PAGE2009 Program and poster abstract titles

Tuesday June 23

10:00-18:00 **Registration**

19:00-20:00 **Opening ceremony**

20:00-22:00 **Welcome cocktail**

Wednesday June 24

08:00-08:45 **Registration**

08:45-09:00 **Welcome and Introduction**

09:00-10:05 **Paediatric Session: Are children Small Adults?** *chair: Alison Thomson and Nick Holford*

09:00-09:30 *Brian Anderson, Catherijne Knibbe and Willem de Winter*

09:30-10:05 *Panel discussion*

10:05-11:35 **Coffee break, Poster and Software session I**

Posters in Group I are accompanied by their presenter

11:35-12:15 **Paediatric session continued (submitted abstracts)** *chair: Alison Thomson and Nick Holford*

11:35-11:55 *Michael Looby* Elucidation of the Optimal Dosing Scheme of an Antiviral Drug in Children

11:55-12:15 *Lutz Harnisch* Population PK of Sildenafil and PK/PD Assessment of Exercise Tolerability in Children with Pulmonary Arterial Hypertension (PAH)

12:15-13:45 **Lunch**

13:45-15:05 **Model Building and Evaluation** *chair: Mats Karlsson*

13:45-14:05 *Chuanpu Hu* Confirmatory Phase III Population Pharmacokinetic Analysis

14:05-14:25	*Julie Bertrand*	Model-based Tests to Detect Gene Effect in Pharmacokinetic Studies
14:25-14:45	*Céline Laffont-Rousset*	A New Exact Test to Globally Assess a Population PK and/or PD Model
14:45-15:05	*Diane Wang*	Standardized Visual Predictive Check - How and When to Use it in Model Evaluation

15:05-16:20 **Tea break, Poster and Software session II**

Posters in Group II are accompanied by their presenter

16:20-17:40 **PK and PD in Oncology** — *chair: Dinesh De Alwis*

16:20-16:40	*Ron Keizer*	Modeling of Hypertension in Response to Anti-angiogenic Therapy
16:40-17:00	*Benjamin Ribba*	Estimating the Kinetic Parameters of Vascular Tumor Growth Models to Optimize Anti-angiogenesis Drugs Delivery
17:00-17:20	*Vladimir Vainstein*	Targeted Drug Delivery by Gemtuzumab Ozogamicin: Mechanism-based Pharmacokinetic Model for Treatment Strategy Improvement and Prediction of Individual Responses.
17:20-17:40	*David Ternant*	Model-based Optimization of Rituximab Dosing Regimen in Follicular non-Hogdkin Lymphoma

Thursday June 25

08:45-10:05 **Lewis Sheiner Student Session** — *chairs: Charlotte Kloft/ Iñaki Trocóniz/ Oscar Della Pasqual*

08:45-09:10	*Julie Antic*	Nonparametric Methods: When to Use Them? Which Method to Choose?
09:10-09:35	*Venkata Pavan Kumar Vajjah*	Novel Graphical Diagnostics for Assessing Fit of Logistic Regression Models
09:35-10:00	*Elena Soto*	Prediction of Haematological Effects of a New Combination of Anticancer Drugs, BI 2536 (a PLK1 Inhibitor) and Pemetrexed, Using a Semi-mechanistic Population Model for Neutropenia

10:00-10:05 **Presentation of Awards**

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

Posters in Group III are accompanied by their presenter

11:20-12:20 **Mechanistic Modelling** — *chair: Stephen Duffull*

11:20-11:40	*Willem de Winter*	Integrating a Model for Weight Change into the Mechanism-Based Model for Type 2 Diabetes
11:40-12:00	*Robert Kalicki*	Modeling of Red Blood Cell (RBC) Lifespan (LS) in a Hematologically Normal Population
12:00-12:20	*Andreas Kuttler*	A 3D Computational Model of Cerebrospinal Fluid Dynamics for Predictive Biosimulation

12:20-13:50	**Lunch**	
13:50-14:35	***Valeri Fedorov and Ivelina Gueorguieva:* Tutorial on Optimal Design in Population PKPD Analyses**	
14:35-15:15	**Optimal Design**	*chair: Marylore Chenel*
14:35-14:55	*Nathalie Gobeau*	Comparison of Different Tools for the Optimization of a Pediatric Clinical Trial
14:55-15:15	*Joakim Nyberg*	Population Optimal Experimental Design for Discrete Type Data
15:15-16:30	**Tea break, Poster and Software session IV**	
	Posters in Group IV are accompanied by their presenter	
16:30-17:10	**Time to Event Modelling**	*chair: Lutz Harnisch*
16:30-16:50	*Andrew Hooker*	Time to Event Modeling of Dropout Events in Clinical Trials
16:50-17:10	*Nick Holford*	The Influence of the Time Course of CD4 and Viral Load on Clinical Outcome Events Before and During Antiretroviral Therapy
19:00-24:00	**Social evening** ***Important note: Buses depart at 18.00 h from St. Petersburg Hotel and at 18:15 h from the other selected hotels. Participants must depart from the hotel where they are staying as buses have been allocated according to reservation details.***	

Friday June 26

09:00-10:00	**Stuart Beal Methodology Session**	*chair: France Mentré*
09:00-09:20	*Birgitte Rønn*	Maximum Likelihood Estimation in Nonlinear Mixed Effect Models: Adaptive Gaussian Quadrature by Sparse Grid Sampling
09:20-09:40	*Matthew Hutmacher*	Estimating Transformations for Population Models of Continuous, Closed Interval Data
09:40-10:00	*Radojka Savic*	A New SAEM Algorithm for Ordered-categorical and Count Data Models: Implementation and Evaluation
10:00-10:30	*Robert Bauer*	Improvements and New Estimation Methods in NONMEM 7 for PK/PD Population Analysis
10:30-11:10	**Coffee Break**	
11:10-11:20	**Preview of PAGE 2010**	

