Stefan Willmann*	Investigation of the Influence of CYP3A4 Inhibition and Renal Impairment on Morphine and M6G Formation after Codeine Administration using Coupled Whole-Body PBPK Modelling
10:20-11:50	**Coffee break, Poster and Software session I**	
	Posters in Group I (see below) are accompanied by their presenter	
11:50-12:30	**Physiology based modelling (continued)**	*chair: Katya Gibiansky*
11:50-12:10	*Pascal Chanu*	Mechanistic Models to Simulate Dose Response of IgE Suppression Following Dosing of Anti-IgE Monoclonal Antibodies
12:10-12:30	*Julia Korell*	Design of survival studies for red blood cells
12:30-14:00	**Lunch**	
14:00-15:15	**Covariate model building**	*chair: Mats Karlsson*

14:00-14:55	***Stephen Senn***	Tutorial: Covariate complications in clinical trials
14:55-15:15	*Akash Khandelwal*	Covariate Model Building Using Linear Approximations

15:15-16:30 **Tea break, Poster and Software session II**

Posters in Group II (see below) are accompanied by their presenter

16:30-17:30	**Methodology**		*chair: France Mentré*
16:30-16:50	*Brigitte Lacroix*	Evaluating the IPPSE method for PKPD analysis	
16:50-17:10	*Dalia Khachman*	You have problems to interpret VPC? Try VIPER!	
17:10-17:30	*Bruno Boulanger*	Trial predictions vs. trial simulations in early clinical development: a framework to evaluate the predictive probability of success based on NONMEM outputs	

Thursday June 10

08:45-10:05	**Lewis Sheiner Student Session**		*chairs: Chantal Csajka, Ferdie Rombout, Willi Weber*
08:45-09:10	*Caroline Bazzoli*	Design evaluation and optimisation in multi-response nonlinear mixed effect models with cost functions: application to the pharmacokinetics of zidovudine and its active metabolite	
09:10-09:35	*Maud Delattre*	Estimation of mixed hidden Markov models with SAEM. Application to daily seizures data	
09:35-10:00	*Lay Ahyoung Lim*	Dose-response-dropout analysis for somnolence in Pregabalin-treated patients with generalized anxiety disorder	
10:00-10:05	**Presentation of Awards**		

10:05-11:20 **Coffee break, Poster and Software session III**

Posters in Group III (see below) are accompanied by their presenter

11:20-12:20	**Clinical applications of PK(PD)**		*chair: Dinesh de Alwis*
11:20-11:40	*Chao Zhang*	Population Pharmacokinetics of Lopinavir/Ritonavir in Combination with Rifampicin-based Antitubercular Treatment in HIV-infected Children	
11:40-12:00	*Jeff Barrett*	Enhancing Methotrexate Pharmacotherapy in Children with Cancer: A Decision Support System Integrating Real-time PK/PD Modeling and Simulation with Patient Medical Records	
12:00-12:20	*Sarah McLeay*	Exploring different body-size metric based dosing strategies for propofol in morbidly obese versus healthy weight subjects by	

		modelling and simulation approach
12:20-13:50	**Lunch**	
13:50-15:15	**Integrating data with literature**	*chair: Lutz Harnisch*
13:50-13:55	*Lutz Harnisch*	Introduction to integrating data with literature
13:55-14:15	*Eugene Cox*	Meta- Analysis of Retention Rates of Post-Marketing Trials to Compare Effectiveness of Second Generation Antiepileptic Drugs
14:15-14:35	*Rocío Lledó-García*	A mechanistic model of the steady-state relationship between HbA1c and average glucose levels in a mixed population of healthy volunteers and diabetic subjects
14:35-15:15	***Jonathan French***	When and how should I combine patient-level data and literature data in a meta-analysis?
15:15-16:30	**Tea break, Poster and Software session IV**	
	Posters in Group IV (see below) are accompanied by their presenter	
16:30-17:10	**Design**	*chair: Marylore Chenel*
16:30-16:50	*Camille Vong*	Rapid sample size calculations for a defined likelihood ratio test-based power in mixed effects models
16:50-17:10	*Lee Kien Foo*	D-optimal Adaptive Bridging Studies in Pharmacokinetics
19:00-01:00	**Social evening**	

Friday June 11

09:00-10:00	**Stuart Beal Methodology Session**	*chair: Oscar della Pasqua*
09:00-09:20	*Marc Lavielle*	Mixture models and model mixtures with MONOLIX
09:20-09:40	*Matthew Hutmacher*	Extending the Latent Variable Model to Non-Independent Longitudinal Dichotomous Response Data
09:40-10:00	*Elodie Plan*	Analysis Approaches Handling Both Symptomatic Severity and Frequency
10:00-10:10	**Preview of PAGE 2011**	
10:10-10:50	**Coffee Break**	

10:50-12:10	**PKPD models**		*chair: Nick Holford*
10:50-11:10	*Sylvain Goutelle*	Mathematical modeling of pulmonary tuberculosis therapy: development of a first prototype model with rifampin	
11:10-11:30	*Alberto Russu*	Integrated model for clinical response and dropout in depression trials: a state-space approach	
11:30-11:50	*Klas Petersson*	Predictions of in vivo prolactin levels from in vitro Ki values of D2 receptor antagonists using an agonist-antagonist interaction model	
11:50-12:10	*Rada Savic*	Adherence and Population Pharmacokinetics of Atazanavir in Naïve HIV-Infected Patients using Medication Events Monitoring System (MEMS) for drug intake timing	

12:10-12:20 **Closing Remarks**

12:20-12:50 **Audience Input for the PAGE 2011 Program**

Software demonstrations-Commercial

S_1: *Stephane Vellay* Pipeline Pilot - Data Integration, Analysis, and Reporting Platform
S_2: *Masoud Jamei* Simcyp Simulator - a comprehensive platform and database for mechanistic modelling and simulation of drug absorption, tissue distribution, metabolism, transport and elimination in healthy and disease populations using in vitro knowledge
S_3: *Sven Janssen* SimBiology: A Graphical Environment for Population PK/PD

Software demonstrations-Non-commercial

S_10: *Juergen Bulitta* Development and Evaluation of a New Efficiency Tool (SADAPT-TRAN) for Model Creation, Debugging, Evaluation, and Automated Plotting using Parallelized S-ADAPT, Perl and R
S_11: *Kajsa Harling* Xpose and Perl speaks NONMEM (PsN)
S_12: *Roger Jelliffe* The MM-USCPACK software for nonparametric adaptive grid (NPAG) population PK/PD modeling, and the MM-USCPACK clinical software for individualized drug regimens.
S_13: *Ron Keizer* Piraña: Open source modeling environment for NONMEM
S_14: *Marc Lavielle* Analysing population PK/PD data with MONOLIX 3.2
S_15: *Sebastian Ueckert* PopED - An optimal experimental design software

Posters Wednesday Morning (group I)

Applications- Anti-infectives

I_1: *Bambang Adiwijaya* Applications of Discrete-Event Dynamic Simulation in HCV Treatment Dynamics

I_2: *Jurgen Bulitta* Mechanism-based Modelling of the Synergy of Colistin Combinations against Multidrug-Resistant Gram Negative Bacteria

I_4: *Emmanuel Chigutsa* Parallel first order and mixed order elimination of pyrazinamide in South African patients with tuberculosis

I_5: *Isabelle Delattre* Population pharmacokinetic modeling and optimal sampling strategy for Bayesian estimation of amikacin in critically ill septic patients

I_6: *Oleg Demin* Application of systems pharmacology modeling approach to optimize Interferon therapy of hepatitis C

I_7: *Thomas Dorlo* Optimal Dosing of Miltefosine in Children and Adults with Leishmaniasis

Applications- Biologicals/vaccines

I_8: *Marion Dehez* Bayesian framework applied to dose escalation studies for biologics

I_9: *Amit Garg* A Mechanism Based Population Pharmacokinetic-Pharmacodynamic Model for Epoetin Alfa and Darbepoetin Alfa in Chronic Kidney Disease Patients

I_10: *Kenneth Luu* A Mechanistic Approach to Predicting Human Pharmacokinetics of Monoclonal Antibodies from Preclinical Data: A Case Example

I_11: *David Ternant* Methotrexate influences neither pharmacokinetics nor concentration-effect relationship of infliximab in axial ankylosing spondylitis

I_12: *Pawel Wiczling* Pharmacokinetics and Pharmacodynamics of Anti-CD3 Monoclonal Antibody, Otelixizumab, in Subjects with Diabetes and Psoriasis

Applications- CNS

I_13: *Neil Attkins* Model based analysis of antagonist binding kinetics at CRF-1 receptors in vitro and in vivo

I_14: *Marcus Björnsson* Modeling of Pain Intensity Measured on a Visual Analogue Scale and Informative Dropout in a Dental Pain Model after Naproxcinod and Naproxen Administration

I_15: *Jacob Brogren* Transit Compartment Model Useful for Describing Absorption of Quetiapine XR and IR

I_16: *Yu-Yuan Chiu* Population Pharmacokinetics of Lurasidone in Healthy Subjects and Subjects with Schizophrenia

I_17: *Vincenzo Luca Di Iorio* Impact of Seizures and Efflux Mechanisms on the Biophase Kinetics and CNS Effects of Anticonvulsant Drugs

Applications- Oncology

I_18: *Nicolas Azzopardi* Pharmacokinetics and concentration-effect relationship of cetuximab in metastatic colorectal cancer

I_19: *Anne Drescher* Pharmacokinetic/Pharmacodynamic Modeling of Platinum-DNA-Adduct Formation in Leukocytes after Oxaliplatin Infusion

I_20: *Jeroen Elassaiss-Schaap* Allometric scaling in oncology disease progression from xenograft tumor growth to human non-small-cell lung cancer

I_21: *Iñaki F. Trocóniz* Predictive ability of a semi-mechanistic model for neutropenia in the development of novel anti-cancer agents: two case studies using diflomotecan and indisulam

I_22: *Ron Keizer* Evaluation of clinical dosing of E7820 from preclinical and clinical data using a biomarker

Applications- Other topics

I_23: *Claire Ambery* Leveraging biomarker exposure-response in drug development

I_24: *Jacqueline Anderson* PK modelling of organophosphorus poisoning in humans

I_25: *Massoud Boroujerdi* Joint model for dropout in longitudinal trials in COPD patients

I_26: *Karl Brendel* Population pharmacokinetics-pharmacodynamics modeling of the QTc

prolongation of Moxiflovoxacin and Levofloxacin in healthy volunteers: selection of the positive control in mandatory QT/QTc studies
I_27: *Karl Brendel* Using Modelling & Simulation techniques to optimise the design of a paediatric PK/PD study
I_28: *Sophie Callies* Integration of preclinical data to support the design of the first in-man study of LY2181308, a second generation antisense oligonucleotide.
I_29: *Roosmarijn De Cock* Predicting glomerular filtration rate using clearance of amikacin
I_30: *Oleg Demin Jr* Can systems modeling approach be used to understand complex PK-PD relationships? A case study of 5-lipoxygenase inhibition by zileuton
I_31: *Pinky Dua* SB-773812: Correlation between in-silico and in-vivo metabolism

Methodology- Model evaluation
I_32: *Roberto Bizzotto* Multinomial logistic functions in Markov-chain models for modeling sleep architecture: external validation and covariate analysis
I_33: *Roberto Bizzotto* PK-PD modeling of Wake after Sleep Onset time-course
I_34: *Roberto Bizzotto* Multinomial logistic functions in Markov-chain models for modeling sleep architecture: internal validation based on VPCs
I_35: *Emmanuelle Comets* Using simulations-based metrics to detect model misspecifications
I_36: *Didier Concordet* A new solution to deal with eta-shrinkage: the Weighted EBEs!
I_37: *Paul Matthias Diderichsen* A comparison of sequential and joint fitting of pain intensity and dropout hazard in acute pain studies
I_38: *Paul Matthias Diderichsen* Sufficiently high observation density justifies a sequential modeling approach of PKPD and dropout data

Methodology- Other topics
I_39: *Margherita Bennetts* Simulation Methodology for Quantitative Study Decision Making in a Dose Response Setting
I_40: *Martin Bergstrand* Semi-mechanistic modeling of absorption from extended release formulations - linking in vitro to in vivo
I_41: *Julie Bertrand* Genetic effect on a complex parent-metabolite joint PK model developed with NONMEM and MONOLIX
I_42: *Martin Boucher* Imputation of missing variance data comparing Bayesian and Classical non-linear mixed effect modelling to enable a precision weighted meta-analysis.
I_43: *Olivier Colomban* Toxicogenomic dose-response model assessed by DNA chips on rats treated by flutamide
I_44: *Paolo Denti* Modelling pre-dose concentrations in steady-state data. The importance of accounting for between-occasion variability and poor adherence.
I_45: *Gemma Dickinson* Evaluation of a Method to Better Predict Human Absorption from Non-Clinical Data; Comparison of an in silico approach with population modelling of in vivo data
I_46: *Aris Dokoumetzidis* Fractional kinetics in multi-compartmental systems

Methodology- PBPK
I_47: *Hesham Al-Sallami* A semi-mechanistic model for estimating lean body weight in children
I_48: *Marilee Andrew* Physiologically Based Pharmacokinetic (PBPK) Modeling of Midazolam Disposition in Pregnant and Postpartum Women
I_49: *Karina Claaßen* Physiology-based Simulations of Amikacin Pharmacokinetics in Preterm Neonates

Late submissions
I_50: *Gudrun Wuerthwein* Population Pharmacokinetics of Liposomal Amphotericin B, Caspofungin and the Combination of Both in Allogeneic Hematopoietic Stem Cell Recipients
I_51: *Peiming Ma* Predicting Free Sclerostin from Free AMG 785 and Total Sclerostin
I_52: *Leonid Gibiansky* TMDD Model for Drugs that Bind Soluble and Membrane-Bound Targets: Can Quasi-Steady-State Approximation Estimate unobservable Membrane-Bound Target Occupancy?

I_53: *Ronald Niebecker* Impact of Different Body Size Descriptors on the Population Pharmacokinetics of a Monoclonal Antibody

Posters Wednesday Afternoon (group II)

Applications- Anti-infectives

II_1: *Monika Frank* Population Pharmacokinetic Model Building for Mothers and Newborns using Additional Information from a Different Nevirapine Dataset
II_2: *Jeremie Guedj* Design Evaluation and Optimization for models of Hepatitis C viral dynamics
II_3: *Seong Bok Jang* Population Pharmacokinetics of Amikacin in Korean Clinical Population
II_4: *Siv Jonsson* Population Pharmacokinetics of Ethambutol in South African Tuberculosis Patients
II_5: *Dalia Khachman* Population pharmacokinetic analysis of ciprofloxacin in intensive care unit adult patients
II_6: *Holly Kimko* Modeling & Simulation Exercise to Recommend Dosage Regimens for Patients with End-Stage Renal Disease Receiving Hemodialysis

Applications- CNS

II_7: *Yuen Eunice* A population pharmacokinetic/pharmacodynamic model for duloxetine in diabetic peripheral neuropathy, plus methods for handling missing data.
II_8: *Martin Gnanamuthu Johnson* Evaluation of a Mechanism-Based Pharmacokinetic-Pharmacodynamic Model for D2 Receptor Occupancy of Olanzapine in Rats
II_9: *Gordon Graham* Continuous time Markov modelling of relapse sojourns for relapse-remitting multiple sclerosis patients
II_10: *Andrew Hooker* Title: Modeling exposure-response relationships in the rat self-administration model
II_11: *Matts Kågedal* Estimation of occupancy and radioligand kinetics in the CNS from PET-data in the absence of a reference region.
II_12: *Kristin Karlsson* Clinical trial simulations using a stroke disease progression model

Applications- CVS

II_13: *Anne Chain* Not-in trial simulation: Prospective use of Not-In-Trial Simulation
II_14: *Carolyn Coulter* Prediction of Torsades de Pointes from QT interval: analysis of a case series with amisulpride
II_15: *Vincent Dubois* Translation of drug-induced QTc prolongation in early drug development.
II_16: *Anne-Kristina Frobel* Physiologically-Based Pharmacokinetic (PBPK) Modelling of Bisoprolol in Adults and Children and External Model Validation in a Paediatric Clinical Trial
II_17: *Florence Hourcade-Potelleret* Preliminary Population PK-PD of Dalcetrapib: an Agent Targeting CETP to Raise HDL-C and Prevent Cardiovascular Morbidity and Mortality
II_18: *Sergej Ramusovic* An integrated whole-body physiology based pharmacokinetic/pharmacodynamic model of enalapril and the RAA-system

Applications- Oncology

II_19: *Martin Fransson* Pharmacokinetics of paclitaxel and its metabolites using a mechanism-based model
II_20: *Maria Garrido* Population pharmacokinetic modelling of unbound and total plasma concentrations of oxaliplatin administered by hepatic arterial infusion to patients with liver-metastases.
II_21: *Kimberley Jackson* A Novel PKPD Model to Describe the Interaction of Drug Response of Combination Therapy: An Application in Preclinical Oncology.
II_22: *Fredrik Jonsson* A Longitudinal Tumor Growth Inhibition Model Based on Serum M-Protein Levels in Patients With Multiple Myeloma Treated by Dexamethasone

Applications- Other topics

II_23: *Anne Dubois* Model-based bioequivalence analysis of recombinant human growth hormone using the SAEM algorithm: liquid or lyophilized formulations of Omnitrope® versus original lyophilized Genotropin®

II_24: *Anne Dubois* Model-based bioequivalence analysis of pharmacokinetic crossover trial compared to standard non-compartmental analysis

II_25: *Iñaki F. Trocóniz* Population PK/PD model of the sedative effects of Flibanserin in healthy volunteers

II_26: *Martin Fink* Phase I trials: Model-based assessment to identify a clinical relevant change in heart rate

II_27: *Nils Ove Hoem* A population PK model of EPA and DHA after intake in phospholipid as well as in triglyceride form.

II_28: *Ibrahim Ince* Critical illness is a major determinant for midazolam and metabolite clearance in children

Methodology- Algorithms

II_29: *Jeff Barrett* A SAS-based Solution for NONMEM run management and post-processing

II_30: *Mike Dunlavey* Derivation of SAEM C-matrix in Phoenix

II_31: *Marc Gastonguay* Comparison of MCMC simulation results using NONMEM 7 or WinBUGS with the BUGSModelLibrary

II_32: *Leonid Gibiansky* Bias and Precision of Parameter Estimates: Comparison of Nonmem 7 Estimation Methods and PFIM 3.2 Predictions on the Example of Quasi-Steady-State Approximation of the Two-Target Target-Mediated Drug Disposition Model

II_33: *Åsa Johansson* New Estimation Methods in NONMEM 7: Evaluation of Bias and Precision

Methodology- Design

II_34:*Caroline Bazzoli* New features for population design evaluation and optimisation using PFIM3.2: illustration on warfarin pharmacokinetics - pharmacodynamics

II_35: *Chao Chen* Test Of Concept By Simulation: Comparing Response-Rate Findings Between Parallel And Titration Designs

II_36: *Marylore Chenel* Optimal design and QT-prolongation detection in oncology studies

II_37: *Nicolas Frances* Influence analysis explores heterogeneity in database before data processing by a parametric population method

II_38: *Thu Thuy Nguyen* Design evaluation and optimisation in crossover pharmacokinetic studies analyzed by nonlinear mixed effects models

Methodology- Model evaluation

II_39: *Julie Grenier* Population Pharmacokinetic and Pharmacodynamic Meta Analysis of Zenvia: Modeling of QT Prolongation

II_40: *Julie Grenier* Population Pharmacokinetic Meta Analysis: Inhibition by Quinidine of the First-Pass and Systemic Metabolism of Dextromethorphan to Dextrorphan

II_41: *Chiara Piana* The Influence Of Covariate Distribution On The Prediction And Extrapolation Of Pharmacokinetic Data In Children.

Methodology- Other topics

II_42: *Charles Ernest* Predictor Identification in Time-to-Event Analyses

II_43: *Farkad Ezzet* Analysis of Adverse Events using Literature Data: a Simulation Study

II_44: *Farkad Ezzet* Modeling Adverse Event rates of Opioids for the Treatment of Osteoarthritis Pain using Literature Data

II_45: *Farkad Ezzet* Bronchial Allergen Challenge in Asthma: A Model for Inhaled Corticosteroids (ICS) and Montelukast using Literature Summary Data

II_46: *Roberto Gomeni* Integrated approach to overcome a food effect in clinical studies: an example of how in vitro, in vivo and simulation tools can help in determining an appropriate strategy

II_47: *Thaddeus Grasela* Forensic Pharmacometrics: Part 1 - Data Assembly
II_48: *Thaddeus Grasela* Forensic Pharmacometrics: Part 2 - Deliverables for Regulatory Submission
II_49: *Ivelina Gueorguieva* Is pharmacokinetic variability in microdosing trials comparable to variability following therapeutic doses?
II_50: *Michael Heathman* Interactive Simulation and Visualization of Drug/Disease Models
II_51: *Roger Jelliffe* Pharmacogenomics and Individualized Dosage Regimens
II_52: *Ron Keizer* Incorporation of concentration data below the limit of quantification in population pharmacokinetic analyses

Posters Thursday Morning (group III)

Applications- Anti-infectives
III_1: *Maria Kjellsson* Penetration of Isoniazid, Rifampicin, Pyrazinamid and Moxifloxacin into Pulmonary TB Lesions in Rabbits
III_2: *Michael Neely* High-dose amoxicillin pharmacokinetics (PK) and pharmacodynamics (PD) in children
III_3: *Thu Thuy Nguyen* Population pharmacokinetic of linezolid in inpatients
III_4: *Elisabet Nielsen* Pharmacokinetic-Pharmacodynamic Modelling for Antibiotics: Static and Dynamic In Vitro Time-Kill Curve Experiments

Applications- CNS
III_5: *Magdalena Kozielska* Predictive performance of two PK-PD models of D2 receptor occupancy of the antipsychotics risperidone and paliperidone in rats
III_6: *SeungHwan Lee* A population analysis of Intravenous Dexmedetomidine in Korean
III_7: *Gailing Li* Towards Quantitative Prediction Of In Vivo Brain Penetration Using A Physiology Based CNS Disposition Model
III_8: *Venkatesh Pilla Reddy* Modeling and Simulation of Placebo Response and Dropout Patterns in Treatment of Schizophrenia

Applications- Oncology
III_9: *Cornelia Landersdorfer* Pharmacodynamic (PD) Modelling of Anti-Proliferative Effects of Tetraiodothyroacetic Acid (Tetrac) on Human Cancer Cells
III_10: *Valerie Nock* Leukopenia following high-dose chemotherapy with autologous stem cell retransfusion in patients with testicular cell cancer

Applications- Other topics
III_11: *Elke Krekels* Paracetamol pharmacokinetics in term and preterm neonates.
III_12: *Yoon Jung Lee* Model-based evaluation of DAS28 as a potential surrogate for ACR20 to establish the dose-response relationship for disease modifying anti-rheumatic drugs. A case study using tasocitinib (CP-690,550), an oral JAK inhibitor.
III_13: *Ivan Matthews* PKPD Modeling of Dose-Response & Time Course of B-Cell Depletion in Cynomolgus Monkeys
III_14: *Jebabli Nadia* Population Pharmacokinetics Of Vancomycin In Tunisian Patients
III_15: *Jebabli Nadia* Pharmacokinetic Modelling Of Methotrexate From Routine Clinical Data In Patients With Acute Lymphoblastic Leukemia
III_16: *Jebabli Nadia* Effect Of Clonidine On Bupivacaine Clearance In Tunisian Patients: Population Pharmacokinetic Investigation.
III_17: *Chiara Piana* Once Daily Pharmacokinetics Of Lamivudine In HIV-Infected Children

Methodology- Algorithms
III_18: *Marc Lavielle* The SAEM algorithm for Non-Linear Mixed Effects Models with Stochastic

Differential Equations
III_19: *Robert Leary* Quasi-Monte Carlo EM Methods for NLME Analysis
III_20: *Hafedh Marouani* Nonparametric Approach using Gaussian Kernels Estimates Multivariate Probability Densities in Population Pharmacokinetics
III_21: *Ines Paule* Estimation of Individual Parameters of a Mixed–Effects Dose-Toxicity Model for Ordinal Data
III_22: *Elodie Plan* Nonlinear Mixed Effects Estimation Algorithms: A Performance Comparison for Continuous Pharmacodynamic Population Models
III_23: *Sebastian Ueckert* New Estimation Methods in NONMEM 7: Evaluation of Robustness and Runtimes

Methodology- Design
III_24: *Sergei Leonov* Optimization of sampling times for PK/PD models: approximation of elemental Fisher information matrix
III_25: *Flora Musuamba-Tshinanu* An optimal designed study for population pharmacokinetic modeling and Bayesian estimation of Mycophenolic acid and Tacrolimus early after renal transplantation
III_26: *Flora Musuamba-Tshinanu* Evaluation of disease covariates in chronic obstructive pulmonary disease (COPD).
III_27: *Coen van Hasselt* Application of a semi-physiological model describing time-varying pharmacokinetics to support optimal clinical study design
III_28: *Joakim Nyberg* Global, exact and fast group size optimization with corresponding efficiency translation in optimal design

Methodology- Model evaluation
III_29: *Joakim Nyberg* Investigations of the weighted residuals in NONMEM 7
III_30: *Mary Lor* Modeling and Simulation of Drug X and its Metabolite in Plasma and Urine

Methodology- Other topics
III_31: *William Knebel* A Strategy for Efficient Implementation of NONMEM 7 and the Intel Fortran Compiler in a Distributed Computing Environment
III_32: *Brigitte Lacroix* Simultaneous modeling of the three ACR improvement thresholds – 20, 50 and 70% - in rheumatoid arthritis patients treated with certolizumab pegol
III_33: *Otilia Lillin-de Vries* Population PK-PD modeling of thorough QT/QTc data allows for mechanistic understanding of observed QTc effects
III_34: *Igor Locatelli* The Development of a Link Model Consisting of in vitro Drug Release and Tablets Gastric Emptying Time: Application to Diclofenac Enteric Coated Tablets
III_35: *Christophe Meille* Probabilistic PK/PD model for ordered categorical toxicological data
III_36: *Eugeniy Metelkin* Application of pharmacokinetic-pharmacodynamic model to optimize dosing regime of antimicrobial drug Grammidin containing gramicidin S
III_37: *Carmen Navarro* Bioequivalence trials simulation to select the best analyte for drugs with two metabolic pathways
III_38: *Ackaert Oliver* A true Markov model for sleep disturbance
III_39: *Henry Pertinez* Bayesian POP-PK analysis of exposure data from a Phase IIb clinical trial
III_40: *Leonid Gibiansky* Target-Mediated Drug Disposition: New Derivation of the Michaelis-Menten Model, and Why It Is Often Sufficient for Description of Drugs with TMDD

Methodology- PBPK
III_41: *Wojciech Krzyzanski* An Interpretation of Transit Compartment Pharmacodynamic Models As Lifespan Based Indirect Response Models.
III_42: *Jörg Lippert* Clinical trial simulation with multiscale models: Integrating whole-body physiology, disease biology, and molecular reaction networks
III_43: *Jörg Lippert* Separating individual physiological variability from drug related properties using PBPK Modeling with PK-Sim® and MoBi® – Theophylline
III_44: *Jörg Lippert* Using relative gene expression measurements for PBPK modeling of

pravastatin
III_45: *Jörg Lippert* Identifying cancer drug MoAs and cell-line properties using signaling cascade models and Bayesian analysis: From throw-away experiments to persistent information
III_46: *Jörg Lippert* Mechanistic analysis of fusion proteins: PBPK applied in an Albuferon case study
III_47: *Jörg Lippert* Influence of CYP1A1 induction by cigarette smoke on pharmacokinetics of erlotinib: a computer-based evaluation of smoke-induced CYP1A1 activity in different tissues
III_48: *Jörg Lippert* Simulation of the pharmacokinetics of flibanserin under itraconazole co-mediaction with an integrated physiologically-based pharmacokinetic model
III_49: *Zinnia Parra* Nonlinear Pharmacokinetic Model For Interleukin-12 Gene Therapy
III_50: *Sabine Pilari* Lumping of Physiologically Based Pharmacokinetic Models and a Mechanistic Derivation of Classical Compartmental Models

Posters Thursday Afternoon (group IV)

Applications- Anti-infectives
IV_1: *Rada Savic* Ciprofloxacin Integrated Plasma, Saliva and Sweat Population Pharmacokinetics and Emergence of Resistance in Human Commensal Bacteria
IV_2: *Wynand Smythe* A Semi-Mechanistic pharmacokinetic enzyme model for the characterisation of rifampicin pharmacokinetics in South African pulmonary tuberculosis infected adults
IV_3: *Ami Fazlin Syed Mohamed* Predictions of Dosing Schedules of Gentamicin in Neonates Based on a Pharmacokinetic/Pharmacodynamic Model Considering Adaptive Resistance
IV_4: *Joel Tarning* Population pharmacokinetics of antimalarial drugs in the treatment of pregnant women with uncomplicated malaria
IV_5: *Toshihiro Wajima* Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling for Integrase Inhibitors with a Simple Viral Dynamic Model
IV_6: *Simbarashe Peter Zvada* Effect of Four Different Meals Types on the Population Pharmacokinetics of single Dose Rifapentine in Healthy Male Volunteers

Applications- CNS
IV_7: *Mahesh Samtani* Switching to Paliperidone Palmitate[1,2] from Other Depot Antipsychotics: Guidance Based on Pharmacokinetic Simulations
IV_8: *Monica Simeoni* Clinical and Genetic factors affecting Alzheimer's disease progression in subjects on stable acetylcholinesterase inhibitor therapy: a comparison between mechanistic and empirical disease progression modelling approaches
IV_9: *Monica Simeoni* Disease System Analysis: Evaluate the structural properties and the physiological implications of an indirect physiologic response model describing the degenerative progression of Alzheimer's disease using a closed-form solution
IV_10: *Armel Stockis* Exposure-response modeling of daily seizure counts in focal epilepsy trials
IV_11: *Mita Thapar* Population Pharmacokinetics of Safinamide and its Effect on Disease Progression in Parkinson's Disease
IV_12: *Pyry Välitalo* Plasma and Cerebrospinal Fluid Pharmacokinetics of Naproxen in Children
IV_13: *Marcel van den Broek* Optimal dosing of lidocaine for seizure control in preterm and term neonates using population pharmacokinetic modelling and simulation
IV_14: *Anders Viberg* Using an Innovative Design in Behavioural Pharmacology Studies Saves Money and Animal Lives
IV_15: *Stefano Zamuner* The assessment of convulsion risk: a translational PK/PD modelling approach

Applications- Coagulation
IV_16: *Anna-Karin Hamberg* Internal and external evaluation of a K-PD model for warfarin using prediction corrected visual predictive check (PC-VPC)

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Oral Abstracts PAGE 2010

Wilhelm Huisinga Physiologically-based pharmacokinetic/pharmacodynamic modelling, mathematical model reduction and a mechanistic interpretation of simple empirical models

Wilhelm Huisinga
Hamilton Institute, National Univerisity of Ireland Maynooth

Objectives: During drug discovery, preclinical and clinical drug development, a variety of in vitro and in vivo data are generated to investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug candidate. Based on these data, different modelling approaches are successfully used to understand, predict and optimize the PK/PD of drug candidates, most importantly classical compartment models, empirical PD models, physiologically-based PK (PBPK) models and systems biology models of targeted processes. So far, however, these modelling approaches are typically used mutual exclusive and with little cross-fertilization. The objective of this talk is to demonstrate the added value of cross-fertilization between the different modelling approaches--illustrated by establishing an explicit link between (i) classical compartment models and PBPK models for small molecule drugs, and (ii) empirical PD models and systems biology models of receptor systems targeted by monoclonal antibodies.

Methods: (i) Starting from an intriguing observation, we establish a new and very simple criterion for lumping (simplifying) detailed PBPK models. This allows us to explicitly establish a link between the parameters of the PBPK model and the lumped parameters of the simple compartment model. We introduce the notion of a minimal lumped model that can be directly linked to classical compartment PK models. (ii) Starting from a systems biology model of receptor trafficking and ligand-receptor interaction, we use mathematical model reduction techniques to link the detailed model to empirical models of drug-receptor interaction that have been used to analyse clinical data of monoclonal antibodies.

Results: (i) We establish the link between PBPK models and classical compartment model via minimal lumped models of low complexity (1-3 compartments) that retain a mechanistic interpretation. This allows us to reduce 13-18 compartment physiologically-based PK models to simple compartment models without compromising the predictions. Importantly, this enables a mechanistic interpretation of empirical compartment models. Applying the lumping approach to 25 diverse drugs, we identified characteristic features of lumped models for moderate-to-strong bases, weak bases and acids. We observed that for acids with high protein binding, the lumped model comprised only a single compartment. (ii) We establish a mechanistic PK/PD model for monoclonal antibodies targeting receptor systems by integrated systems biology models of drug-receptor inaction into empirical models of drug PK. We illustrate the approach for anti-EGFR antibodies in cancer therapy based on in vitro determined receptor system's parameters and pharmacokinetic data from cynomolgus monkeys. We contribute new insight and a simple criterion to the discussion, which model to use for receptor-mediated endocytosis of monoclonal antibodies.

Conclusions: Many drug-related data from different sources are generated during the drug discovery and development process. Physiologically and mechanism-based PK/PD modelling offers a way to integrate these data into a consistent framework , and mathematical techniques are available to link these detailed models to empirical PK/PD models, providing a mechanistic interpretation of the latter.

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Emilie Hénin Semi-physiological modeling of absorption kinetics: application to diclofenac

Emilie Hénin, Mats O. Karlsson
Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Objectives: To investigate a semi-physiological model approach to describe drug absorption kinetics when only plasma concentrations are available.
A similar approach based on Marker Magnetic Monitoring (MMM) studies was presented elsewhere[1]: individual tablet movement and plasma concentration profiles could be predicted correctly, without using tablet position measurements, but population estimated parameter distributions from MMM modeling.
The aim of this work is to apply a relatively complex model structure accounting for a priori knowledge on tablet transit through gastrointestinal tract (GI) to an example were MMM measurements were not performed.

Patients & Models: The model has been developed from a previously proposed model for GI tablet movement[2] and a separately developed diclofenac disposition model. The two models were linked by an absorption model in order to predict simultaneously tablet position in GI tract and diclofenac plasma concentration. The discrete movement of tablet has been translated into step functions, where each position (fundus, antrum, proximal small intestine, distal small intestine and colon) corresponds to specific absorption characteristics. It has also been assumed that tablet GI transit times remained unchanged across drugs.
30 healthy adult volunteers were administered 50mg diclofenac under fasting conditions in a bioequivalence study[3]; two formulations were compared, entero-coated tablet and suspension. Samples were taken at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 6, 9, and 12h after administration.
The semi-physiologic approach has been applied to diclofenac entero-coated data.
Diclofenac disposition was estimated from intravenous pediatric data[4], and well characterized by a bi-exponential elimination, with parameters scaled to weight. In our approach, disposition parameter distributions were fixed to population estimates, and total bioavailability and absorption rates for each GI region were estimated using NONMEM 7.