11:20-12:20	**Methodology and applications in PK (TK/TD) studies**		*chair: Oscar Della Pasqua*
11:20-11:40	*Fran Stringer*	Genotyped Versus Phenotyped Dosing to Account for UGT Polymorphism of the Novel PPAR Agonist Sipoglitazar	
11:40-12:00	*William Denney*	Modeling and Simulation for Determination of the Therapeutic Window of MK-2295: a TRPV1 Antagonist	
12:00-12:20	*Billy Amzal*	Population TK/TD for Chemical Risk Assessment and Drug Safety: the Cadmium Example	

12:20-12:30	**Closing Remarks**

12:30-12:45	**Audience Input for the PAGE 2010 Program**

Software demonstrations

Balaji Agoram PulmoSim: A Physiologically-Based Mathematical Model Software Package to Predict Lung Retention and Inhaled Pharmacokinetics of Therapeutic Candidates
William J. Bachman PDx-Pop® 4 for NONMEM® 7
Caroline Bazzoli New features for population design evaluation and optimization with R functions: PFIM Interface 3.1 and PFIM 3.2
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.
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.
Marc Lavielle Analysing population PK/PD data with MONOLIX 3.1
Piet van der Graaf A4S: a user-friendly PKPD simulation software for non experts
Stephane Vellay Pipeline Pilot - Data Integration, Analysis, and Reporting Platform
Justin Wilkins Census: NLME project management for NONMEM
Pharsight Corporation Phoenix NLME and Phoenix

Posters Wednesday Morning (group I)

Applications- Other topics

001. Claire Ambery Population PK-PD Modelling of Wheal and Flare Area in a First-Time-in-Human Study
005. Kyle Baron Evaluation of Assumptions in the Clinical Use of the Cockcroft-Gault Equation
009. Martin Bergstrand Semi-mechanistic PK/PD modeling of Paracetamol and Sulfapyridine to characterize effects on gastric emptying and small intestinal transit
013. Dmitry Bordin Relating Pharmacokinetics and Pharmacodynamics of Proton Pomp Inhibitors (Ppis) to Clinical Performance in Patients with Gastroesophageal Reflux Disease (GERD)
017. Jonathan French Safety monitoring of a kidney transplant study using a Bayesian time-to-event model
021. Iztok Grabnar Population Pharmacokinetics of the Active Metabolite of Leflunomide in Patients with Rheumatoid Arthritis
025. Thaddeus Grasela Improving the Efficiency and Ensuring the Quality of Data Assembly for Pharmacometric Analysis
029. Roger Jelliffe Optimal Stochastic Control Of Drug Dosage Regimens
033. Patrick Johnson Enhanced quantitative drug development (EQDD) of a selective PDE5 inhibitor for the treatment of benign Prostatic hyperplasia (BPH).
037. Helene Karcher Interpreting QT in a Patient Population After Surgical Intervention
041. Andreas Kuttler A 3D mechanical model of the gastric esophageal junction: model-based assessment of

Methodology- Other topics

185. James Yates Validation of in vivo Mouse PK Assay by Mixed Effects Modelling: Estimation of between-study variability.

Posters Wednesday Afternoon (group II)

Applications- Anti-infectives

002. Chantal Csajka Population pharmacokinetics of voriconazole in patients with invasive mycoses
006. Oleg Demin Application of pharmacokinetic-pharmacodynamic model to optimize dosing regime of antimicrobial drug Grammidin containing gramicidin S
010. Anne laure Flaugere Population pharmacokinetics of imipenem bone concentrations in pigs
014. Monika Frank Population pharmacokinetic model development and evaluation after nevirapine administration to mothers and newborns
018. Maria Kjellsson Modeling the permeability of Fosfomycin into Abscess Fluid
022. Chantal Le Guellec Population pharmacokinetics of Ceftriaxone in intensive care unit (ICU) adult patients
026. Ana Martin Suarez Population pharmacokinetic model for Ritonavir (RTV) in HIV-infected patients treated with Lopinavir (LPV)/RTV (KaletraTM)
030. France Mentré Parameter estimation of long-term HIV dynamic model in the COPHAR2 - ANRS 111 trial using MONOLIX
034. Michael Neely Voriconazole Population Pharmacokinetics and Pharmacodynamics in Children
038. Saeed Rezaee Population Pharmacokinetics of Vancomycin in Iranian Paediatric Patients
042. Mª Dolores Santos Buelga Population Pharmacokinetics of Lopinavir (KaletraÒ) in HIV-Infected Patients
046. Wynand Smythe Mechanistic pharmacokinetic enzyme model for the characterisation of rifampicin pharmacokinetics in South African pulmonary TB infected adults
050. Ami Fazlin Syed Mohamed Pharmacokinetic/Pharmacodynamic Modeling of Adaptive Resistance of Gentamicin
054. Mita Thapar Population pharmacokinetics of artesunate and dihydroartesunate in adults and children following administration of a fixed dose combination formulation of chlorproguanil-dapsone-artesunate
058. Jan-Stefan van der Walt Effect of rifampicin-based antitubercular therapy and cotrimoxazole on the population pharmacokinetics of stavudine (d4T) in HIV-1 infected patients
062. Jianping Zhang Use of Eltrombopag Exposure-Platelet Response Relationship for Dose Optimization in Patients with Chronic HCV-Infection with and without Interferon