Results: After transit intact through stomach (fundus + antrum), the tablet sequentially moves to proximal small intestine, distal small intestine, and colon. The transit through stomach was estimated to take 2 hours in average (ranging from 35 min to 3.5 hours across the studied individuals). Compared to a more empirical model, the applied approach with prior information on tablet movement and location was able to better characterize the large variability in lag-time before diclofenac systemic uptake.
Absorption was estimated to occur mainly in the distal small intestine, and to a smaller extent in the proximal small intestine. Most of the dose was absorbed before the remaining tablet reaches the colon.
Total bioavailability was estimated to be 65%, which is in accordance with values reported in the litterature.[5]

Conclusion: We were able to estimate different absorption rates for different GI regions, accounting for a priori knowledge on tablet movement through GI tract.

An integrated PK model for absorption, drug release, GI transit and disposition will aim to discriminate between system-, drug- and formulation- specific parameters. Semi-physiological approaches integrate higher complexity, which can be valuable to better capture complex phenomena, such as drug absorption. However, applying complex, discrete-event, models to a combination of pharmacokinetic data and prior physiological model parameters is a sparsely explored area. This example shows that although challenging, this is feasible.

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Stefan Willmann Investigation of the Influence of CYP3A4 Inhibition and Renal Impairment on Morphine and M6G Formation after Codeine Administration using Coupled Whole-Body PBPK Modelling

T. Eissing, J. Lippert, S. Willmann
Systems Biology and Computational Solutions, Bayer Technology Services GmbH, 51368 Leverkusen, Germany

Objectives: The objective of this study was to systematically investigate the influence of UGT2B7 activity, CYP3A4 inhibition, and renal impairment on the extent of morphine and morphine-6-glucuronide (M6G) exposure after oral codeine administration by means of a virtual trial using coupled whole-body physiologically-based pharmacokinetic (WB-PBPK) simulations.

Methods: A coupled WB-PBPK model for codeine, its primary metabolite morphine (formed by the polymorphic enzyme CYP2D6) and its secondary metabolite M6G (formed by UGT2B7 from morphine) was developed. Plasma concentration time profiles of codeine, morphine, and M6G after oral codeine administration were simulated in virtual populations of female and male adult individuals representing poor (PM), intermediate (IM), extensive (EM), and ultrarapid (UM) CYP2D6 metabolizers for different degrees of UGT2B7 activity, renal impairment and CYP3A4 inhibition.

Results: The simulated plasma pharmacokinetics of codeine, morphine, and M6G were in very good agreement with published data obtained in vivo by several authors in CYP2D6 genotyped or phenotyped individuals with normal kidney function and no co-administration of a CYP3A4 inhibitor [1-4]. The simulations further demonstrated that a decreasing kidney function leads to an increase of morphine and, in particular, M6G concentrations. Co-administration of a CYP3A4 inhibitor further increases the plasma exposure of morphine and M6G due to a (partial) block of codeine and morphine metabolization pathways that produce inactive metabolites (norcodeine and normorphine). UGT2B7 activity has nonlinear and opposing effects on morphine and M6G exposure, as this enzyme also catalyzes the formation of codeine-6-glucuronide, the major (inactive) primary codeine metabolite.

Conclusions: In conclusion, the developed coupled WB-PBPK model is capable of simulating the plasma pharmacokinetics of codeine, morphine, and M6G after oral codeine administration in dependence of the CYP2D6 phenotype, UGT2B7 activity, and the degree of renal function and CYP3A4 inhibition. This clinical trial simulation allows a quantitative assessment of safety and efficacy aspects of codeine administration in adult populations considering various covariates.

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Pascal Chanu Mechanistic Models to Simulate Dose Response of IgE Suppression Following Dosing of Anti-IgE Monoclonal Antibodies

Pascal Chanu (1), Balaji Agoram (2), Rene Bruno (1)
(1) Pharsight, a CertaraTM company, St. Louis, MO, USA; (2) Pfizer, Clinical Pharmacology, Sandwich, UK

Objectives: The aim of this study was to use mechanistic models to simulate dose response of IgE suppression for anti-IgE monoclonal antibodies such as omalizumab vs. higher affinity antibodies.

Methods: A previously published instantaneous equilibrium (IE) drug-IgE binding model for omalizumab [1,2] was used to perform simulations of expected IgE suppression for anti-IgE monoclonal antibodies. The equilibrium assumption being only valid for limited ranges of drug affinity and dose, the IE model was extended to a full target-mediated disposition (TMD) model [3]. The models were implemented in Pharsight® Trial Simulator™ to perform simulations. Model implementation was evaluated by simulating multiple replicates of the data in the original papers and comparing with published plots and results. The TMD model was then used to simulate dose response (proportion of patients with IgE suppression below threshold levels, e.g. 50 ng/mL) in specific regions of the omalizumab dosing table including patients non-treatable by omalizumab (Xolair package insert) for omalizumab, and other more potent anti-IgE antibodies (10-to 30-fold increase in affinity) to characterize the affinity-potency relationship of such antibodies.

Results: Both the IE and TMD models reproduced well the data in the original papers. The IE model however, predicted continuous increase in in-vivo potency with increasing IgE affinity whereas the TMD model predicted a maximum 2.4 to 3-fold increase in potency with a 10-fold increased affinity and no difference between 10-fold and 30-fold increase in affinity. The latter is consistent with clinical data [4]. Simulations demonstrated that a 10-fold more potent drug would suppress free IgE below 50 ng/mL in 95% of the patients (a suppression associated with clinical efficacy in asthma) at 350 mg every 4 weeks in the most challenging patient subgroup (i.e. patients with high IgE and large body weight).

Conclusions: A fully mechanistic TMD model is required for PKPD translation across anti-IgE antibodies and should be pursued in the clinical setting wherever possible. There is potential to treat a larger patient population with a more convenient dosing paradigm and a higher potency anti-IgE antibody.

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Julia Korell Design of survival studies for red blood cells

Julia Korell, Carolyn V. Coulter, Stephen B. Duffull
School of Pharmacy, University of Otago, Dunedin, New Zealand

Background:

The lifespan of red blood cells (RBCs) is unknown. The primary methods for determining RBC lifespan involve labelling with a radioactive marker. Two labelling techniques have been developed: cohort labelling, where cells of a certain age are labelled, and random labelling, where all cells present at a moment in time are labelled. Of these the random labelling technique has been more commonly used. All current labelling methods contain significant flaws including loss of the label from viable RBCs or reincorporation of the label into new RBCs after the death of the originally labelled cells. Loss of label may occur from decay of the radioactive compound, dissociation of the radioactive compound from the target and loss by vesiculation. From a modelling perspective, previously proposed models for the lifespan of RBCs either assume a fixed lifespan for all cells [1], or a continuous distribution of lifespans where the cells are thought to die solely due to senescence [2,3]. Recently, Kalicki *et al.* have shown that combining a finite lifespan with random destruction improves the performance of these models [4].

Objectives:

1. To develop a model for RBC survival based on statistical theory that incorporates known physiological mechanisms of RBC destruction.

2. To assess the local identifiability of the parameters of the lifespan model under ideal cohort and random labelling techniques.

3. To evaluate the precision to which the parameter values can be estimated from an *in vivo* RBC survival study using a random labelling technique with loss of the label.

Methods:

1) A statistical model for the survival time of RBCs with respect to the physiology of RBC destruction was developed. The model was derived from established models that were developed to describe the lifespan of humans [5].

2) The local identifiability of the parameters was determined informally using the theory of design of experiments. In this method the information matrix was constructed for an experiment based on ideal cohort and ideal random labelling and it was assessed whether the matrix was positive definite for a

given fixed design, indicating local identifiability. Measurement noise was included as a combined error model, with an additive variance of 1.73 (counts per minute/mL)^2 and a coefficient of variation of 2.32% for the proportional error, based on i*n vitro* experiments in our laboratory.

3) A D-optimal design was applied to determine optimal blood sampling times for *in vivo* RBC survival studies using a random labelling method with loss of label. A hypothetical *in vivo* study with 100 patients was assumed that uses radioactive chromium as a label for RBCs. A dose of radioactive label was determined that provided an initial concentration of 400 counts per minute (cpm) per mL of blood sample. The lower limit of detection was 0.8 cpm per sample analysed. The percentage standard errors (%SE) of the parameter estimates were determined from the inverse diagonal entries of the corresponding Fisher Information matrix. Measurement noise was the same as in (2).

Results & Discussion

1) The model was described by a combination of flexible and reduced additive Weibull distributions. The underlying combined distribution of RBC lifespans accounts for the known processes of RBC destruction, including death due to senescence, random loss during circulation, as well as death due to early or delayed failures. These processes are controlled by five parameters in the model, while a sixth parameter combines the two underlying Weibull distributions. The resulting survival model was used to simulate *in vivo* RBC survival studies using different RBC labelling techniques. Predictions from the model agreed well with models from the literature for cohort labelling techniques as well as for random labelling techniques. Furthermore, the decay of radioactive chromium with a half-life of 27.7 days was included into the model, together with the dissociation of the chromium-haemoglobin complex with an approximate half-life of 70 days and a vesiculation-related loss of 20% of the total haemoglobin together with bound label from the cells during their median lifetime. These values are in accordance with the literature.

2) The Fisher information matrix was positive definite for both the ideal cohort and random labelling studies, indicating that the model was locally identifiable for a given finite design. For the ideal cohort labelling study with 100 patients the percentage standard error (%SE) values for all but one parameter were

3) The D-optimal design was located for the random labelling method including the various loss mechanisms of label from RBCs. Optimal sampling times were on day 1, 28, 55, 56, 78 and 112 after labelling. One blood sample per day was taken at each of these days from each of the 100 patients in the hypothetical study. The %SE for the parameter estimates were as follows: 54% and 49% for the two main parameters controlling the senescence component of RBC survival, 36% for the parameter controlling random destruction, 43% for the parameter controlling death due to delayed failures, and 4% for the mixing parameter that combines the two underlying Weibull distributions. The %SE of the parameter controlling the initial destruction was not estimable (%SE >200%). This initial destruction is the only parameter in the model that cannot be estimated from a study using a random labelling technique with radioactive chromium.

Conclusions:

The developed model incorporates plausible processes of RBC destruction in the body. Simulations of RBC survival studies using cohort labelling techniques as well as random labelling techniques are plausible. The model accounts for the known shortcomings of radioactive chromium as the most commonly used random label for RBCs. The model shows local identifiability of all parameter values

under ideal labelling techniques. Using a random labelling technique with loss of the label, all but one parameter can be estimated with reasonable precision. The model and design are intended to be used for setting up and interpretation of current *in vivo* studies of RBC survival. However, there is a clear need for better labelling techniques for RBCs in the future.

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Stephen Senn Some considerations concerning covariates in clinical trials

Stephen Senn
Department of Statistics, University of Glasgow

The closer you get to registration in drug development, the greater the resistance to using covariate information. There is a lamentable prejudice against modelling[1] that is reflected in a series of superstitions, in particular

1. That randomisation means that prognostic information can safely be ignored[2].
2. That simpler approaches (for example the log-rank test) are more robust than more sophisticated ones (such as for example proportional hazards regression).
3. That nonparametric methods are more exact than parametric ones.
4. That marginal predictions require marginal models[3].
5. That change from baseline uses baseline information adequately[4].

I consider these points and provide some examples. I show that using covariates information can often bring benefits equivalent to studying more patients. As a technical matter, I consider the relationship between stratification, which is generally more widely accepted, and analysis of covariance which has greater resistance.

In addition to adjusting for main effects, covariates can be modelled as ‘effect modifiers'. This raises more difficult issues, in particular of bias-variance trade-off. A simple illustration using mean square error is illuminating of the general philosophical issue but the precise solution remains difficult to agree.

I conclude that the analysis of phase III trials could be improved by adopting some of the spirit of the ‘population school'.

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Akash Khandelwal Covariate Model Building Using Linear Approximations

Akash Khandelwal, Kajsa Harling, E Niclas Jonsson, Andrew C Hooker, Mats O Karlsson
Dept of Pharmaceutical Biosciences, Uppsala University, Box 591, 75124, Uppsala Sweden

Background: Methods for exploratory covariate model building that rely on individual, empirical Bayes, parameter estimates are not appropriate whenever data per individual are sparse or when covariates are varying in time. Screening that is based on multiple analyses of non-linear mixed effects models are routinely used, but such model building is time-consuming especially when a large number of parameter-covariate relations are to be explored. A method utilizing a first-order (FO) linearization of covariate relations and variability terms, where derivatives and typical subject predictions arise from a nonlinear mixed effects base model, has previously been presented [1]. In covariate model building, it performed similarly to non-linear mixed effects modeling.

Aim: To implement and evaluate existing and new linearization methods for covariate model building.

Methods: The published method is based on a FO approximation for interindividual variability and covariate relations. Here also methods based on conditional first- (FOCE) and second-order (SOCE) approximations, with or without interaction between random effects are developed and evaluated. Both simulated data and real data examples, including studies with phenobarbital, moxonidine and dofetilide, have been explored. .

Results: The FO linearization method performed similarly to previous reports [1]. The conditional linearization methods (utilizing FOCE- and SOCE-derivatives) improved on the FO method and agreed well with estimation with nonlinear mixed effects models for both real and simulated data sets. For covariate relations of weak to moderate strength, where the decrease in the objective function (OFV) was <15 units, there was good agreement between nonlinear and linearized models. For strong covariate relations, OFV differences between the linear and nonlionear models were in general larger, but both methods identified similar covariate effects as significant.

Discussion: Linearized models can provide information on covariate effects that is very similar to that of nonlinear models but with run-times that seldom will exceed a few seconds. Such rapid runtimes allow explorative covariate model building to utilize computer-intensive techniques (variation of initial estimates for each model, randomization tests, cross-validation and case-deletion diagnostics) that can provide important information but are often impossible when nonlinear mixed effects models are analyzed. .

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Brigitte Lacroix Evaluating the IPPSE method for PKPD analysis

Brigitte D. Lacroix(1,2), Lena E. Friberg(1) and Mats O. Karlsson(1)
(1)Department of Pharmaceutical Biosciences, Uppsala University, Sweden;(2)Pharmacometrics, Global Exploratory Development, UCB Pharma SA, Belgium

Background: To develop PKPD models based on previously determined individual PK parameter (IPP) estimates is a common alternative to the simultaneous (SIM) analysis of PK and PD data. In the IPP analysis, individual PK parameters are fixed, which is equivalent to assume that they are estimated without error. The IPPSE method is similar to the IPP method but takes into account that individual parameters are estimated with imprecision (SE).

Objectives: To compare the IPPSE with the IPP and SIM methods.

Methods: Data sets (n=200) with various study designs were simulated according to a one-compartment PK model and direct Emax PD model. The study design of each dataset (number of subjects, number and sampling times of PK and PD observations, and nominal population parameters) was randomly selected using Latin hypercube sampling as described by Zhang et al. [1].

The same PK and PD models were fitted in NONMEM 7 to the simulated observations using the SIM, IPP and IPPSE methods. The uncertainty around individual estimated parameters was provided as a default output by NONMEM 7.

We compared the performance of the 3 methods with respects to estimation precision and bias, computation time and NONMEM estimation status, as a function of the number of PK and PD observations, shrinkage, and degree of uncertainty in the individual (empirical Bayes) PK estimates.

Results: Estimates of bias and precision for IPP and SIM agreed with those of Zhang et al. [1]. Estimated precision and bias for the IPPSE method were similar to that of SIM, while IPP had higher bias and imprecision. Similar results were obtained when removing the variability in Emax in the PD model in order to reduce the over-parameterization. Moreover, in comparison with the SIM method, nearly as much computational run time was saved with the IPPSE method (50 to 60% according to the PD model tested - full or reduced) as with the IPP method (70%).

Conclusions: The IPPSE method seems to be a promising alternative for PKPD analysis, combining the advantages of the SIM (higher precision and lower bias of parameter estimates) and the IPP (shorter run time) methods.

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Dalia Khachman You have problems to interpret VPC? Try VIPER!

Dalia Khachman, Celine M. Laffont and Didier Concordet
UMR181 Physiopathologie et Toxicologie Expérimentales, INRA, ENVT, Toulouse, France.

Objectives: Model evaluation has become a key component of the modelling process. In this respect, Visual Predictive Checks (VPC) are very popular as they allow direct comparison of observations (concentration or effects) with their predictive distribution under the model, diagnosing both structural and random effects' models [1]. Despite these advantages, VPC present several limitations [2,3]. First, their interpretation is quite subjective since it is not always possible to know the number of observations that should be outside prediction intervals due to correlations within individuals. Second, stratification of the data is often necessary in case of different dosage regimens and whenever covariates are included in the model. Such stratification may lead to uninformative VPC as several VPC plots are performed with fewer data per plot. In that context, we propose a new graphical tool called VIPER (VIsual Predictive Extended Residuals). This new tool was designed to perform an accurate and easier evaluation of the model in a VPC-like manner without VPC drawbacks.

Methods: For each individual *i*, we calculate from the observations the vector of standardised predictions errors (U_i) using the expectation and diagonal variance matrix estimated empirically over *k* simulations. We then calculate the sup-norm of U_i, keeping information on the sign, and compare this sup-norm with the corresponding predictive distribution under the model (taking into account the subject's characteristics). Since individuals are independent, so are their sup-norms. Therefore, it was possible to represent all sup-norms of all individuals on a single graph (provided some rescaling) and define prediction intervals so that the overall probability of observing more than a given amount of data points out of the prediction intervals was less than 0.001 under the null hypothesis (H_0). The performance characteristics of VIPER were tested using various population PK models under H_0 and several alternative hypotheses (H_1).

Results: VIPER showed good performances for global model evaluation and allowed to overcome VPC-related issues in all tested models. Advantages towards other visual tools (NPC [1], PC-VPC [3]) are discussed.

Conclusions: Based on the present evaluation, VIPER appear to be an easy and powerful visual tool for global model evaluation.