Applications- Coagulation

066. Ekaterina Gibiansky Population Pharmacokinetics of Eltrombopag in Healthy Subjects and Patients with Chronic Idiopathic Thrombocytopenic Purpura
070. Anna-Karin Hamberg A longitudinal model describing the relationship between warfarin dose and INR response taking CYP2C9, VKORC1 and age into account
074. Siobhan Hayes Population PK/PD Modeling of Eltrombopag in ITP Patients and Optimization of Response-Guided Dosing
078. Toshihiro Wajima A comprehensive model for the coagulation network in humans

Applications- CVS

082. Anne Chain Not-In-Trial Simulation: Predicting cardiovascular risk from clinical trial data
086. Stefanie Hennig Characterizing time to conversion to sinus rhythm under digoxin and placebo in acute atrial fibrillation
090. Carlos Hoyo-Vadillo Pharmacokinetic Model for Losartan Administered to Young Mexican Healthy Volunteers.
094. Fredrik Jonsson A pharmacokinetic-pharmacodynamic model for ECG pattern changes in dog and monkey
098. Etienne Pigeolet Introducing the renin-angiotensin-aldosterone (RAAS) hypertension platform: an in-silico approach to evaluating efficacy of RAAS modulating drugs on blood-pressure control and end-organ protection
102. Patanjali Ravva Population Pharmacokinetic-Pharmacodynamic Analysis of Weight Loss Efficacy of CP-945,598 in Adult Obese Subjects

Methodology- Design

106. Caroline Bazzoli Prediction of power of test of discrete covariates in population analyses and influence of design: application to gender effect in joint pharmacokinetic models of nucleoside analogs and their active metabolites
110. Massimo Cella Scaling of fixed dose combinations in children

114. Thaddeus Grasela Modeling and Simulation Approach to Pediatric Drug Development
118. Ivelina Gueorguieva Desipramine Population Pharmacokinetic Model and Designing CYP2D6 Drug-Drug Interaction Studies
122. Stefanie Hennig Optimal design for models with semi-parametric distributions
126. Andrew Hooker Autocorrelation reduces sample time clustering in optimal design
130. Frank Kloprogge A model-based approach for dose selection of fixed dose combinations in paediatric indications.
134. Sergei Leonov Estimation of Population Pharmacokinetic Measures and Selection of Sampling Times
138. Rocio Lledo Seeking ethically attractive dose-finding designs for narrow therapeutic index drugs
142. Kayode Ogungbenro Sample Size/Power Calculations for Population Pharmacodynamic Experiments Involving Repeated Count Measurements
146. Patanjali Ravva Enhanced Clinical Trial Design of a Proof-of-Concept Study via Bayesian simulation analyses
150. Marcus Scholz Optimal Design for the improvement of sampling schedules of microdialysis studies.
154. Mike Smith MSToolkit - An R library for simulating and evaluating clinical trial designs and scenarios
158. Shuying Yang Bayesian Adaptive Designs for Phase IIb Dose-ranging Study in Rheumatoid Arthritis (RA)

Posters Thursday Morning (group III)

Applications- CNS

003. Maurice Ahsman Population Pharmacokinetics of Midazolam and Metabolites during Venoarterial Extracorporeal Membrane Oxygenation in Neonates
007. Roberto Bizzotto Multinomial logistic functions in Markov-chain models for modelling sleep architecture after placebo administration
011. Marcus Björnsson A two-compartment effect site model describes the Bispectral Index Score (BIS) after administration of propofol
015. Kristina Bondareva External Validation of the Population Models for Carbamazepine Pharmacokinetics and the Individualizing Carbamazepine Dosage Regimen Procedure
019. Irina Bondareva Population Pharmacokinetics of Carbamazepine and Estimation of Influencing Factors
023. Chao Chen Concentration-Response Modelling of Adjunctive Lamotrigine Extended-Release for Primary Generalised Tonic-Clonic Seizures
027. Chantaratsamon Dansirikul Population pharmacokinetic analysis of pramipexole extended-release formulation in Parkinson's Disease (PD) patients
031. Jeroen Diepstraten Population pharmacokinetics and pharmacodynamics of Propofol in morbidly obese patients
035. Pinky Dua ADAS-Cog Placebo Modelling in Alzheimer's Disease
039. Bart Laurijssens Integrated analysis of Human PET data across multiple brain regions and receptors to make inferences from limited data.
043. Amelie Marsot External validation of pharmacokinetic population model of alfentanil in obese patients.
047. Amir Hooshang Mohammadpour Population pharmacokinetics of carbamazepine in Iranian epileptic and manic patients
051. MYM Peeters The pharmacodynamics of isoflurane in children using Bispectral index and composite auditory evoked potentials
055. Klas Petersson Could prolactin levels be a more informative predictor for clinical effect of D2-receptor antagonists than drug concentrations in the treatment of schizophrenia?
059. Monica Simeoni Prediction of remifentanil metabolic ratio using sparse data collected during non-steady-state infusion with rapidly changing rate
063. Nicolas Simon Population Kinetic Pharmacodynamic and Logistic Regression Analysis of Intravenous Morphine Titration in Immediate Postoperative Period
067. Pyry Välitalo CSF and Plasma Pharmacokinetics of Flurbiprofen in Children
071. Katarina Vucicevic Effect of Valproic Acid Daily Dose on its Clearance in Adult Patients with Epilepsy - Population analysis of TDM data
075. Jonathan Wagg Estimation of cortical amyloid beta turnover rates