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Bruno Boulanger Trial predictions vs. trial simulations in early clinical development: a framework to evaluate the predictive probability of success based on NONMEM outputs

B. Boulanger, A. Jullion & P. Lebrun
UCB Pharma and Université de Liège

Objective: In a Model-Based Drug Development strategy, the very first objective is to design studies such that the most reliable model estimates are obtained, in order to optimize the design of future studies and to take decisions based on predictions. The objectives of the work is to present from a theoretical and practical point of view how to perform trial predictions, as opposed to trial simulations, by integrating the uncertainty of the parameters directly from NONMEM outputs. The difference between prediction and simulation is particularly important in early development when limited data or prior information are available: in that case ignoring the uncertainty of parameter estimates can bias the predictive probability of success and yield to wrong decisions.

Method: First, in the light of Bayesian statistical prediction, will be provide methodology to perform trial predictions from the parameter estimates and their uncertainty, when obtained with conventional frequentist population methods as those used by NONMEM. Second, a practical implementation in R will be shown. This implementation extracts directly the necessary information from NONMEM outputs into a generalized prediction shell that can cope with any kind of structural population models: ODE, single & multiple doses, infusion, loading dose etc... The proposed shell is also flexible enough to allow the testing of various scenarios and study designs, including drop-outs for example

Results: When limited prior information is available as in early development, integrating the uncertainty of the parameter estimates is crucial for making prediction-based decision and optimizing study designs. The proposed approach permits to directly evaluate the predictive probability of success in different conditions, such as dose, regimen etc... When several joint models for efficacy and safety are established, the Prediction-based Clinical Utility Index (P-CUI) and its distribution can directly be obtained for more reliable decision making. This is the Design Space thinking applied to dose & regimen conditions. Examples with different amount of prior information will be made to highlight in early phases the differences existing between trial prediction and trial simulation. In late phases, when information is rich, the difference becomes practically negligible.

Conclusion: The proposed approach derived and adapted from the Bayesian statistical prediction methodology, combined with flexible technology as provided by R, permits to establish simple and practical solutions for conducting trial prediction, deriving P-CUI and more important, supporting decision making. The interfacing with NONMEM makes this methodology easy to implement for supporting Model-Based Drug Development strategy and impacting decision, particularly in early clinical phases.

Caroline Bazzoli Design evaluation and optimisation in multi-response nonlinear mixed effect models with cost functions: application to the pharmacokinetics of zidovudine and its active metabolite

Caroline Bazzoli, Sylvie Retout, France Mentré
UMR738, Inserm and, University Paris Diderot, Paris, France.

Introduction: Models with multiple responses within patients are increasingly used in population analyses. Main examples are joint pharmacokinetic-pharmacodynamic models, complex pharmacodynamic models and pharmacokinetic models of parent drug and metabolite(s). In this context, efficient tools for population designs evaluation and optimisation are necessary. For complex models it is indeed difficult to guess good empirical designs especially when limitations are imposed in the number of samples in each patient. The methodology for optimal population design based on the Fisher information matrix for nonlinear mixed effect models has been initially developed and evaluated **[1, 2]** for single response models. It has been implemented in several softwares including PFIM, an R function **[3]**. Regarding design optimisation, algorithms are required either to optimise exact designs or statistical designs. The Fedorov-Wynn algorithm is particularly adapted to this last approach optimising both proportions of subject associated to each group (design structure) and the samples and their allocation in time.

Our objectives were: 1) to evaluate the expression of the Fisher information matrix for multiple response models, 2) to propose a new extension of the Fedorov-Wynn including cost functions, 3) to extend the R function PFIM for multiple response models with discrete covariates and intra-occasion variability, 4) to apply these new developments to the joint pharmacokinetic modeling of zidovudine and its active metabolite.

Design evaluation and optimisation for multiple response models

a) Expression of the Fisher information

We extended the expression of the Fisher information matrix for multiple response models **[4, 5]** using a linearisation of the model as proposed for a single response by Mentré *et al.* **[1]**. Using a pharmacokinetic / pharmacodynamic model example **[6]**, we evaluated the relevance of the predicted standard errors (SE) computed by linearisation. To do that, first, we compared those SE to those computed under asymptotic convergence assumption using the SAEM algorithm **[7]** through a simulation of 10000 subjects. We also compared those predicted SE to the empirical SE, defined as the standard deviation on the 1000 estimates, obtained with three algorithms: two algorithms based on a linearisation of the model (FO, FOCE) in the software NONMEM and the SAEM algorithm in MONOLIX. The SE computed by linearisation are equivalent to those predicted by SAEM and to the empirical ones obtained with FOCE and SAEM. Regarding FO, the empirical ones are much larger than the SE computed by linearisation and those obtained with FOCE or SAEM.

b) Design optimisation: extension of the Fedorov-Wynn algorithm

Usually, design optimisation is done for a fixed total number of samples without any consideration on the relative feasibility of the optimised sampling times or the group structure. Mentré *et al*. **[1]** proposed an approach allowing to take into account the cost of each sample in the context of single response model. From the extension of the Fisher information matrix for multiple responses, the Fedorov-Wynn algorithm was extended to the introduction of cost functions allowing design optimisation for several responses for a fixed total cost **[8]**. The classical cost function defined the cost of an elementary design as the sum of the number of samples for each response. More complex cost functions can be implemented as for instance an additional cost for a new patient, different cost for the different responses, penalties for delay between samples.

Extensions of PFIM

a) PFIM 3.0

From the relevance of the expression of the Fisher information matrix for multiple responses and the interest of the use of the Fedorov-Wynn algorithm for design optimisation, we proposed extensions of the software tool PFIM. We first developed PFIM 3.0 **[9]** to accommodate multiple response models. Other options were added in PFIM 3.0 for model specification or optimisation. Models can be specified either with their analytical form or by using a system of differential equations and library of analytical pharmacokinetic models was added. Design optimisation is performed using the D-optimal criterion optimization and the Fedorov-Wynn algorithm was implemented in PFIM 3.0 as an alternative to the Simplex algorithm.

b) PFIM 3.2

More recently, we proposed the version PFIM 3.2 based on an extension of the R function PFIM 3.0. This new version, released in January 2010, includes several new features in terms of model specification and expression of the Fisher information matrix. Regarding model specification, the library of standard pharmacokinetic models was completed and a library of pharmacodynamic models is now available. It is now also possible in PFIM 3.2 to use models including inter-occasion variability (IOV) with replicated designs at each occasion **[10]** and to compute the Fisher information matrix for models including fixed effects for the influence of discrete covariates on the parameters **[11]**. It can be specified if covariates change or not accross occasions. The computation of the predicted power of the Wald test for comparison or equivalence tests, for a given distribution of the discrete covariate, as well as the number of subjects needed to achieve a given power can be computed.

PFIM versions and extensive documentations **[12, 13]** are freely available on the PFIM website: http://www.pfim.biostat.fr/.

Application to the pharmacokinetic of zidovudine and its active metabolite

a) Methods

We applied these developments to the plasma and intracellular pharmacokinetics of zidovudine (ZDV), a nucleoside reverse transcriptase inhibitors (NRTI), in HIV patients. Indeed, all NRTI undergo a series of sequential phosphorylation reactions producing triphosphates (TP) in the cell. ZDV is thus metabolised intracellularly to its active metabolite (ZDV-TP), necessary for antiviral activity **[14]**. We first determined the first joint population model of ZDV and its active metabolite ZDV-TP. Data are obtained from the COPHAR 2-ANRS 111 trial **[15]** in 75 naïve HIV patients receiving oral

combination of ZDV, as part of their HAART treatment. Four blood samples per patient were taken after two weeks of treatment to measure the concentrations at steady state. Intracellular concentrations, costly to analyse, were measured in 62 patients. Using the SAEM algorithm implemented in the MONOLIX software, we estimated the pharmacokinetic parameters of ZDV and its active metabolite. We then aimed at designing new trial for this joint population analysis. Based upon the joint population pharmacokinetic model, we evaluated the empirical design used in COPHAR 2 assuming 50 subjects with 4 measurements of each response. We then explored D-optimal population designs with PFIM 3.0. First, the optimisation was done for a fixed total number of samples meaning that the cost of a design was proportional to the number of samples. We then optimised designs through the use of three different cost functions using a working version of PFIM. Optimisation was done for a same total cost defined by the total number of sampling times of the empirical design i.e. 400 for both responses.

b) Results

A one compartment model with first order absorption and elimination best described plasma ZDV concentration, with an additional compartment describing the metabolism of the drug to intracellular ZDV -TP with a first order elimination **[16]**. The optimal design with the classical cost function shows that a design with only three samples for ZDV and two samples for ZDV-TP with adequate allocation in time, allows to estimate parameters as precisely as the empirical design but with less samples per patient. In addition, optimal designs were different according to the cost functions used. They are different in terms of sampling times but also in terms of group structure, reflecting the imposed penalties. Indeed, the optimal design penalising for example the addition of a new patient involve more sampling times per patient and a smaller number of patients.

Conclusion: We evaluated the extension of the Fisher information matrix for nonlinear mixed effect models with multiple responses using the usual first order linearisation. We used simulation and showed its relevance. We then developed and illustrated the usefulness of the Fedorov-Wynn algorithm with cost functions for design optimisation especially when substantial constraints on the design are imposed. We implemented these developments in new versions of the R function PFIM and we applied them to plasma and intracellular pharmacokinetics of zidovudine, an antiretroviral drug. We performed the first joint population analysis of zidovudine and its active metabolite in patients. We showed that population design optimisation allows to derive efficient designs according to clinical and technical constraints for further joint population pharmacokinetic analysis of this drug.

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Maud Delattre Estimation of mixed hidden Markov models with SAEM. Application to daily seizures data.

M. Delattre (1), R. Savic (2), R. Miller (3), M. O. Karlsson (4), M. Lavielle (5)
(1) University of Paris-Sud; (2) INSERM U738; (3) Pfizer Global R & D; (4) Uppsala University; (5) INRIA Saclay Île-de-France

Objectives: In some specific medical contexts, the values of biological markers at successive time points are the only informations available to assess the seriousness of a given pathology in patients. Considering a unique sequence of observations, hidden Markov models (*HMM*) are thus a particularly relevant modeling tool. In those models, the different presupposed disease stages are treated as a Markov process with finite state space and memory one. Such models also allow a correct handle on the dependency between consecutive observations.

When the data to be described include several individuals, specific care is needed to account correctly for the between-subjects heterogeneity. Mixed effects hidden Markov models (*MHMM*) have been recently developped [1] as an extension of hidden Markov models to population studies. In our area, mixed hidden Markov models would provide an accurate description of longitudinal data collected during certain clinical trials, especially when distinct (hidden) disease stages are supposed to condition the distribution of some biological markers. Those particular models are quite easily interpretable and could even show similarities in the biological process that governs certain pathologies.

Mixed hidden Markov models include several levels of definition. Assume we have at our disposal observations from n subjects, which respective distributions could reasonnably be supposed to be driven by an underlying Markov chain. First, a hidden Markov model is put on the observations of each of the n subjects. Each individual model is thus specified by its own transition probabilities and its own emission probabilities. Second, those individual parameters are given a common probability distribution. The parameters of this shared distribution, also called population parameters, give access to the mean tendency of the examined phenomenon and capture the potential heterogeneity in the population studied.

Our work mainly aimed at developping and evaluating a complete methodology for estimating parameters in those new models. Our algorithms were applied in the clinical context of epilepsy, to model daily seizure counts in epileptic patients and to assess the effects of a given anti-epileptic drug on the evolution of the epileptic symptoms.

Methods: Making inference on mixed hidden Markov models is a challenging issue. We need to interest in three consecutive angles. The *MHMM*'s population parameters have to be estimated to allow next the estimation of the individual parameters and the decoding of the the most likely sequence of hidden states for each subject.

The maximum likelihood approach is often chosen in practice to estimate the population parameters. However, in addition to their highly non linear structure, mixed hidden Markov models show similarities with incomplete data models. Indeed, both the (random) individual parameters and the hidden sequences of visited states could be considered as "missing" data. As a consequence, the likelihood has a complex expression, and locating its maximum is directly intractable. In a classical *HMM*, where only emissions are given, the likelihood is difficult to express also, but the Baum-Welch algorithm makes us able to compute it quickly. We consequently suggest estimating the population parameters of mixed hidden Markov models by combining the SAEM algorithm with the Baum-Welch algorithm. Then, the individual parameters for each subject's *HMM* are estimated using the MAP (*Maximum A Posteriori*) approach. The estimates for the individual parameters incorporate all the prior information on the data. Therefore, each individual *HMM* can be considered separately, and the Viterbi algorithm can finally be computed to decode the optimal sequence of hidden states for each subject.

The evaluation of the estimation properties was based on Monte Carlo studies, especially focusing on the performances of the SAEM algorithm.

An application on a real dataset followed. The data coming from a double-blind, placebo-controlled, parallel-group and multicenter study consisted of daily seizure counts collected in epileptic patients during 12 weeks screening phase and 12 weeks treatment phase. A placebo/drug model was suggested using mixed hidden Markov models. For that purpose, a two state Poisson *MHMM* was built, assuming the epileptic patients go through periods of low and high seizure susceptibility [2]. The treatment dose was included as a covariate at both transition and emission levels in the model to identify clearly the treatment effects on epileptic symptoms.

Our analysis were performed using Monolix and Matlab programs.

Results: First, the good behavior of the SAEM algorithm was a very encouraging result. The convergence was clear and fast. Then, based on the Monte Carlo studies, the population estimates were close to the true values. Indeed, the relative estimation errors (REE) were computed and showed small ranges for the estimates and very little bias. This suggested our algorithm would estimate parameters with a certain accuracy in large databases. Then, the estimated standard errors for each parameter were low.

A first application of mixed hidden Markov models on real data gave good results also. Based on the 788 individual sets of daily seizures in screening phase, a two state Poisson *MHMM* provided a good description of daily seizures' evolution over time. According to the BIC criteria, Poisson mixed hidden Markov models appeared to be better candidates than Poisson models and mixtures of Poisson for describing epilepsy data. In particular, *MHMMs* pretty well described the characteristic overdispersion of the data. Moreover, our models mainly showed the drug had a non negligible effect on the Poisson parameters describing the daily seizure counts in each state. To be more precise, the estimations suggested the drug reduces the number of daily seizures in both states of epileptic activity. The estimations also revealed a large interpatient variability at both transition and emission levels.

Conclusion: The algorithms developped for estimating parameters in mixed hidden Markov models appeared to be performant and fast. Based on Monte Carlo studies, the Baum-Welch-SAEM algorithm was shown to provide accurate estimates. The consistency of the maximum likelihood estimates is thus expected, but this point keeps to be studied rigorously by the following.

More generally, mixed hidden Markov models offer very promising statistical applications. In some cases, their structure could even help better understand some disease mechanisms and provide a new way to analyze some drugs' pharmacodynamics. Those new models should thus offer improvement in the analysis of some clinical trials, by envisaging a given treatment could influence not only the mean disease symptoms but the time spent in each disease stage too.

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Lay Ahyoung Lim Dose-Response-Dropout Analysis for Somnolence in Pregabalin-treated Patients with Generalized Anxiety Disorder

Lay Ahyoung Lim (1), Raymond Miller (2), Kyungsoo Park (1)
(1) Department of Pharmacology, College of Medicine, Yonsei University, Seoul, Korea (2) Pfizer Global R&D, New London, CT, USA

Background: Pregabalin (Lyrica®) is a voltage-gated calcium channel α2-δ ligand for the treatment of partial seizure, neuropathic pain and generalized anxiety disorder (GAD). It is reported that dizziness and somnolence are the most common adverse events (AEs) in pregabalin treatments. These AEs might be among the major reasons that cause people to drop out of the treatment. Quantitative understanding of such AEs, in terms of incidence and severity over the course of study, therefore would provide the better treatment guideline for patients. With this as a background, this study was designed to analyze daily somnolence scores collected from 6 randomized, double-blind, multiple-dose, placebo-controlled, parallel-group studies in patients with GAD. Treatment was up to five to seven weeks and ranged from the dose of 150 to 600 mg/day given as BID or TID regimen with a one-week dose titration and a one-week taper period.

Objectives: This study aimed to investigate the dose-AE(somnolence)-dropout relationship of pregabalin, in terms of incidence and severity, following oral doses given in patients with GAD.

Methods: The relationship of dose-AE-dropout was modeled using the two-part mixture AE model in which separate models were developed for the incidence of AE and for the severity of AE given that an AE has occurred [1], [2]. The data were analyzed using NONMEM 7.

Incidence model: A logistic regression model was used to describe the incidence data where the logit was described as a sum of baseline and drug effect. No interindividual random effect was considered because each subject had only one incidence record of either "occurred (AE=1)" or "not occurred (AE=0)". Several types of models for drug effect were tested such as linear, Emax, and sigmoid Emax models. In each model, the resulting predicted incidence was compared by dose, and 95% confidence intervals (CI) were calculated by a nonparametric-bootstrap method (n=1000).

Conditional severity model: A longitudinal proportional odds model [3] was used to describe the relationship between the probability of daily AE scores measured by the ordered categorical scale (none, mild, moderate, and severe) and pregabalin exposure (titrated daily dose). The logit was described as a sum of baseline parameters, placebo and drug effects, with interindividual random effects being included. Several drug effect models including linear, Emax and sigmoid Emax models were tested, considering time-dependent effects of drug exposure and exponential attenuation of AE. The model was further elaborated by incorporating a first-order Markov model [3], [4] to account for the correlation between adjacent observations, in which the prediction was assumed dependent on the previous observation.

Unconditional severity probability: The incidence and the conditional severity probabilities were then multiplied each other to obtain the joint probability for the incidence and the severity of AE. The joint probabilities were summed over the possible outcomes for AE status (i.e., AE = 0 and 1) to obtain the marginal (unconditional) severity probability.

Dropout model: To explore the influence of AE on the patient withdrawal status, the dropout model was incorporated into both the incidence and the conditional severity model. For the incidence model, the dropout likelihood was estimated by dose, then the overall likelihood was obtained by multiplying the incidence likelihood and the dropout likelihood for each dose. For the conditional severity model, the time to dropout was treated as a survival variable where the hazard of dropout was assumed constant at each severity level, with no interindividual variation included. The overall likelihood was obtained as the severity likelihood multiplied by the dropout likelihood for each severity level [5].

Results: The dataset consisted of 47,218 observations collected from 1,630 patients. For the incidence model, the drug effect in the logit was adequately described by the Emax model. The predicted mean (95% CI) incidence was 24.6% (20.2-29.5%) at the dose of 150 mg/day, which was about 2-fold higher compared to the placebo group of 11.8% (8.9-14.8%).The predicted incidence tended to increase with dose, reaching 32.4% (28.8-36.5%) at the dose of 600 mg/day. For the conditional severity model, a monoexponential function was chosen for the placebo effect in the logit, and the Emax model for the drug effect, in which both time-dependent effects of drug exposure and attenuation of AE significantly improved the model fit. Adding a Markov component further improved the model, yielding the rate constants (half-life) for the placebo effect, time-dependent drug exposure effect, and attenuated AE effect of 3/day (0.23 day), 0.689/day (1 .01 days), and 0.102/day (6.8 days), respectively. The visual inspection of unconditional severity probability versus time computed from the above choice of model revealed that after reaching the peak probability in about 5 days the incidence and the severity of AE declined over 3-4 weeks, as expected from the estimated half-life of attenuation effect of 6.8 days. For the incidence-dropout model, the predicted dropout rate matches well with the observed dropout rate, with placebo and drug effect parameters being almost identical to the case not modeling dropout events. For the severity-dropout model, the predicted dropout rate was lowest for patients who experienced no AE and abruptly increased for those with severe somnolence. It was predicted that the probability of dropout for no AE was as high as for the mild AE partly because other kinds of AEs such as dizziness have occurred to these patients, which might have acted as other sources of dropout.

Conclusions: This study showed that the probability of somnolence incidence increases with the dose in pregabalin treatments. A combined model of the proportional odds model and the Markov model well described the time course of AE rates where time-dependent effects of drug exposure and attenuation of AE were found significant. Including a dropout model did not improve the model fit, indicating no significant dropout effect present. A further study will be needed to validate the proposed model.

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Chao Zhang Population Pharmacokinetics of Lopinavir/Ritonavir in Combination with Rifampicin-based Antitubercular Treatment in HIV-infected Children

Chao Zhang1, Paolo Denti1, Jan-Stefan van der Walt1,2, Ulrika SH Simonsson2, Gary Maartens1, Mats O.Karlsson2, Helen McIlleron1

1 Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; 2 Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden.

Objectives: Children with HIV associated tuberculosis often require coformulated lopinavir/ ritonavir (LPV/RTV)-based antiretroviral treatment with rifampicin-based antitubercular treatment (ATT). Rifampicin (RIF), a potent inducer of drug-metabolizing systems, profoundly reduces the bioavailability of LPV. The aims of this study were to develop an integrated population pharmacokinetic (PK) model describing LPV and RTV PK in children with and without concomitant ATT using two different dosing approaches and to estimate doses of LPV/RTV achieving target exposures during ATT in young children.

Methods: A population PK analysis was conducted in NONMEM. During ATT 15 children were given LPV with extra RTV (LPV/RTV ratio 1:1) and 20 children were given twice the usual dose of LPV/RTV (ratio 4:1) 12 hourly; 39 children without tuberculosis and 11 children undergoing repeated sampling after ATT were treated with standard 12 hourly doses of LPV/RTV (median LPV dose 11.6 mg/kg). Goodness-of-fit plots and visual predictive checks were used to evaluate the models.

Results: In a one-compartment model with first-order absorption to describe LPV PK, and a one-compartment model with transit absorption for RTV, the dynamic influence of RTV concentration on the clearance of LPV was modeled as direct inhibition with an E_{max} model. Allometric scaling for weight was used for clearance and volume of both LPV and RTV. During ATT, the relative oral bioavailability of LPV was reduced by 79% in children receiving twice the usual dose of LPV/RTV. The clearance of RTV was 19 L/h with, and 12.7 L/h without, ATT.The baseline clearance of LPV, when RTV was undetected, estimated 4.27 L/h. With increasing concentrations of RTV, clearance of LPV decreased in a sigmoid relationship (EC_{50} 0.0497 mg/L). Volume of distribution for LPV and RTV were 11.7 and 105 L, respectively. Simulations predicted that children weighing 4-5.9, 6-7.9, 8-11.9 and 12-18 kg need respective doses of 65, 50, 40 and 35 mg/kg LPV/RTV (4:1) 12 hourly in order to maintain LPV concentrations > 1 mg/L in at least 5% of children.

Conclusions: The model describes the drug-drug interaction between LPV, RTV and RIF. Using 8 hourly doses, approximately 2.5 to 5.5 times the standard doses are required to maintain therapeutic LPV concentrations in young children during ATT.

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Rada Savic Adherence and Population Pharmacokinetics of Atazanavir in Naïve HIV-Infected Patients using Medication Events Monitoring System (MEMS) for drug intake timing

Radojka Savic (1,2), Aurélie Barrail-Tran (3) , Xavier Duval (1,3), Georges Nembot (1,3), Xavière Panhard (1), Diane Descamps (3), Bernard Vrijens (4), France Mentré (1,3), Cécile Goujard (3), Anne-Marie Taburet (3) and the ANRS 134 study group

(1) INSERM UMR 738 (2) Stanford University, Division of Clinical Pharmacology, Stanford, USA (3) AP-HP Hôpital Bichat, Paris, France (4) Pharmionic Research Center, Visé, Belgium.

Objectives: Individual drug pharmacokinetics (PK) and treatment adherence are key determinants of HIV sustained virological response. Assessment of adherence performed with MEMS, which records exact times of bottle opening for drug intake, in combination with a reliable population PK model, allows quantification of individual drug exposure. The aim of this analysis is to describe population PK of atazanavir using accurate patient dosing-histories, and to demonstrate how different dosing-history assumptions may impact the population PK analysis outcomes.

Methods: A prospective study was conducted in 35 HIV-infected naïve pts. Atazanavir (300 mg), ritonavir (100 mg), and tenofovir (300 mg) + emtricitabine (400 mg) were given once daily during 6 months. All drugs were supplied in bottles with a MEMS cap. Blood samples were drawn at week 4, then bimonthly. Population PK analysis was performed using non-linear mixed effects under three dosing-history assumptions: (i) all patients are at steady state (SS) and the last reported time of dose intake by the patient before a PK visit is accurate, (ii) full dosing-histories as recorded by MEMS are exact, and (iii) "reliable" dosing-history data consists only of MEMS records concordant (within 3 hours) with last reported time of dose intake before a PK visit (gold standard). Dosing-history assumption impact on population PK analysis outcomes were compared to the gold standard reference.

Results: A one compartment model best described plasma atazanavir concentrations. Apparent clearance (CL) and volume of distribution (Vd) were 6.93 L/hr and 81.1 L, with associated inter-individual variabilities of 40% and 31%. The transit compartment model described the absorption well with absorption rate constant of 3.1 hr-1, mean transit time of 1.35 hr and 11.5 transit compartments. Assuming SS in all patients gave rise to significant quantifiable inter-occasion variability in CL (26.5% CV), while using unmodified MEMS dosing-history led to biased Vd parameter estimates and numerical difficulties during estimation procedure thereby potentially adversely affecting individual patient drug exposures.

Conclusions: The proposed model described the atazanavir PK well. It is important to critically assess MEMS data in order to collect reliable dosing records. Erroneous dosing-history assumptions without taking into account adherence information may lead to biased parameter estimates and significant inter-occasion variability. In combination with exact dosing history as recorded by MEMS, the proposed model provides a useful tool for correct quantification of an individual patient's drug exposure which is essential information for understanding individual virological response and potential success/failure of the therapy.

Sarah McLeay Exploring different body-size metric based dosing strategies for propofol in morbidly obese versus healthy weight subjects by modelling and simulation approach

Sarah C McLeay (1), Glynn A Morrish (1), Carl MJ Kirkpatrick (1) & Bruce Green (2)
(1) School of Pharmacy, University of Queensland, Brisbane, Australia; (2) Model Answers Pty Ltd., Brisbane, Australia

Objectives: Propofol is an intravenous anaesthetic that is dosed based upon the subject's body weight. Although effective for subjects of healthy weight (BMI<25kg/m2), use of total body weight (TBW) dosing in morbidly obese subjects (BMI≥40kg/m2) can result in overdose due to a nonlinear increase in clearance (CL) with TBW[1]. The aims of this study were to identify a linear body-size based dosing strategy to normalize pharmacodynamic (PD) response across a large weight range and compare PD outcomes to those from TBW label dosing.

Methods: A population pharmacokinetic (PK) and PD analysis was performed using NONMEM VI on data from 419[2,3] adults who received propofol. Two PD models were developed: a binary model for hypnosis (awake/asleep) and a categorical model describing stages of awakening (asleep/disoriented/awake). An adverse event model describing the inhibitory effect of propofol on ventilation[4] was also linked to the PK model. Stochastic simulations were performed using the best optimised dose (based upon the identification of the best PK model) and label dosing. PD responses for the different dosing strategies and different weight groups were compared.

Results: A 3-compartment model with lean body weight[5] (LBW) and age on CL best described propofol PK. The hypnosis model was described by an Emax function in the logit with predicted concentration in the effect-site compartment[6] as the exposure variable. The awakening model was described by an Emax function using predicted concentration in the central compartment. The optimised dose based on LBW of a 140mg bolus followed by a 7.6mg/kgLBW/h infusion resulted in similar PD between morbidly obese and healthy weight subjects. For healthy weight subjects, TBW dosing resulted in similar responses to LBW dosing. For morbidly obese subjects however, TBW dosing resulted in faster induction and longer awakening, with the median subject taking 7min longer to reach 50% probability of being awake and oriented than the median healthy weight subject. TBW dosing also resulted in earlier and greater ventilatory depression in the morbidly obese group with a maximum decrease to 7% of normal ventilation at 1.7min for the median subject versus 16% at 2min for the median healthy weight subject.

Conclusion: A fixed induction dose of propofol followed by a maintenance dose scaled by LBW may be appropriate to normalize subject responses across all weights and minimize ventilatory depression on induction in the morbidly obese.

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Eugene Cox Meta- Analysis of Retention Rates of Post-Marketing Trials to Compare Effectiveness of Second Generation Antiepileptic Drugs

Eugène Cox (1), D. Russell Wada (1), Nancy Zhang (1) & Frank Wiegand (2)
(1) Quantitative Solutions, Menlo Park, CA, USA & Breda, The Netherlands ; (2) Johnson & Johnson Pharmaceutical Services, L.L.C., Raritan, NJ, USA

Objectives: Retention is the duration of time a patient stays on treatment. It reflects the overall patient experience with the efficacy and tolerability of a drug. The current meta-analysis develops a methodology to analyze the time-course of retention from post-marketing clinical trial publications on second generation antiepileptic drugs (AEDs) in patients with partial onset seizures (POS).

Methods: From a comprehensive literature search 34 post marketing studies for five AEDs used as adjunctive therapy in patients with POS were selected (topiramate, 11; levetiracetam, 13; lamotrigine, 9, gabapentin, 7, and tiagabine, 5). Longitudinal retention data was extracted along with other relevant trial data. A constant hazard model that accounts for long term-steady state retention was used. Various drug and covariate effects were evaluated, and random study-effect was included in the model. Parameters were estimated using nonlinear mixed-effects regression using the nlme function in S-plus 6.1. Model quality was evaluated by considering the effect of trial size and publication date on the magnitude of effect.

Results: This methodology resulted in good model fit of the retention profiles over time for each of the five drugs. Each AED appears to have a unique and consistent retention profile across trials, with the following rank order in retention rates (1 year rate, 95% CI): lamotrigine (74%, 68%-80%) >levetiracetam (71%, 64%-77%) >topiramate (64%, 56%-71%) >gabapentin (49%, 40%-59%) ~tiagabine (48%, 36%-64%). The covariate analysis indicated baseline AEDs and year of publication, but not sample size, are correlated to retention.

Conclusions: The presented hazard model worked well in describing the time-course of retention for five second generation AEDs. The analysis suggests that each drug demonstrates a distinct retention profile.

Rocio Lledo A mechanistic model of the steady-state relationship between HbA1c and average glucose levels in a mixed population of healthy volunteers and diabetic subjects

Rocío Lledó-García, PhD1, Norman A. Mazer, MD, PhD2 and Mats O. Karlsson, PhD1
(1) Pharmacometrics research group. Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. (2) F. Hoffmann-La Roche Ltd., Pharma Research and Early Development (pRED), Translational Research Sciences (TRS), 4070 Basel, Switzerland

Background: A mechanism-based model exists that describes the fasting plasma glucose (FPG) and HbA1c relationship[1]. However, a mechanistic description of the underlying relationship between average glucose concentration (Cg,avg) - a better descriptor of chronic glycemia- and HbA1c is lacking.

Objective: To build a dynamic, mechanism-based, model for the Cg,avg - HbA1c relationship using information from the literature.

Methods: Different sources were combined to build a mechanism-based model. Pairs of Cg,avg-HbA1c digitized measurements from Nathan et al. publication[2] (N=507 diabetic patients and healthy volunteers) were re-analysed in a formal population analysis with NONMEM VI using the prior functionality[3] to incorporate literature prior information in RBC life-span and life-span distribution (LS)[4], erythroid cell life-span (LSP)[5], glycosylation rates (KG)[6-9] and Cg,avg and HbA1c measurement errors[2]. Finally, literature data was used as external validation for the mechanisms incorporated in the relationship[1, 10].

Results: The integration of the information made it clear that a mechanistic component beyond those previously described quantitatively for the glucose - HbA1c relationships was required. A model incorporating a decrease in RBC LS with increasing glucose concentrations was in good agreement with all literature sources and the formal integration allowed estimation of the strength of this relationship. The estimated strength was in good agreement with additional literature sources[1, 10-12].

The RBC model consisted of 12 transit compartments -previously shown to describe well the LS[4]- with a LS estimate of 91.7 days and IIV of 8.22 %. RBC LS covaries with Cg,avg, so that LS is shorter at higher Cg,avg.

At any given age stage, Hb can become glycosilated to HbA1c. KG ($8.37x10^{-6}$ dL/mg/day) was in agreement with literature values[6-9]. HbA1c erythroid cells contribution depends on Cg,avg and LSP. A LSP (8.2 days) close to that published[5] and the same KG as for RBCs was in agreement with the data.

Conclusions: To our knowledge this is the first quantitative description of the Cg,avg-HbA1c relationship on mechanistic basis. This was possible by combining different literature data sources: i)

digitized literature data as main source of information; ii) mechanistic reinforcement by literature priors in the structural and variability parameters; iii) digitized data and clinical data to support the mechanisms with highest impact on driving the relationship.

Our mechanism-based model describes well the relationship observed in HV and diabetic patients. The model can predict the impact of changes in Cg,avg (due to diet changes/therapeutic interventions) on HbA1c levels. It can predict the time-course of HbA1c in response to changes in Cg,avg, or conversely. If any of the processes involved changes in an individual patient (e.g. LS decreased in uremic patients[10]), the expected temporal and steady state change of HbA1c can also be predicted.

This shows how literature data can be used not only to support parameter estimates, but combined from different sources to test hypotheses and build structurally novel models.

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Jonathan L. French When and how should I combine patient-level data and literature data in a meta-analysis?

Jonathan L. French
Pfizer, Inc.

Meta-analysis is an integral part of the model-based drug development paradigm [1]. While meta-analysis of individual patient data (IPD) is the gold-standard against which other types of meta-analyses are compared, IPD is not always available for all studies included in a meta-analysis. In particular, a sponsor will typically have access to IPD from their internal compounds, but only have access to aggregate level data (AD) from literature sources for studies which they did not conduct. When both IPD and AD are available, it seems intuitively attractive to combine both types of data into a single model. In this talk we will discuss three approaches for doing this: a two-stage approach in which the IPD are reduced to AD, a hierarchical model approach [2,3] in which a model for the AD is derived from an IPD model, and a Bayesian approach in which the AD is used to form prior distributions for parameters in a model for the IPD. We will demonstrate some of the difficulties with all three of these approaches, including the potential for ecological bias when constructing non-linear models under the hierarchical or Bayesian approach [4,5]. We conclude with some recommendations about when and how best to combine IPD and AD in a meta-analysis.

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Camille Vong Rapid sample size calculations for a defined likelihood ratio test-based power in mixed effects models

Camille Vong, Martin Bergstrand, Mats O. Karlsson
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: Efficient power calculation methods have previously been suggested for Wald test based inference in mixed effects models (1) but for Likelihood ratio test (LRT) based hypothesis testing, the only available alternative has been to perform computer-intensive multiple simulations and re-estimations (2). For correct power calculations, a type 1 error assessment to calibrate the significance criterion is often needed for small sample sizes, due to a difference between the actual and the nominal (chi squared) significance criteria(3). The proposed method is based on the use of individual Objective Function Values (iOFV) and aims to provide a fast and accurate prediction of the power and sample size relationship without any need for adjustment of the significance criterion.