Applications- Endocrine

079. Paolo Denti Covariate Selection for the IVGTT Minimal Model of Glucose Disappearance
083. Paolo Denti A NonLinear Mixed-Effects Approach to the Estimation of the Glucose Disposition Index
087. Srividya Neelakantan Exposure-Response Analysis of a DPP-IV Inhibitor, PF-00734200 on HbA1c in Type 2 Diabetic Subjects on Stable Metformin Treatment
091. Sergej Ramusovic A physiologically based pharmacodynamic model of the Renin-Angiotensin-Aldosterone-System

095. Elba Romero Impact of pharmacokinetic information reported as being below limit of quantification on the prediction of important response endpoints.
099. Hanna Silber An integrated model for glucose-insulin regulation to describe oral glucose tolerance test data in healthy volunteers

Methodology- Algorithms

103. Radel Ben-Av Comprehensive Virtual Patient Platform Implemented For Anti-Angiogentic Drugs Development
107. Emmanuelle Comets A bibliographic review of non-parametric methods and their application
111. Vivek Dua Initial Estimates for Parameter Estimation
115. Anne Dubois Extension of the SAEM algorithm and evaluation of Wald and likelihood ratio tests for interaction or bioequivalence studies
119. Charles Ernest Improved parameter estimation and design optimization for In Vitro ligand binding experiments
123. Kevin Feng A New Framework for Combining the 'Bottom-Up' PBPK Paradigm and POP-PK Data Analysis Using Genetic Algorithms and SAEM
127. Bo-Hyung Kim Hierarchical-likelihood approach for nonlinear mixed-effect models
131. Elodie Plan New models for handling correlated underdispersed Likert pain scores
135. Klaas Prins Comparison of a maximum likelihood versus a full bayesian method to jointly model individual with summary level data

Methodology- PBPK

139. Balaji Agoram A Physiologically-Based Mathematical Model to Predict Lung Retention and Inhaled Pharmacokinetics of Therapeutic Candidates
143. Corina Becker Whole-Body Physiologically-Based Pharmacokinetic (WB-PBPK) Modeling of Moxifloxacin (MFX) to Support a Translational Approach in Pediatric Study Design
147. S. Y. Amy Cheung Development of a closed loop whole body (WB) physiologically based pharmacokinetic model (PBPK) of beta-blockers in the rat
151. Brenda de Winter Mechanism-based pharmacokinetic modelling of protein binding of mycophenolic acid and its glucuronide metabolite in renal transplant recipients
155. Gemma Dickinson Prediction of a Metabolic Drug-Drug Interaction in a Virtual Human Population using in vitro Enzyme Kinetic Information
159. Andrea Edginton Parameterization of a physiologically-based pharmacokinetic (PBPK) model for the simulation of ibuprofen pharmacokinetics under exercise and heat stress with validation from clinical data
163. Cecile Gerard Link between cyclosporin exposure in tissues and graft versus host disease in paediatric bone marrow transplantation: analysis by a PBPK model
167. Cecile Gerard Influence of cyclosporin infusion duration on efficacy in paediatric bone marrow transplantation: analysis by a PBPK model
171. Hannah Jones Use of PBPK modelling in drug discovery at Pfizer
175. Klaas Prins Characterization of the population pharmacokinetics of UK-369,003 using a semi-mechanistic model
179. Anastassia Viglinskaya A physiology-based pharmacokinetic model describing the disposition of a novel selective anxiolytic drug afobazole and its metabolites in rats.

Posters Thursday Afternoon (group IV)

Applications- Biologicals / vaccines

004. Leonid Gibiansky Population Pharmacokinetics of AMG 317, a Fully Human Anti-IL-4R±IgG2 Monoclonal Antibody Evaluated in Healthy and Asthmatic Subjects
008. Helene Karcher Harnessing clinical knowledge on ligand-targeting drug to develop a new compound targeting the associated receptor : an example of model-based biologics design in pre-clinical development
012. Wojciech Krzyzanski Receptor Mediated Disposition PK/PD Model of Filgrastim in Healthy Adults following Intravenous and Subcutaneous Administrations.
016. Brigitte Lacroix Comparison between the Exposure-Response Modeling of the ACR20 and ACR50 Scores in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol.
020. Philip Lowe Omalizumab (Xolair) may normalise IgE production rate in patients with moderate-to-severe atopic asthma
024. Philip Lowe Pharmacokinetics of canakinumab and pharmacodynamics of IL-1ß binding in patients with cryopyrin associated periodic fever syndromes

028. Philip Lowe On the ability to predict free ligand suppression when free ligand assays are not available or impossible
032. Philip Lowe Relationship between omalizumab pharmacokinetics and IgE pharmacodynamics in adult and pediatric patients with moderate to severe persistent allergic (IgE-mediated) asthma
036. Scott Marshall Population Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis of the Effect of Tanezumab on Overall Daily Pain Score Data in Adults with Moderate-to-Severe Pain due to Osteoarthritis of the Knee
040. Etienne Pigeolet Artefactual inflation of pharmacokinetic difference between two Granulocyte Colony Stimulating Factor (G-CSF) drug products by non compartmental analysis.
044. Elisabeth Rouits Target-Mediated Drug Disposition model to describe non-linear kinetics of a Monoclonal Antibody