Methods: The principle of the iOFV sampling method is as follows: (i) a large dataset (e.g. 1000 individuals) is simulated with a full model and subsequently the full and reduced models are re-estimated with this data set, (ii) iOFVs are extracted and for each subject the difference in iOFV between the full and reduced models is computed (ΔiOFV), (iii) ΔiOFVs are sampled according to the design for which power is to be calculated and a starting sample size (N), (iv) the ΔiOFVs sum for each sample is calculated (∑ΔiOFVs), (v) steps iii and iv are repeated many times, (vi) the percentage of ∑ΔiOFVs greater than the significance criterion (e.g. 3.84 for one degree of freedom and α=0.05) is taken as the power for sample size N, (vii) steps iii-vi are repeated with increasing N to provide the power at all sample sizes of interest. The power versus sample size relationship established via the iOFV method was compared to traditional assessment of model-based power (200 simulated datasets) for a selection of sample sizes. Two examples were investigated, a one-compartment IV-Bolus PK model with sex as a covariate on CL (3) and a more complex FPG-HbA1c model with a drug effect on kout for FPG (4).

Results: Power generated for both models displayed concordance between the suggested iOFV method and the nominal power. For 90% power, the difference in required sample size was in all investigated cases less than 10%. To maintain a 5% type 1 error a significance criteria calibration at each sample size was needed for the PK model example and the traditional method but not for power assessment with the iOFV sampling method. In both cases, the iOFV method was able to estimate the entire power vs. sample size relationship in less than 1% of the time required to estimate the power at a single sample size with the traditional method.

Conclusions: The suggested method provides a fast and still accurate prediction of the power and sample size relationship for likelihood ratio test based hypothesis testing in mixed effects models. The iOFV sampling method is general and mimics more closely than Wald-test based methods the hypothesis tests that are typically used to establish significance.

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Lee Kien Foo D-optimal Adaptive Bridging Studies in Pharmacokinetics

Lee-Kien Foo, Stephen Duffull
University of Otago, New Zealand

Background:
Bridging studies are a method for extrapolating information gathered from clinical study in an original region (prior population), e.g. an adult patient population, to a new region (target population), e.g. a paediatric patient population. Since the PK profile of the prior and target populations may be different then optimally designed studies based solely on the prior population may be suboptimal when applied to the target population. Optimal adaptive design can be used to address this issue which the design phase and estimation phase is updated in the experiment, where the parameter estimates obtained in the current iteration are used to design the experiment for the next iteration. This approach can provide reliable estimates of PK parameters under uncertainty and sampling restrictions [1]. Here we propose a new method for applying optimal adaptive design to bridging studies.

Objective:
To develop a D-optimal adaptive bridging study (D-optimal ABS) that has general applicability to pharmacokinetics.

Methods:
Our proposed D-optimal ABS starts with collecting sample data from all prior population patients enrolled following an initial (arbitrary) study design. Patients of the target population will be divided into B batches. The prior population sample data will be modelled and the estimated parameter values from the best model used to locate a D-optimal sampling schedule (D1) that will be applied to the first batch target population patients. The first batch of target population patients will be enrolled and data collected according to D1 will be pooled with a reduced data set arising from the prior population, where the prior population data is reduced by an amount proportional to the size of the batch of the target population. The pooled data will be modelled and the D-optimal design (D2) is located for the new model. Subsequently a second batch of target population patients is enrolled and data collected according to D2. The iterative process of estimation and design was repeated until all batches of the target population patients have been enrolled. The size of batches will also be considered for optimization.

Simulation Study:
The D-optimal ABS was designed and assessed using simulations under two different scenarios. In scenario 1, the PK profile of prior and target populations are similar where the design optimized based on prior population PK profile is a good but not optimal design for target population. In scenario 2, the PK profile of the prior and target populations are different and a design optimized based on prior population PK profile will perform poorly for the target population. The simulations are carried out in MATLAB and NONMEM, called from MATLAB, is used for estimation. For each scenario, 100 adaptive bridging studies were simulated. The relative percentage difference of the estimated parameter

values from the empirical (true) parameter values were used to assess performance of the adaptive bridging study.

Scenario 1: *{adult to paediatric}*
In this scenario the D-optimal ABS is for an adult (prior) to paediatric (target) patients for a small molecule drug. The drug is taken orally and assumed to follow a Bateman PK model. Two hundred adult patients and twenty five paediatric patients were simulated and the paediatric patients were divided into five enrolment batches with five patients in each batch. The nominal parameter mean of adult patients were CL = $4Lh^{-1}$, V = 20L, Ka = $1h^{-1}$ and dose = 100 mg. The nominal parameter mean of CL and V for paediatric patients are scaled allometrically to CL = $1.56Lh^{-1}$, V = 5.71L. Ka is assumed to be the same as adult patients and dose = 29 mg. The variance of the log-normal between subject variability was 0.1 for both populations. A combined residual error model was assumed. The two hundred adult patients each provided 6 blood samples following an arbitrary sampling schedule.

Scenario 2: *{normal weight to obese adult}*
In this scenario, the D-optimal ABS is for a normal weight (prior) to obese (target) adult patients for a large molecule drug which is given subcutaneously. We assumed the disposition phase to follow a 1-compartment model. In both populations the absorption profile followed a transit compartment model, with the obese patients having significantly greater mean transit time. The populations consisted of 60 normal weight and 60 obese adult patients. The obese patients were divided into five batches with twelve patients in each batch. The nominal parameter mean of normal weight patients were CL = $4Lh^{-1}$, V = 20L, MTT (mean transit time) = 3h, N (number of transit compartment) = 2 and dose = 100mg. The nominal parameter mean of obese patients were CL = $5.2Lh^{-1}$, V = 30L, MTT = 20h, N = 20 and same dose is given. The variance of the log-normal between subject variability for CL, V and MTT are assumed to be the same for both populations with value 0.2. We assumed there is no between subject variability for N in both populations. A combined residual error model was assumed. The 60 normal weight patients each provided 8 blood samples following a D-optimal sampling schedule.

Results and Discussion:
Scenario 1:
Two hundred adult patients with 6 samples per patient provided precise parameter estimates for the adult population. The adaptive design with fixed reduction rate of adult patient data (20% per iteration) provided precise parameter estimates for the paediatric population at the 5th (final) iteration. Results from scenario 1 showed that D-optimal ABS was not inferior compared to the study design optimized on prior population used directly in the target population.

Scenario 2:
Sixty normal weight adult patients with 8 D-optimal samples per patient provided precise parameter estimates for the normal weight adult population. The D-optimal ABS with fixed reduction rate of normal weight adult patient data (20% per iteration) provided acceptable parameter estimates for the obese adult population at the 5th (final) iteration. In this setting a D-optimal ABS design performed better than when a D-optimal design from the prior population was applied to the target population.

Conclusions:
Optimal adaptive designs for bridging studies are a potentially useful method for learning about new populations. The proposed design method for bridging studies provided reasonable parameter estimates for the target population even when the PK profile of the prior and target populations were widely divergent.

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Marc Lavielle Mixture models and model mixtures with MONOLIX

Marc Lavielle (1), Hector Mesa (1), Kaelig Chatel (1), An Vermeulen (2)
(1) INRIA Saclay, (2) J & J Pharmaceutical R & D

Objectives: A patient population is usually heterogeneous with respect to response to drug therapy. In any clinical efficacy trial, patients who respond, those who partially respond and those who do not respond present very different profiles. Then, diversity of the observed kinetics cannot be explained adequately only by the inter-patient variability of some parameters and mixtures are a relevant alternative in such situations:

- Mixture models are useful to characterize underlying population distributions that are not adequately explained by the observed covariates. Some non observed "latent" categorical covariates assign the individual patients to the components of the mixture.
- Between-subject model mixtures (BSMM) also assume that there exist subpopulations of patients. Here, different structural models describe the response of each subpopulation and each patient belongs to one subpopulation.
- Within-subject model mixtures (WSMM) assume that there exist subpopulations (of cells, of virus,...) within the patient. Different structural models describe the response of each subpopulation and proportions of each subpopulation depend on the patient.

Our objective is to develop a methodology for analyzing these different models, to implement it in MONOLIX and to apply it to some simulated and real viral kinetic data.

Method: We have extended the SAEM algorithm for mixture models and model mixtures. The algorithms were first evaluated using simulated PK data.
We then applied the proposed methodology for analyzing viral load data arising from 578 HIV infected patients. The randomized, controlled, partially blinded POWER studies were conducted by TIBOTEC and comprised 3 studies of up to 144 weeks, performed in highly treatment experienced patients, using darunavir/ritonavir (DRV/RTV) or an investigator-selected control PI, combined with an optimised background regimen (OBR), consisting of nucleoside reverse transcriptase inhibitors with or without the fusion inhibitor enfuvirtude.
We propose to describe these viral load data with a mixture of three models. Indeed, the data seem to exhibit three different typical profiles: responders, non-responders and rebounders.

Results: The between-subject model mixture (BSMM) is able to properly assign each patient to one of the three subpopulations. The conditional probabilities to belong to each group are computed for each patient. Nevertheless, the boundary between these different subpopulations is not obvious and several profiles seem to be "somewhere in-between". The within subject model mixture (WSMM) decomposes each profile into a linear combination of the three typical profiles. The proportions of the mixture are computed for each patient. This can well describe the profile of each individual. Furthermore, the BIC criteria clearly selects the WSMM model: BIC(WSMM)=14 668, whereas BIC(BSMM)=15029.

Conclusion: Between-subject and within-subject mixtures are relevant alternatives to mixture models for describing different profiles in a whole population. The SAEM algorithm is shown to be efficient

for estimating mixture models and model mixtures in a general framework. These algorithms are now implemented in MONOLIX.

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Matt Hutmacher Extending the Latent Variable Model to Non-Independent Longitudinal Dichotomous Response Data

Matthew M. Hutmacher
Ann Arbor Pharmacometrics Group, Ann Arbor, MI, USA

Background: Sheiner and Sheiner et. al. brought attention to generalized nonlinear mixed effects modeling of ordered categorical data, and the utility of such for drug development. Since the publication of these articles, exposure-response analyses of such data are being increasingly performed to inform decision making. Hutmacher et. al. expanded upon this work, relating the models reported to the concept of a latent variable (LV). The LV approach assumes an underlying unobserved continuous variable, which can be mapped to the probability of observing a response using an unknown threshold parameter. The objective was to promote incorporation of pharmacological concepts when postulating models for dichotomous data by providing a framework for including, for example pharmacokinetic (effect compartment) or pharmacodynamic onset (indirect response) of drug effect. The LV approach was developed assuming independence between the dichotomous responses within a subject. Recently, Lacroix et. al. reported that fewer transitions between response values were observed than would be predicted by assuming the responses are independent. The authors implemented methods developed by Karlsson et. al., and incorporated a Markov component to address this dependence between responses. The probability of observing the current response was shown to be related to prior responses.

The focus of this current work is to extend the LV approach to accommodate non-independent longitudinal dichotomous response data. This multivariate latent variable (MLV) approach attributes the dependence between responses to correlations between latent (unobserved) residuals. The latent residuals are assumed to be distributed as a multivariate normal. General correlation structures can be applied to the latent residuals, but the first-order auto regressive and the spatial power structure, which relates the degree of correlation to the time (distance) between the responses, are obvious choices. The method is convenient with respect to testing for correlation. Setting the correlation parameters to 0 yields a model in which the responses are considered independent; thus, the LV approach is nested within the MLV approach. Additionally the MLV parameters are interpretable relative to the LV parameters. The MLV approach is flexible in that it can generate data that range from independent (correlations equal to 0) to complete dependence (correlations equal to 1), and it is parsimonious in that the amount of dependence can be governed by very few parameters.

Methods: Simulation using the MLV framework is straightforward. However, model fitting and estimation is complicated by the intractability of the cumulative multivariate normal distribution. The likelihood, conditioned on the subject-specific random effects, is constructed using a sequence of probabilities, each probability conditioned on the previous latent residuals (Cappellari and Jenkins). The latent residuals in the probability statements are translated to independence using the Cholesky factorization of the correlation matrix. This permits each probability statement to be considered separately, simplifying estimation. The conditional probabilities are approximated using a pseudo stochastic approximation which uses samples from truncated normal distributions. Adaptive Gaussian

quadrature is used to construct the overall marginal likelihood, which is unconditional on the subject-specific random effects.

A simulation study was performed to evaluate the MLV method. The design was based on the ACR20 trial reported in Hutmacher, but the model used to generate the data was simplified. A first-order auto regressive structure with a correlation parameter of 0.5 was used to simulate the dependent data. LV and MLV models were fitted using the NLMIXED procedure in SAS to the dependent data as well as independent data for comparison. Biases in the fixed and random effects parameters for both approaches were quantified.

Results: No appreciable biases of the estimates were noted for either method fitted to the independent data. However, biases greater than 20% for the fixed effects and 100% for the random effects parameters were reported for the LV approach fitted to the dependent data.

Conclusion: Failure to address the dependence between dichotomous response data can lead to biased parameter estimates. The MLV approach is a viable method to handle such data and it is not difficult to implement. The approach is not likely to be practical however when subjects have large numbers of observations unless the latent variable correlation structure is simplified.

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Elodie Plan Analysis Approaches Handling Both Symptomatic Severity and Frequency

Elodie L. Plan, Kristin E. Karlsson, Mats O. Karlsson
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Background

Graded events analyses are often accompanied with a loss of information by not handling the true nature of the data. Pharmacodynamic outcomes commonly consist of symptoms that are defined as events happening at a certain point with a certain degree of severity. Pharmacometric modelling having substantially improved over the past two decades, the response rate (RR) approach is more and more replaced by the use of a cumulative logit model for longitudinal data. Lewis Sheiner introduced this population model in 1994[1] following an analgesic trial[2] and enabling the analysis of ordered categorical (OC) data. The state of the patient reported at regular time-points is adequately described with the OC model; however, spontaneous events happening at specific time-points involve data simplification, e.g. by utilizing the number of events or the maximal severity of events within equispaced time-intervals[3]. In order to pursue learning[4] and theory[5], analysis approaches handling both symptomatic severity and frequency are suggested and explored in this work.

Objectives

(i) To identify shortcomings of currently used approaches analyzing symptoms reported as graded on a severity scale,
(ii) To introduce new mixed-effects models retaining the original nature of data,
(iii) To illustrate benefits of the novel methods in terms of *(a)* data description, *(b)* drug effect assessment, *(c)* data simulation properties, *(d)* drug effect detection power, *(e)* real case analysis.

Methods

Repeated Time-To-Categorical Event model (RTTCE) model: The RTTCE model is based on a repeated time-to-event (RTTE) model describing the hazard for an event to occur. The hazard consists of a mixed-effects baseline parameter potentially affected by a function depending on time, and/or covariates, including the exposure. In order to capture the severity of the events that occur, in the same single step, the RTTE model is combined with an OC model. Cumulative probabilities of the different categories of severity are modelled on the logit scale.

Repeated Categorical Events per Time-interval (RCEpT) model: If reported data do not correspond to graded events at each occurrence, but rather only to maximal scores across time periods, they require the model to be adapted. The RCEpT model, built in the same fashion as the RTTCE one, but considering time-intervals of a defined length, is able to fit such data. Depending on whether the hazard is assumed to be varying or constant within time-intervals, the RTTE part follows an ordinary differential equation or its analytical solution, respectively. As records represent maxima over n number of events undergone during time-intervals, the discrete probability distribution of n enters the equation of the OC part. The expected number of occurrences λ entering the Poisson distribution

function is the integrated hazard in the time-interval. The probability distribution of maximal severity score is a function of the OC sub-model and the frequency distribution given by the integrated RTTE sub-model.

Data: The RTTCE model was employed to simulate data mimicking a Phase IIa clinical trial. The design included 72 individuals equally allocated to placebo or one of the five drug treatment dose levels, 10, 50, 100, 200 or 400 mg. Observations, time and grade of the symptoms, were recorded with a 2-minute precision during 12 hours.

Study: Stochastic simulations and estimations (SSE) were performed 500 times to produce vectors of parameters subsequently used for computations and resimulations. SSEs were facilitated by a routine developed in PsN[6] running NONMEM VII[7] and enabling alternative models for the estimation step, RCEpT and OC in this case.

Results

(a) Objective function values displayed a systematic drop when analyzing summarized RTTCE data with an RCEpT compared to an OC model.
(b) Drug effect could be characterized on both the hazard of the events, through an Emax function, and the probabilities of their grades, with a linear function. Individual response distributions at dose levels excluded during estimation step were correctly retrieved, using the RTTCE and RCEpT models, but not the OC model.
(c) OC generated maximal grades per time-intervals, but RTTCE and RCEpT were able to reproduce realistic graded events. When computing summarized data, severity proportions were more accurately mimicking original data with simulations from RTTCE-type models than from OC model.
(d) Power observed with the novel models was substantially increased for the given study settings, thus a smaller sample size than initially considered was needed to detect the same treatment effect.
(e) Real data of spontaneous symptoms recorded as maximal grade per day were successfully analyzed with OC and RCEpT; the latter presented a better fit to the data.

Conclusions

Modeling graded symptoms by extensively summarizing the information originally contained in the data, results in a poor description of the events, an incomplete assessment of the drug effect, and a large sample size required. RTTCE-type models demonstrated multiple benefits, which include good population and individual predictions, appropriate simulations properties, and high power. Given that one of the main challenges in pharmacometrics is to adequately measure the effect of a drug[8], the novel methods presented above represent a step further, by enabling a two-dimension evaluation of the exposure-response relationship, which can be performed simultaneously, unlike previously done[9], and incorporate correlation.