Applications- Oncology

048. Lorea Bueno Semi-Mechanistic Modelling of the Tumour Growth Inhibitory Effects of a New Anti-angiogenic Drug.
052. Damien Cronier A fully integrated PK/IVTI/IVE model in mouse to help design the FHD trial for a cell cycle inhibitor X
056. Maxime Fontanillles Modelization of bevacizumab effect on tumour perfusion assessed by Dynamic Contrast Enhanced Ultrasonography
060. Ludivine Fronton Population model of Human Chorionic Gonadotropin to predict resistance in low risk gestational trophoblastic neoplasia patients
064. Maria Garrido Pharmacokinetics and antitumor efficacy characterization of cisplatin-loaded PLGA nanoparticles in tumor-bearing mice.
068. Marianne Guery Data mining analysis of survival data in cancer of pancreas : first exploratory step for identification and validation of explicative variables
072. Emma Hansson Pharmacokinetic-Pharmacodynamic Modeling of the Angiogenic Factors VEGF, sVEGFR-2, sVEGFR-3 and sKIT following Sunitinib Treatment in GIST
076. Georg Hempel Physiologically-Based Pharmacokinetic (PBPK) Model for High- and Low Dose Etoposide: From Adults to Children
080. Åsa Johansson Pharmacokinetics of high-dose methotrexate in adults and children
084. Andreas Lindauer Pharmacokinetic/Pharmacodynamic Modeling of Sunitinib in Healthy Volunteers
088. Laurent Nguyen Validation of a neutropenia PK/PD model built from intravenous vinflunine and its application to design phase I trials with oral vinflunine
092. Celine Pitou Modelling of PK/Efficacy/Toxicity in rats to help design a First Human Dose for a cell cycle inhibitor X
096. Christian Pobel Time to event models of survival in cancer of pancreas : confirmation of explanatory variables pre-selected by bootstrap analysis.
100. Angelica Quartino A semi-mechanistic myelosuppression model of docetaxel treatment in liver impaired patients
104. Alexandre Sostelly Simultaneous modelling of PSA production in Prostatic Benign Hyperplasia (PBH) and prostatic adenocarcinoma patients treated by prostate surgery
108. Mirjam Trame Population Pharmacokinetics of Dimethylacetamide in Children During Once-daily and Standard IV Busulfan Administration
112. Johan Wallin Model Based Neutrophil Guided Dose Adaptation in Chemotherapy
116. Xiaofeng Wang Population PK modeling and simulation to select a dosing schedule in Phase II trials for a novel TKI agent with time-dependent and nonlinear PK

Methodology- Model evaluation

120. Martin Bergstrand Visual Predictive Checks for Censored and Categorical data
124. Anton Korobeynikov Comparison of Parameter Estimates for One Special Model of Survival Curves for Sample with Interval Censoring
128. Elke Krekels Evaluation of two models for morphine pharmacokinetics in neonates and infants.
132. Sergei Kulikov New parametric model for survival fitting
136. Bojan Lalovic Impact of Dosing Regimens on Dropout Across Pregabalin Trials in the Treatment of Generalized Anxiety Disorder: Model Refinements and External Validation
140. Marta Neve Assessment of NONMEM and WinBUGS performances when estimating power and sigmoid Emax models
144. Richard Nixon Using short-term evidence to predict six-month outcomes in clinical trials of signs and symptoms in rheumatoid arthritis
148. Elodie Plan Eleven ordered categories data: which modelling options?
152. Alberto Russu Dose escalation studies: a comparison among Bayesian models

PAGE 2009 Abstracts: Oral Presentations and software demosntrations

Oral Presentation : Lewis Sheiner Student Session

Julie ANTIC Nonparametric Methods: When to use them? Which method to choose?

Antic J. (1,2), Chenel M. (2), Laffont C. M. (1), Concordet D. (1).
(1) UMR181 Physiopathologie et Toxicologie Expérimentales, INRA, ENVT, Toulouse, France ;(2) Institut de Recherches Internationales Servier, Courbevoie, France.

Background. Parametric methods, routinely used for population pharmacokinetics (PK) and/or pharmacodynamics (PD) analyses, rely on the normality of random effects for interindividual variability (ETAs). However, this normality assumption can be too restrictive, especially in phase II or phase III of clinical trials, which involve heterogeneous population of patients: the distribution of ETAs can be multimodal, because of sub-populations, heavy-tailed, because of outliers... Identifying such departures from normality is important to develop efficient and safe drugs. A graphical procedure to evaluate the normality assumption is based on ETAs' individual predictions following parametric estimation, known as Empirical Bayes Estimates (EBEs). Unfortunately, when data are sparse, the EBEs can be unreliable because of ETA-shrinkage ([1]). In that context, nonparametric (NP) methods, which do not rely on a normality assumption, are attractive. However, their use remains limited: they can be difficult to handle while their interest is few documented.

Objectives. To give practical answers to the following questions. For parametric estimation, is the inspection of EBEs reliable to detect departures from normality? When NP methods should be preferred over parametric ones? Have all NP methods equivalent statistical properties? Which NP method achieves the best compromise between implementation/computation burden and ability to detect departures from normality?

Methods: We studied four widespread NP methods: NPML [2], NPEM [3], SNP [4] and NP-NONMEM [5]. We evaluated and compared these NP methods, first in theory thought a bibliography review, and then in practice, based on simulations studies ([6], [7]). Several datasets were simulated from more and more challenging scenarios:

- in scenario 1, inspired from the PK analysis of Phenobarbital [8], the model was an one-compartment model, with *intravenous bolus* administration (first order elimination, 2 random effects). The residual error was proportional. There were 200 individuals and, on average, 2.15 individual observations (range 2-3). ETA-shrinkage was low (<25%).
- scenario 2, was the same as scenario 1 except for the individual information: the average number of observations per individual was 1.3 (range 1-3). ETA-shrinkage was moderate (<50%).
- in scenario 3, inspired from the PK analysis of Phenobarbital [9], the model was an one-compartment model, with oral administration (first order absorption and elimination, 3 random effects). The residual error was proportional. There were 200 individuals and, on average, 2.3 individual observations (range 2-4). ETA-shrinkage was moderate (<50%).

- in scenario 4, which mimics the PK/PD analysis of Gliclazide MR [5], the PK/PD model was an Emax model with compartment effect and linear disease progression model (5 random effects, 1 for the baseline, 1 for the disease progression, and 3 for drug's effect). The residual error was constant. There were 634 individuals, and on average 8.3 individual observations (range 3-13). Individual information was rich but ETA-shrinkage was high (>50%) due to a non optimal design.

In each scenario, the simulated distribution of ETAs was not normal, since we simulated a sub-population of individuals with lower clearance (scenario 1, 2 and 3) or treatment's effect (scenario 4). The aim was to assess the abilities of the tested methods to detect this departure from normality. We simulated as many datasets as necessary to have 100 datasets with successful termination of the parametric NONMEM $ESTIMATION subroutine. The NP methods were computed on these 100 datasets. NPML and NPEM were implemented in C++. SNP was computed using the nlmix fortran 77 code ([4]). NPNM was computed using NONMEM VI with default options.

Results: *(i)Theoretical comparison.* Theoretical knowledge of NP methods appeared few documented. It mainly concerns the consistency of the methods (which insures that increasing the sample size improves the estimation accuracy). The consistency of NPML, NPEM and SNP has been established, under more or less restrictive conditions. However, to the best of our knowledge, the consistency of NPNM is still unproved. For NPML, NPEM and NPNM, some important theoretical questions appeared still open. How to estimate the parameters describing residual error? How handling covariates? For SNP, these questions have roughly been addressed.

(ii)Ease and time of computation. Implementation was easy for NPNM, more demanding for the others NP methods. None NP method failed to complete estimation on a dataset. The computation times increased with the sample size and the number of random effects. The average computation time of NPNM ranged from less than 1 minute per dataset (scenario 1) to 14 minutes per dataset (scenario 4). Computation times of the others methods were very sensitive to computational settings (initializations, stopping criteria...). With our settings, SNP was the fastest method (less than 5 min per dataset), NPEM was the slowest (up to more than 3 hours per dataset), NPML was a bit slower than NPNM (average 29 min per dataset in scenario 4).

(iii)Detection of the bimodality. To assess the ability to detect the simulated sub-population, we graphically inspected the distribution of clearance (scenario 1, 2 and 3) or drug's effect (scenario 4) estimated with NP methods. More precisely, we plotted this distribution for all datasets (for each scenario and NP method). These graphs, compared to the true distribution, allow to evaluate the bias and the variability of the methods. In scenario 1, the bimodality was generally detected by all the methods (parametric inspection of EBEs and NP). In scenario 2, it appeared difficult to suspect the bimodality with the inspection of EBEs. NP methods roughly allowed to detect the bimodality. In scenario 3, the bimodality seemed well described by NPEM and SNP than by NPNM and NPML. In scenario 4, the subpopulation of non-responders was never detected by the inspection of EBEs. Only NPEM and SNP allowed to clearly detect it on some datasets. The variability of the NP methods was always larger than the variability of the parametric inspection of EBEs.

Conclusions: Based on our extensive bibliographic and simulation studies, we can give some recommendations for the use of NP methods. The inspection of EBEs seems sufficient to detect departures from normality when EBEs are reliable like in phase I clinical trials. However, when individual information is sparse, it can be misleading, even for a very simple PK model such as a monocompartmental model with *intravenous bolus* administration. In that case, the NP methods should

be preferred over classical parametric method. With an easy implementation and reasonable computation times, NP-NONMEM seems suitable for datasets with moderate ETA-shrinkage (<50%). However, for datasets with high ETA-shrinkage (>50%), only more demanding NP methods (like SNP or NPEM) seems satisfactory.

References:

[1] Savic, R.M., Wilkins J.J. & Karlsson M.O., 2006. (Un)informativeness of empirical Bayes estimate-based diagnostics. The American Association of Pharmaceutical Scientists. 8:S2.
[2] Mallet A. A maximum likelihood estimation method for random coefficient regression models. Biometrika, 73 (3):645-656, 1986.
[3] Schumitzky A. Nonparametric EM algorithms for estimating prior distributions. Applied Mathematics and Computation, 45 (2, part II):143-157, 1991.
[4] Davidian M. and Gallant A.R. The nonlinear mixed effect model with a smooth random density. Biometrika, 1993, 80:475-488.
[5] Boeckmann A.J., Sheiner L.B. and Beal S.L. NONMEM users guide, 2006.
[6] Antic J., Laffont C.M., Chafaï D. and Concordet D. Comparison of nonparametric methods in non linear mixed effects models. Computational Statistics and Data Analysis, 53:642-656, 2009.
[7] Antic J., Chenel M., Laffont C.M. and Concordet D. Evaluation and application of nonparametric methods on the population pharmacokinetics/pharmacodynamics of Gliclazide. To Submit to the Journal of Pharmacokinetics and Pharmacodynamics, 2009.
[8] Grasela T.H. and Donn S.M. Neonatal population pharmacokinetics of phenobarbital derived from routine clinical data. Developmental pharmacology and therapeutics, 8 (6):374-383, 1985.
[9] Yukawa E., Suematsu F., Yukawa M. and Minemoto M. Population pharmacokinetic investigation of Phenobarbital by mixed effect modeling using routine clinical pharmacokinetic data in Japanese neonates and infants. Journal of Clinical Pharmacy and Therapeutics, 30:159-163, 2005.
[10] Frey N., Laveille C., Paraire M., Francillard M., Holford N.H.G. and Jochemsen R. Population PKPD modeling of the long-term hypoglycaemic effect of gliclazide given as a once-a-day modified release (MR) formulation. Journal of Clinical Pharmacology, 55:147-157, 2003.