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Sylvain Goutelle Mathematical modeling of pulmonary tuberculosis therapy: development of a first prototype model with rifampin

S. Goutelle (1,2), L. Bourguignon (1,2), R.W. Jelliffe (3), J.E. Conte Jr (4,5), P. Maire (1,2)
(1) University of Lyon 1, UMR CNRS 5558, Lyon, France; (2) University Hospitals of Lyon, Geriatric Hospital Group, Department of Pharmacy and ADCAPT, Francheville, France; (3) Laboratory of Applied Pharmacokinetics, USC Keck School of Medicine, Los Angeles, USA ; (4) Department of Epidemiology & Biostatistics, University of California, San Francisco, San Francisco, USA; (5) American Health Sciences, San Francisco, USA

Objectives: There is a critical need for a shorter tuberculosis (TB) treatment to improve TB control. Current experimental models of TB, while still valuable, are poor predictors of the antibacterial effect of drugs *in vivo*. Mathematical models may be helpful to understand current problems associated with TB therapy and to suggest innovations. The objective of this study was to set up a prototype mathematical model of TB treatment by rifampin (RIF), based on pharmacokinetic (PK), pharmacodynamic (PD), and physiological submodels.

Methods: A pulmonary diffusion model of RIF was used as the PK model [1]. The PD model was a Hill equation-based model with parameter values derived from experimental data [2,3]. Those two submodels were assembled with the Kirschner's model which describes the dynamics of bacteria, cytokines and cells in the lungs during TB infection [4]. The full model implemented in Matlab software featured 21 differential equations. PK variability was introduced in the model by using the parameter values of 34 subjects estimated in the population study [1]. Therapeutic simulations were performed with the full model to study the antibacterial effect of various dosage regimens of RIF in lungs. The log-reductions of extracellular bacteria (B_E) over the first days of therapy simulated by the model were compared with published values of early bactericidal activity (EBA). In addition, simple PK/PD models derived from the full model were analysed to study the consequences of model reductions on the simulated antibacterial effect.

Results: The full model can simulate the time-course of the bacterial population in lungs from the first day of infection to the last day of therapy. The bactericidal activities (mean ± SD $\log_{10}$ B_E/ml/day) predicted by the model over the first 2 days in 34 subjects were 0.102 ± 0.090 and 0.277 ± 0.229 for a 300 mg and a 600 mg daily dose, respectively. Those results were in agreement with published values of EBA [5]. The kill curves simulated by the model showed a typical biphasic decline in the number of bacteria consistent with observations in TB patients. Simulations performed with simple PK/PD models indicated a possible role of a protected intracellular bacterial compartment in such biphasic decline.

Conclusions: This work is a very preliminary effort towards a complete mathematical description of TB therapy. However, this first prototype model suggests a new hypothesis for the bacterial persistence during TB treatment.

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Alberto Russu Integrated model for clinical response and dropout in depression trials: a state-space approach

A. Russu (1), E. Marostica (1), G. De Nicolao (1), A.C. Hooker (2), I. Poggesi (3), R. Gomeni (3), S. Zamuner (3)
(1) Department of Computer Engineering and Systems Science, University of Pavia, Pavia, Italy; (2) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; (3) Clinical Pharmacology / Modelling & Simulation, GlaxoSmithKline, Verona, Italy

Objectives: GSK372475 is an equipotent reuptake inhibitor of serotonin, norepinephrine and dopamine neuronal reuptake and has been investigated as a potential treatment of major depressive disorder (MDD). In traditional modelling approaches in MDD, efficacy and dropout are rarely integrated. Using state-space models the observed depression scales (HAMD-17) can be modelled as a function of variables (states) describing the status of a patient; one or more of these states (rather than the clinical score alone) can be used for describing the dropout process, allowing a more natural integration of the study observations. In the present work, we develop a joint clinical response and dropout model for GSK372475 using a state-space approach.

Methods: A double-blind, randomized, placebo controlled, flexible dose trial was analyzed using a longitudinal model for depression scores.[1] The model was expressed in algebraic equations and re-formulated as a state-space model. Flexible dose scheme was implemented as a covariate of the structural parameters. Dropout data were analysed using a parametric time to event model (Weibull hazard function)[2]. Completely Random Dropout (CRD), Random Dropout (RD) and Informative Dropout (ID) mechanisms were investigated[3]. Analyses were implemented in WinBUGS. Performances were evaluated by comparing residuals, posterior distributions of individual parameters, and the Deviance Information Criterion[4] (DIC). The goodness-of-fit to dropout data was checked through the modified Cox-Snell residuals[5] and by visually comparing the estimated survival curve to the usual Kaplan-Meier estimate.[6]

Results: Modelling the flexible dosing schedule as a covariate substantially improved the model performance in terms of goodness-of-fit and DIC. In the placebo arm, the joint analysis of DIC and residuals showed better performances of RD and ID mechanisms compared to CRD. In the treatment arm, inspection of residuals pointed out misspecification of the hazard model, suggesting that additional covariates (e.g. related to safety/tolerability) should be considered in the model development.

Conclusions: The proposed state-space approach was shown to be a valuable option to account for time-to-event data (i.e. dropouts) and discontinuities such as flexible doses. Dropout mechanism needs to be properly accounted for, together with its relationship with efficacy and/or safety. Interpretation of residual plots provided valuable suggestions on how to modify the hazard model to better describe the dropout pattern.

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Klas Petersson Predictions of in vivo prolactin levels from in vitro Ki values of D2 receptor antagonists using an agonist-antagonist interaction model.

Petersson KJF (1), Vermeulen AM (2), Friberg LE (1)
(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden (2) Advanced PK/PD Modeling and Simulation, Johnson & Johnson Pharmaceutical Research and Development, a Division of Janssen Pharmaceutica N.V., Beerse, Belgium

Objectives: Treatment of schizophrenia has traditionally been focused on antagonizing the central D2-receptor and sufficient central D_2 occupancy is a prerequisite for treatment efficacy. However, antagonism of peripheral and central dopamine D_2-receptors does result in a range of other, unwanted effects such as elevated serum prolactin levels and extrapyramidal side effects. Prolactin release from the anterior pituitary is tonically inhibited by endogenous dopamine occupying D_2-receptors. Antipsychotic treatment with D_2-receptor antagonists abolishes this inhibition and as a result serum prolactin levels are elevated. The drug-induced elevation in prolactin levels has been shown to be correlated with the affinity of the drug, where older, high-affinity drugs show a higher prolactin response than newer drugs with lower affinities.

A model including this agonist-antagonist interaction between endogenous dopamine and drug, in addition to the diurnal rhythm of prolactin release, was developed earlier and used to describe the prolactin-time profiles following risperidone and paliperidone treatment [1]. The model has also been successfully applied to remoxipride data [2]. In both these analyses, the ratios of the estimated Ki values to the K_i values determined from *in vitro* assays on D_2-recpeptor affinity were approximately the same.

The aim of this work was to apply the agonist-antagonist interaction model to new data sets from a number of other compounds, spanning a range of D_2-receptor affinities and varying data density and compare model-estimates of K_i to those determined in vitro. If the model is successful in describing prolactin release for a range of drugs with similar system-related parameters estimated across data sets, and there is a relationship between *in vitro* K_i and model-estimated K_i, the model may allow prediction of prolactin-time profiles early in development using drug D_2-receptor affinities as determined *in vitro*. This could eventually lead to optimizing dose selection early in development.

Methods: Rich pharmacokinetic and prolactin Phase I data from 2 compounds (A and B) and sparse olanzapine Phase III comparator data from risperidone and paliperidone trials were included in this analysis, in addition to the risperidone and paliperidone data the model was developed from. The *in vitro* K_i values for these compounds ranged from 0.9 ng/mL for risperidone/paliperidone to 62 ng/mL for remoxipride.

In total 2132 individuals and 16291 prolactin observations were analysed using NONMEM. Phase I data originated from both single ascending and multiple ascending dose trials with one or more full PK profiles as well as one or more full 24 hour prolactin profile(s). In the sparser olanzapine data set prolactin was sampled pre-dose at baseline, day 14, day 35 and end of trial across the seven week trial period. Individual PK profiles derived from developed PK models were used to drive the prolactin

model.

The agonist-antagonist interaction model was applied to each dataset independently, on the one hand with the system-specific parameters fixed to published values, estimating only the drug-dopamine interaction, and on the other hand re-estimating all parameters for the rich data sets. The comparison between the predicted *in vivo* prolactin response using *in vitro* determined Ki and Ki estimated by the model was made with the elevation expressed as the 24 hour prolactin AUC after the first dose and at steady state.

Results: The semi-mechanistic model was successful in describing the prolactin data from all trials. There was a good correlation between the K_i estimated from the model using the clinical data and the K_i values determined *in vitro* (r^2=0.91). The relative differences between *in vitro* Ki and estimated Ki ranged from 56% for compound A to 397% for olanzapine. These relative differences translated into predicted relative differences in prolactin elevations during 24 hours that ranged from 47% for remoxipride to 232% for olanzapine.

When re-estimating all parameters for the rich datasets, system-related parameters showed good concordance across different data sets both for prolactin and dopamine turnover as well as for the circadian rhythm.

Conclusions: The agonist-antagonist interaction model performed well over the 80-fold range in D_2 affinity values investigated and was shown to estimate similar system-related parameters across the different drugs. The estimates of the *in vivo* derived K_i values were all less or around a factor 2 of the *in vitro* values, except for olanzapine where the *in vivo* information was sparse and may have resulted in a poor K_i estimate by the model.

For four out of five substances the estimated K_i values were higher than those determined *in vitro* resulting in over prediction of *in vivo* prolactin response. Accounting for that unbound concentrations was used in the *in vitro* experiments and total concentrations *in vivo* did however not fully account for the observed discrepancies. Affinity to other receptor systems counteracting prolactin release *in vivo* could be one explanation to the differences. This could possibly be corrected for by taking the intermediate step of performing animal studies. This is being investigated by applying the model to longitudinal prolactin measurements after administration of D_2 - receptor antagonists in rat.

Since the typical prolactin-time profiles predicted based on *in vitro* values were similar to those estimated from the trials this indicates that typical prolactin-time profiles in both patients and in healthy volunteers for different dose levels may be predicted early in development based on *in vitro* K_i for the compound, the agonist-antagonist interaction model and its system-related parameters, and some information on PK. This could help decision making in choosing between drug candidates and dose levels, both from a safety perspective and from an efficacy perspective, as prolactin elevation is a sign of at least peripheral D_2 - occupancy.

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Jeff Barrett Enhancing Methotrexate Pharmacotherapy in Children with Cancer: A Decision Support System Integrating Real-time PK/PD Modeling and Simulation with Patient Medical Records

Jeffrey S Barrett1, Sundararajan Vijayakumar2, Kalpana Vijayakumar2, Sarapee Hirankarn1, Bhuvana Jayaraman1, Erin Dombrowsky1, Mahesh Narayan1, Julia Winkler1,3, Marc Gastonguay3
1Laboratory for Applied PK/PD, Clinical Pharmacology & Therapeutics Division, The Children's Hospital of Philadelphia; Pediatrics Department, School of Medicine, University of Pennsylvania; 2Intek Partners, Bridgewater, NJ; 3Metrum Institute,Tariffville, CT

Objectives: Methotrexate (MTX) is an anti-folate chemotherapeutic agent used in the therapy of several childhood cancers, including acute lymphoblastic leukemia, non-Hodgkin lymphoma, and osteosarcoma. Our objectives were to design an interface to the hospital's electronic medical records system facilitating the management of MTX therapy, develop a decision support system (DSS) that provides early assessment of high dose MTX renal toxicity and recommendation for leucovorin (LV) rescue, verify the outcomes of the DSS against historical controls and current best practices, and design a testing strategy for implementation.

Methods: Patient data obtained from source electronic medical records (EMR) included MTX concentrations, laboratory values and medical record number. Joined data was generated in NONMEM and SAS dataset formats and ultimately loaded into the Oracle database using SQL loader. Several generations of MTX population-based models have been evaluated and the current model is based predominantly on EMR data. The NONMEM-based Bayesian forecasting model incorporates population priors to forecast future MTX exposure events. The MTX dashboard was developed based on a three-tier architecture comprising a back end database tier, a business logic middle tier and a data presentation/user interface. The database tier consists of EMR patient data merged with data from patient registration, lab data and adverse event management systems. Predictions are conducted in an external computational platform (modeling and simulation workbench) which can execute code in a variety of languages that run in batch mode (e.g., NONMEM, SAS and R). The user interface is web-based and utilizes a combination of HTML, JavaScript and XML. Validation contained three distinct components: (1) qualification of the PPK model and forecasting algorithm derived from the model, (2) assessment of the clinical performance of clinical decisions derived from the forecasting routine and interface and (3) system validation of the dashboard integration with the EMR system.

Results: The MTX PPK model is generalizable across a broad range of pediatric patients. Clinical validation of the forecasting tool confirms the value of MTX exposure prediction and LV guidance. Screen captures and validation results show (A) the most recent MTX dose event with monitored MTX plasma concentrations and safety markers, (B) MTX exposure against the protocol-specific LV dosing nomogram, (C) MTX exposure projected after the dosing guidance menu button is selected, (D) Effect of the run number and the number of observations on the precision error of the current model in forecasting MTX concentrations and (E) representative evaluation of LV guidance nomogram overlaid with TDM and predicted data.

Conclusions: This application provides real-time views of complementary data related to the clinical care of these patients that is essential for the management of MTX therapy (e.g., urine pH, hydration, serum creatinine). Future development will provide prediction of increased risk of MTX toxicity and drug interaction potential. Clinical evaluation of the production application is ongoing; international test sites are being sought to provide additional feedback on the system.

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Jurgen Bulitta Development and Evaluation of a New Efficiency Tool (SADAPT-TRAN) for Model Creation, Debugging, Evaluation, and Automated Plotting using Parallelized S-ADAPT, Perl and R

Jürgen B. Bulitta (1), Ayhan Bingölbali (1), Cornelia B. Landersdorfer (1)
(1) Ordway Research Institute, Albany, NY

Objectives: 1) To develop an efficiency tool (SADAPT-TRAN) as an add-on for S-ADAPT that greatly facilitates nonlinear mixed-effects modelling and provides fully automated diagnostic plots and summary tables using parallelized S-ADAPT, Perl, and R. 2) To evaluate the standard settings of SADAPT-TRAN with regard to estimation by the Monte Carlo Parametric Expectation Maximization (MC-PEM) algorithm.

Methods: We developed Perl scripts to translate the core components of pharmacokinetic / pharmacodynamic (PK/PD) models into Fortran code for S-ADAPT (v 1.56). The standard settings of SADAPT-TRAN were evaluated via simulation estimation studies using nine population PK/PD models. These cases included two models for antibacterials, one covariate effect model with two patient groups, and one model with between occasion variability (BOV) on Vmax and Km of a sequential mixed-order plus first-order absorption model combined with a parallel Michaelis-Menten and linear elimination model. For each model, between 20 and 80 datasets were simulated in Berkeley Madonna (version 8.3.14). Datasets contained frequent sampling at three dose levels (usually 500, 2000, and 8000 mg; n=32 subjects each). Initial estimates were set 2-fold off for every population mean. Initials for the between subject variability were set to large values (100% CV for log-normally distributed parameters) and forced to be large during the first 20 iterations.

Results: The SADAPT-TRAN Perl scripts support automatic specification of Fortran code for S-ADAPT, do not restrict the flexibility of S-ADAPT or its scripting language, and account for covariate effects and BOV. Individual parameter estimates can be automatically constrained via a logistic transformation. Summary tables and diagnostic plots are fully automatically prepared over one or multiple models, multiple dependent variables, and continuous & categorical covariates. Bias was

Conclusion: The SADAPT-TRAN Perl scripts greatly facilitated model specification, debugging, and evaluation both for experienced and beginner users of S-ADAPT. The standard settings of the SADAPT-TRAN package provided robust and largely unbiased estimates over a diverse series of population PK/PD models.

Kajsa Harling Xpose and Perl speaks NONMEM (PsN)

Kajsa Harling, Sebastian Ueckert, Andrew C. Hooker, E. Niclas Jonsson and Mats O. Karlsson
Pharmacometrics group, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Xpose 4 is an open-source population PK/PD model building aid for NONMEM. Xpose tries to make it easier for a modeler to use diagnostics in an intelligent manner, providing a toolkit for dataset checkout, exploration and visualization, model diagnostics, candidate covariate identification and model comparison. PsN is a toolbox for population PK/PD model building using NONMEM. It has a broad functionality ranging from parameter estimate extraction from output files, data file sub setting and resampling, to advanced computer-intensive statistical methods and NONMEM job handling in large distributed computing systems. PsN includes stand-alone tools for the end-user as well as development libraries for method developers. Recent feature additions include new covariate model building methods and support for NONMEM7, utilizing its new output. Xpose and PsN include cooperative functionality to take advantage of the strong points of both programs. Through the combined use of the two programs the end user can easily compute and display various predictive checks and other diagnostics. Both Xpose and PsN are freely available at http://xpose.sourceforge.net and http://psn.sourceforge.net respectively.

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Masoud Jamei Simcyp Simulator - a comprehensive platform and database for mechanistic modelling and simulation of drug absorption, tissue distribution, metabolism, transport and elimination in healthy and disease populations using in vitro knowledge

Jamei M, Feng F, Abduljalil K
Simcyp Ltd

Simcyp Simulator - **a comprehensive platform and database for mechanistic modelling and simulation of drug absorption, tissue distribution, metabolism, transport and elimination in healthy and disease populations using *in vitro* knowledge**

Simcyp is a University of Sheffield spin-out company that develops algorithms along with population and drug databases for modelling and simulation (M&S) of the absorption, disposition and pharmacological effects of drugs in patients and specific subgroups of patients across different age ranges.

The Simcyp Population-based ADME Simulator is a particularly powerful tool for carrying out virtual clinical trials for recognition of covariates of PK/PD and optimising early in man studies. Similar capabilities have been developed for preclinical species, namely rat and dog. The platform and its database are licensed to Simcyp's Consortium member clients for use in drug discovery and development. The Consortium guides scientific development at Simcyp, ensuring that the platform and databases continue to meet, and in many cases exceed, industry needs. Simcyp maintains strong academic links and our science team conducts internationally recognised cutting-edge research and development which accelerates decision making in drug discovery and development for member pharmaceutical companies. The Simcyp science team:

- provides a user friendly simulator that integrates genetic information on drug metabolising enzymes into PBPK models for the prediction of pharmacokinetics (PK) and pharmacodynamics (PD) of drugs in diverse patient populations with relevant demographic and physiological characteristics,
- offers consultancy and advice on a broad spectrum of DMPK issues (including optimal study design for metabolic drug-drug interactions, data interpretation, prediction of *in vivo* ADME from *in vitro* studies, dose selection for different age groups (particularly neonates and young children), assessing the likely effects of renal impairment, cirrhosis and ethnic variations on ADME, *etc*)
- delivers an educational program consisting of hands-on workshops and courses covering the concepts and applications of *in vitro* - *in vivo* extrapolation (IVIVE) to predict drug clearance, drug-drug interactions, gut absorption handling metabolism/transport interplay, and covariates that determine drug disposition (see http://www.simcyp.com/ProductServices/Workshops/)

Currently, 13 of the top 15 pharmaceutical companies worldwide have access to Simcyp expertise through Consortium membership. Members include Actelion, Allergan, AstraZeneca, Daiichi-Sankyo, Dainippon Sumitomo, Eisai, Eli Lilly, Johnson & Johnson PRD, Lundbeck, Novartis Pharma, Nycomed, Otsuka, Pfizer, sanofi-aventis, Servier, Takeda, UCB Pharma among others. Value is added to decision-making processes by collaboration with regulatory bodies (the FDA, MPA, NAM) and academic centres of excellence worldwide, also within the framework of the Consortium.

In the demonstration session we provide an overview of the capabilities of the Simcyp Simulator to predict drug absorption from gut, lung and skin, enterohepatic recirculation, clearance and metabolic drug-drug interactions, transport in the gut and liver, transport drug-drug interactions and PBPK modelling from *in vitro* and physiochemical information in diverse populations including paediatric, obese, cirrhosis and renally impaired.

The recently developed parameter estimation (PE) module within the Simcyp Simulator is also presented. This module bridges typical 'bottom-up' PBPK approaches and common pharmacometric analyses of clinical data to accelerate model building and covariate recognition in drug development. It allows Simcyp models, including PBPK, drug-drug interaction, ADAM and gut and liver transporters, to be fitted to observed clinical data (*e.g.* concentration-time profiles) for the purpose of estimating unknown/uncertain drug or physiological parameters. Further, it provides a platform for scientists to optimally use information accumulated during drug discovery and development in combination with knowledge on systems biology of healthy and disease populations.

In addition to classical optimisation algorithms, users may select genetic algorithms or hybrid methods which enhance the performance of the PE module for individual fitting of observed data. For population fitting, maximum likelihood (ML) and maximum *a posteriori* (MAP) algorithms using the Monte Carlo expectation maximisation approach can be employed.

Some details of the scientific background to Simcyp's approaches can be found in our recent publications:

- Rowland Yeo K *et al.* Physiologically-based mechanistic modelling to predict complex drug-drug interactions involving simultaneous competitive and time-dependent enzyme inhibition by parent compound and its metabolite in both liver and gut-the effect of diltiazem on the time-course of exposure to triazolam. European Journal of Pharmaceutical Sciences 39(5), 298-309, 2010.
- Johnson TN *et al.* A Semi-Mechanistic Model to Predict the Effects of Liver Cirrhosis on Drug Clearance. Clinical Pharmacokinetics 49(3), 189-206, 2010.
- Johnson TN *et al.* Assessing the efficiency of mixed effects modelling in quantifying metabolism based drug-drug interactions: using in vitro data as an aid to assess study power Pharmaceutical Statistics, 8(3), 186-202, 2009.
- Jamei M *et al.* Population-based mechanistic prediction of oral drug absorption, The AAPS Journal, 11(2), 225-237, 2009.
- Jamei M *et al.* A framework for assessing inter-individual variability in pharmacokinetics using virtual human populations and integrating general knowledge of physical chemistry, biology, anatomy, physiology and genetics: a tale of 'Bottom-Up' vs 'Top-Down' recognition of covariates, Drug Metabolism & Pharmacokinetics, 24(1), 53-75, 2009.
- Jamei M *et al.* The Simcyp® Population-Based ADME Simulator, Expert Opinion On Drug Metabolism and Toxicology, 5(2), 211-223, 2009.
- Rostami-Hodjegan A and Tucker GT. Simulation and prediction of in vivo metabolic drug clearance from in vitro data. Nature Reviews 6(2), 140-149, 2007

Sven Janssen SimBiology: A Graphical Environment for Population PK/PD

Ricardo Paxson
MathWorks

Objective: To demonstrate the capabilities of SimBiology® for pharmacokinetic/pharmacodynamic (PK/PD) modeling and analysis

Background: SimBiology® is a graphical environment for pharmacokinetic/pharmacodynamic (PK/PD) modeling and analysis. The SimBiology environment provides point-and-click tools to make PK/PD modeling and analysis accessible, even if you have little to no programming experience. Built on MATLAB®, SimBiology provides direct access to an industry-tested simulation solver suite and enables you to integrate PK/PD modeling with other functionality such as parallel computing, statistics, and optimization. SimBiology also lets you experiment with new approaches, such as integrating PK models with mechanistic or physiologically based PK models.
SimBiology 3.2, released in March 2010, provides several new features including:

- Stochastic approximation expectation-maximization (SAEM) algorithm for fitting of population data
- New mode for accelerating simulations
- Support for application of dosing schedules to a model
- Additional features for parameter fitting including parameter transformations, error models, and multiple dosing
- Improved support for importing NONMEM® formatted files

Results: A software demonstration will highlight:

Implementing a Pharmacokinetic (PK) workflow in SimBiology

- Working with PK data files
- Constructing PK models using the model library
- Estimating parameters using population and individual fitting methods
- Algorithms for NLME modeling, including SAEM
- Visualizing fits using diagnostic plots

Custom modeling in SimBiology

- Graphically integrating PD models with built-in PK models
- Managing multiple models using the SimBiology project explorer
- Understanding core elements - species, reactions and compartments

Simulating and analyzing SimBiology Models

- Simulation basics
- Simulating different dosing regimes
- Analysis tasks, such as Monte Carlo simulation
- Integrating with MATLAB, such as Custom Tasks
- Accelerating and parallelizing SimBiology

References:

[1] SimBiology User Guide.
[2] SimBiology product page featuring demos, on-demand webinars, and product information.
[3] On-demand webinar: Population Pharmacokinetic Modeling Using Nonlinear Mixed-Effects Methods in SimBiology

Ron Keizer Piraña: Open source modeling environment for NONMEM

Ron J Keizer, JG Coen van Hasselt, Alwin DR Huitema
Dept. of Pharmacy and Pharmacology, The Netherlands Cancer Institute / Slotervaart Hospital

Introduction

Piraña is a modeling environment for NONMEM, and provides an easy-to-use toolkit for both novice and advanced modelers. It can be used for modeling on a local system or on computer clusters, and provides interfaces to NONMEM, PsN and Wings for NONMEM. Piraña can be used to run, manage and edit models, interpret output, and manage NONMEM installations. It is easily extendible with custom scripts, and integrates smoothly with R, Xpose, Excel and other software. Piraña fully supports NONMEM version 7 and runs on Windows, Linux and Mac OSX.

Model management

- Logbook-like interface for model management
  Add descriptions, notes, and coloring to models and results. Choose between condensed / detailed model information, and list / tree views.
- Create and edit models
  Create new models from templates, duplicate model with updated run- and table numbers and parameter estimates. Delete model files and all associated results and table files.

Results management

- Create HTML / LaTeX run reports
  Quickly create formatted reports for a run, containing basic model specifications and estimations results for all estimation methods that were used, including parameter estimates, uncertainty, shrinkage etc. Piraña is compatible with output from NONMEM version 5, 6 and 7.
- Extend Piraña with custom scripts
  Custom scripts (R / Perl / Awk / Python) can be used conveniently from within Piraña and run on a specific model, e.g. to automate creation of goodness-of-fit plots. The output image / PDF / html-file can be loaded automatically. Multiple useful scripts are already included with Piraña, which can be customized.
- Built-in Data Inspector
  Allows detailed investigation of e.g. goodness-of-fit plots, or plots of covariates against individual parameter estimates.
- Overview of datasets, output, Xpose files, R scripts
  Quickly open, edit data files and Xpose datasets with a spreadsheet, code editor or in R. Make notes to datasets.
- Convert NONMEM table files to CSV format and vice-versa.
- Multiple other functionality included

NONMEM, PsN and WFN

- Install and manage local / cluster NONMEM installations
  Install NONMEM 5, 6, or 7 from Piraña, or add existing installation to be used in Piraña. Manage and view SIZES variables for NM6 and NM7 installations.
- Run a selected model in the current folder or in a separate folder. Conveniently choose the desired NONMEM installation from a list.
- Follow NONMEM run progression
  Piraña reads intermediate NONMEM output and provides numerical and graphical view of parameters and gradients
- Start model execution using the PsN dialog
  All PsN commands can be used from a dialog window. The NONMEM version used by PsN for the command can be chosen from a list. The actual command line that is used is displayed and can be edited. The dialog also shows all PsN information for the specific command.
- Run models using Wings for NONMEM, using NMGO or NMBS

Cluster support

- Connect to computer clusters through SSH
  Computer clusters running NONMEM can be accessed directly through SSH, both from/to Linux and Windows systems.
- Piraña can be installed on the cluster server, and run by multiple clients through SSH-X-window tunneling
- Simple cluster set-up under Windows networks [1]
  This feature allows the construction of a simple cluster using dedicated or non-dedicated PCs, e.g. desktop PCs from co-workers. This may be specifically interesting for small modeling groups.

Software

Piraña is written in Perl/Tk and released under an open-source license (GNU/GPL). It runs on Windows, Linux, and Mac OSX. The current version is 2.3.0, which can be downloaded from http://pirana.sf.net. Future development may include: more advanced QA functionality, support for S-ADAPT / WinBUGS / Monolix, or a Piraña iPhone / Android App, but depends on time and needs of the developers.

References

[1] Keizer RJ, Zandvliet AS, Huitema ADR. A simple infrastructure and graphicaluser interface (GUI) for distributed NONMEM analysis on standard network environments. PAGE 17 (2008) Abstr 1237

Marc Lavielle Analysing population PK/PD data with MONOLIX 3.2

Marc Lavielle (1), Hector Mesa (1), Kaelig Chatel (1), Benoît Charles (1), Eric Blaudez (1), France Mentré (2) and the Monolix group
(1) INRIA Saclay, (2) INSERM U738

MONOLIX is an open-source software using Matlab. The full Matlab version and a stand-alone version of MONOLIX can be downloaded from the MONOLIX website : http://software.monolix.org/

MONOLIX performs maximum likelihood estimation in nonlinear mixed effects models without linearization. The algorithms used in MONOLIX combine the SAEM (stochastic approximation version of EM) algorithm with MCMC (Markov Chain Monte Carlo) and a Simulated Annealing procedure. The convergence of this algorithm and its good statistical properties have been proven and published in the best statistical journals [1,2]. The algorithm is fast and efficient in practice. MONOLIX 3.1 already propose many important and useful features:

- MLXTRAN (a NMTRAN-like interpreter) allows writing complex models (ODEs defined models, count data and categorical data models, complex administrations, multiple compartments, transit compartment...)
- An extensive library of PK model (1, 2 and 3 cpts ; effect compartment ; bolus, infusion, oral0 and oral1 absorption ; linear and nonlinear elimination ; single dose, multiple doses and steady state)
- An extensive library of PD models (immediate and turn-over response models ; disease models, viral kinetic models)
- A basic library of count data and categorical data models, including hidden Markov models
- Continuous and categorical covariate models,
- Constant, proportional, combined and exponential error models,
- Use of several distributions for the individual parameters (normal, lognormal, logit, probit, Box & Cox, ...)
- Model selection: information criteria (AIC, BIC) and statistical tests (LRT, Wald test)
- Data in NONMEM format,
- Goodness of fit plots (VPC, weighted residuals, NPDE, ...),
- Data simulation,
- Automatic reporting,

A beta version of release 3.2 will be available on the MONOLIX website in June 2010. This version will contain several new important features such as:

- Mixture models (parameter mixture, between subject model mixture, within subject model mixture),
- XML control file.

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Michael Neely The MM-USCPACK software for nonparametric adaptive grid (NPAG) population PK/PD modeling, and the MM-USCPACK clinical software for individualized drug regimens.

R Jelliffe, A Schumitzky, D Bayard, R Leary, M Van Guilder, M Neely, S Goutelle, A Bustad, M Khayat, and A Thomson
Laboratory of Applied Pharmacokinetics, USC Keck School of Medicine, Los Angeles CA, USA

The **BigNPAG** maximum likelihood nonparametric population adaptive grid modeling software runs in XP. The user runs the BOXES routine to make the structural PK/PD model. This is compiled and linked transparently. Routines for checking data and viewing results are provided. Likelihoods are exact. Behavior is statistically consistent - studying more subjects gives estimates progressively closer to true values. Stochastic convergence is as good as theory predicts. Parameter estimates are precise [1]. The software is available by license from the University for a nominal donation.

The **MM-USCPACK** clinical software [2] uses NPAG population models, currently for a 3 compartment linear system, and computes multiple model (**MM**) dosage regimens to hit desired targets with minimum expected weighted squared error, providing maximal precision in dosage regimens. Models for planning, monitoring, and adjusting therapy with aminoglycosides, vancomycin (including continuous IV vancomycin), digoxin, carbamazepine, and valproate are available. For maximum safety, **hybrid MM** Bayesian posteriors composed of MAP estimates plus added support points in that area now assure adequate support points to augment the population model for the new data it will receive, increasing safety of posteriors and maximal precision in the subsequent regimen. The interactive multiple model (**IMM**)Bayesian fitting option [3] allows parameter values to change if more likely during the period of data analysis, and provides most precise tracking of drugs in over 130 clinically unstable gentamicin and 130 vancomycin patients [4]. In all the software, creatinine clearance is estimated based on one stable or two unstable serum creatinines, age, gender, height, and weight [5].

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Sebastian Ueckert PopED - An optimal experimental design software

Joakim Nyberg, Sebastian Ueckert, Mats O. Karlsson and Andrew C. Hooker
of Pharmaceutical Biosciences, Uppsala University, Sweden

PopED is an Optimal Experimental Design tool for Non-Linear Mixed Effect Models [1]. Key features of PopED include the ability to optimize over multiple possible models as well as to assume distributions around model parameter values (ED-optimal design). For the latter PopED can use asymptotically exact Monte-Carlo methods or faster performing Laplace approximations for the integration step. PopED allows the user to optimize over any design variable (sample times, doses, number of individuals, start and stop time of experiments, infusion lengths etc...) greatly enhancing the information content of experiments. In addition to that, the possibility to use inter-occasion variability has been included in the latest version.

PopED consists of two parts, a script version, responsible for all optimal design calculations, and a Graphical User Interface (GUI), facilitating the setup of an optimization task for users. The script version can use either Matlab or Freemat as an underlying engine. The GUI is a window based application written in C# that can be run with .NET 2.0 (MS Windows) or with Mono (Linux/MacOS). In addition to easing the building up of an experimental design optimization, the GUI also provides model templates and examples as well as tools for interpretation of the optimal design outcome and ways to validate and simulate models prior to optimization. All these tools are also accessible via the script version of PopED. PopED is freely available at poped.sf.net.

References:

[1]. Foracchia, M., et al., *POPED, a software for optimal experiment design in population kinetics.* Comput Methods Programs Biomed, 2004. **74**(1): p. 29-46.

Stephane Vellay Pipeline Pilot - Data Integration, Analysis, and Reporting Platform

Stephane Vellay, Guillaume Paillard, Eddy Vande Water, Richard Compton
Accelrys

Workflow technology is being increasingly applied in research and development information to organise and analyse data. **Pipeline Pilot** is a scientifically intelligent implementation of a workflow technology known as data pipelining. It allows scientists to construct and execute workflows using components that encapsulate many algorithms. This flexible visual programming language captures and deploys your best-practice processes.

1. **Data Integration**
   - Search, summarise & share your data aggregated from multiple disparate sources, Databases or Files, using In-House format checking rules
   - Join together applications within a variety of areas, such as chemistry, cheminformatics, bioinformatics, on-line content integration, image analysis, high throughput screening, and laboratory data management
   - Features related to security, scalability, database integration, and distributed computing make it an ideal solution for enterprise use
2. **Application Integration - Model Building & Simulation**
   - Pipeline Pilot allows you to integrate your existing computational resources within a single work environment: NONMEM, WinBUGS, Monolix, Xpose, WinNonLin, PsN, simCYP, MC Sim, etc.
   - Use standard scripting environments for rapid development of new components: R, MATLAB, SAS, Perl, Java, Python, VBScript, ORACLE, etc.
   - Automate workflows to schedule jobs, then log & archive associated data and reports
3. **Reporting - Exploratory Analysis, Diagnostics & Decision Tool**
   - Automate the creation of standardised reports in various formats: HTML, PDF, PowerPoint, Word, Excel, etc.
   - Present analysis results in a more accessible way, using interactive charts and forms with easy-to-use reporting tools or by integrating third party applications reporting tools
   - Extend Pipeline Pilot protocols throughout your organisation via Web Portals like SharePoint or LifeRay, giving non-expert users access to previously constructed workflows

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[2] Learn more about data integration, analysis, and reporting with Pipeline Pilot.
[3] Accelrys Home Page
[4] Accelrys Community Forums contain discussion groups where users can discuss information about the products, report issues, and post scripts and components.