Elena Soto Prediction of haematological effects of a new combination of anticancer drugs, BI 2536 (a PLK1 inhibitor) and pemetrexed, using a semi-mechanistic population model for neutropenia

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Background:

BI 2536 is a inhibitor of Polo-like kinase 1 (Plk1) currently in clinical development. Plk1 plays an essential role in the regulation of mitotic progression, (Nigg 1998). Pemetrexed is a cytotoxic anticancer drug approved for the treatment of several cancers.

The haematological effects of BI 2536 have previously been described using Phase I study data (Soto et al; 2008), and the same semi-mechanistic model (Friberg et al; 2002) has been used to describe neutropenia caused by pemetrexed without vitamin supplementation (Latz et al; 2005a, Latz et al; 2005b).

Objective:

To predict the neutropenic effects for the novel combination of BI 2536 and pemetrexed including supplementary administration of folic acid, vitamin B12 and dexamethasone in non-small-cell lung cancer (NSCLC) patients, using a semi-mechanistic modeling approach.

To achieve this goal, first a semi-mechanistic model for pemetrexed related neutropenia in presence of vitamin supplementation and dexamethasone was developed. Then, under the assumption of an additive interaction [as described previously for other chemotherapy combination treatments (Sandstrom et al; 2005, Sandstrom et al; 2006)], the models for neutropenia developed for pemetrexed and BI 2536 when given as single cytotoxic anticancer drugs were combined to predict the outcome of a combination study of these two drugs in NSCLC patients.

Patients and Methods:

Data from 66 NSCLC patients receiving either: (*i*) Pemetrexed, vitamin supplementation therapy (folic acid and vitamin B_{12}) and dexamethasone, together with BIBF 1120, a novel potent triple angiokinase inhibitor (without neutropenic effects on its own) (*Study A, n=26*) or (*ii*) BI 2536, pemetrexed, vitamin supplementation therapy and dexamethasone (*Study B, n=40*) were included in the analysis.

In both studies patients received a 10 minutes infusion of pemetrexed every 21 days at doses of 500 mg/m^2 or 375 mg/m^2 and a concomitant therapy of twice daily dexamethasone (4 mg the day before,

the day of and the day after pemetrexed administration), daily folic acid (350-1000 mg) and vitamin B12 (1000 mg every 9 weeks). In *Study B* BI 2536 was given as an one hour infusion starting 30 minutes after the pemetrexed infusion. The BI 2536 doses ranged from 100 mg to 325 mg.

The analysis of the time course of the absolute neutrophil count (ANC) following the combination therapy was done sequentially using the population modelling approach in NONMEM VI.

The analyses were performed as follows:

(*i*) Development of the neutropenia model for pemetrexed with vitamin and dexamethasone treatment. Given the lack of model information regarding the neutropenic effects of pemetrexed in presence of vitamin supplementation and dexamethasone, the model was evaluated in detail by reproducing clinical haematological results from literature using simulations.

(*ii*) Simulations based on the developed model for BI 2536 and pemetrexed under the assumption of an additive neutropenic effect of the two compounds were conducted and the model based results were compared with raw data obtained from a recent clinical trial in which BI 2536 and pemetrexed were given in combination (*Study B*).

(*iii*) Finally a model building process was performed with the data from *Study B* to refine model parameters and to explore the significance of other types of interaction (antagonism/synergism) using the response surface analysis (Minto et al; 2002). During this modelling exercise the PRIOR subroutine in NONMEM was used allowing the estimation of the drug dependent parameters based on the estimates from the previous studies.

Results:

(*i*) The neutropenic effects of pemetrexed given together with vitamin supplementation and dexamethasone therapy were adequately described by an extension of Friberg's model in which the initial increase in ANC due to dexamethasone administration is considered (Ozawa et al; 2007). The slope parameter was estimated in 0.000121 mL/ng which represents a 50% reduction of the estimate reported for pemetrexed when no vitamin supplementation was given, and very similar to the one just recently reported for white population receiving vitamin supplementation (Latz et al; 2009)

The external validation using literature data showed that the percentages of patients showing neutropenia grade III or IV predicted from this model (30% and 15%) was similar to the ones reported by Takimoto et al, 2007 (32% and 18%, respectively).

(*ii*) Results showed a very good agreement between simulated and observed data from study B. For example for the first treatment cycle the model predicted 38% of patients experiencing grade IV neutropenia and an average nadir of 1.2. These values very close to the ones obtained from the clinical trial; 43% and 1.3 respectively.

(*iii*) The additive neutropenic effect of BI 2536 and pemetrexed was further supported by the analysis of the *Study B* data, in which a synergistic or antagonistic interaction was not supported by the observations. The estimates of the slope (mL/ng) parameters for both BI 2535 and pemetrexed using prior knowledge (0.0158, 0.000121) were similar to those obtained from the analysis from the single drug trials (0.0147, 0.000190).

Conclusions:

The neutropenic effects of the combination of BI 2536 and pemetrexed were adequately predicted assuming an additive interaction between the drugs, and based on information from previous single drug studies. The drug related parameters in this model are consistent between studies and independent of study type (single drug or combination therapy) suggesting a promising opportunity for predicting future trial outcomes.

References:

-Friberg LE, Henningsson A, Maas H, Nguyen L, Karlsson MO. Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. J.Clin.Oncol. 2002 Dec 15;20(24):4713-4721.
-Latz JE, Karlsson MO, Rusthoven JJ, Ghosh A, Johnson RD. A semimechanistic-physiologic population pharmacokinetic/pharmacodynamic model for neutropenia following pemetrexed therapy. Cancer Chemother.Pharmacol. 2006 Apr;57(4):412-426.
-Latz JE, Rusthoven JJ, Karlsson MO, Ghosh A, Johnson RD. Clinical application of a semimechanistic-physiologic population PK/PD model for neutropenia following pemetrexed therapy. Cancer Chemother.Pharmacol. 2006 Apr;57(4):427-435.
-Latz JE, Schneck KL, Nakagawa K, Miller MA, Takimoto CH. Population pharmacokinetic/pharmacodynamic analyses of pemetrexed and neutropenia: effect of vitamin supplementation and differences between Japanese and Western patients. Clin.Cancer Res. 2009 Jan 1;15(1):346-354.
-Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL. Response surface model for anesthetic drug interactions. Anesthesiology 2000 Jun;92(6):1603-1616
-Nigg EA. Polo-like kinases: positive regulators of cell division from start to finish. Curr. Opin. Cell Biol. 1998 Jul;10 (6):776-783.
-Sandstrom M, Lindman H, Nygren P, Lidbrink E, Bergh J, Karlsson MO. Model describing the relationship between pharmacokinetics and hematologic toxicity of the epirubicin-docetaxel regimen in breast cancer patients. J.Clin.Oncol. 2005 Jan 20;23(3):413-421.
-Sandstrom M, Lindman H, Nygren P, Johansson M, Bergh J, Karlsson MO. Population analysis of the pharmacokinetics and the haematological toxicity of the fluorouracil-epirubicin-cyclophosphamide regimen in breast cancer patients. Cancer Chemother.Pharmacol. 2006 Aug;58(2):143-156.
-Soto E, Staab A, Tillmann C, Trommeshauser D, Fritsch H, Munzert G and Trocóniz I. A semi-mechanistic population pharmacokinetic/pharmacodynamic model for neutropenia following therapy with the new PLK-1 inhibitor BI 2536 and its application in clinical, PAGE 17 (2008) Abstr 1282 [www.page-meeting.org/?abstract=1282].
-Ozawa K, Minami H, Sato H. Population pharmacokinetic and pharmacodynamic analysis for time courses of docetaxel-induced neutropenia in japonese cancer patients, Cancer Sci. 2007 Dec;98(12):1985-92.

Venkata Pavan Kumar Vajjah Novel graphical diagnostics for assessing fit of logistic regression models

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Background:

Assessment of goodness of fit of a model to the data set is essential to ensure the model provides a reasonable description of the events seen. In this setting graphical diagnostics, such as visual predictive checks, have an advantage over numerical criteria, such as minus twice the log-likelihood, for assessing model fit since the latter cannot determine whether the model accurately describes the data. For logistic regression a common graphical diagnostic used to assess model fit is binning the data and comparing the empirical probability of an event in each bin to the model predicted probability for the mean covariate value in the bin. Although intuitively appealing this method, termed simple binning, may not have useful properties for diagnosing model problems when the study design is unbalanced.

Objective:

To develop graphical diagnostics to assess the fit of logistic regression models.

Methods:

Study design: Three different types of study designs were considered. Design 1: Studies which were balanced on events (y-axis) and dose (x-axis covariate); Design 2: studies balanced on only events but unbalanced on dose. Design 3: Studies that are unbalanced on both events and dose.

Simulation: Each of the simulated data sets consisted of 500 subjects. The administered dose was the only covariate and could be 0, 1, 5, 10 and 20 units for design 1, and could be any integer from 0 to 20 for designs 2 and 3. The number of individuals per dose level was equal for design 1 and unequal in designs 2 and 3. The number of events was approximately 50% for designs 1 and 2 and approximately 10% in the case of design 3. The data were simulated with the dose being related to the outcome according to E_{max} model on the logit scale as shown in equation 1.

$$\ln(\pi/(1-\pi))=E_0+((E_{max}\times D)/(ED_{50}+D)) \quad \text{Equation 1}$$

In the equation E_0 and E_{max} are the baseline and maximum probability (π) of having an event and ED_{50} is the dose (D) at which probability of event is half E_{max}. The values of π (E_0), π (E_{max}) and EC_{50} were 0.2, 0.9 and 5 for designs 1 and 2 and 0.05, 0.85 and 5 for design 3. The coefficients of variation of the parameters for simulation were 15%. An E_{max} model was used as the model since in PKPD it is common that the probability of an event asymptotes below 1.0. Thirty data sets were simulated using

MATLAB. This number was chosen to provide a 90% chance that both an excellent case and worst case visual diagnostic would be seen.

Estimation: Estimation was performed in WinBUGS 1.4.3. All the data sets were estimated using the E_{max} model (correct model) and a linear model (wrong model) with dose as the only covariate and using a logistic transformation to the probability domain.

Diagnostics: We propose 2 diagnostics (1) random binning and (2) a simplified Bayes marginal model plot[1].

(1).The idea behind random binning is to generate a distribution of empirical probabilities at various dose levels. This is achieved by randomly binning the data set based on dose or number of individuals to produce 1000 different sets of bins. For each of these 1000 random sets of bins the empirical probabilities in each bin is estimated. The estimated empirical probabilities and model predictions are plotted to visually inspect the model fit.

(2) In the case of simplified Bayes marginal model plots, the hypothesis is that 'if the model describes data, then if we simulate 'n' observations, from the posterior distribution of model then the spline should be one of those observations'. The methodology follows. A linear spline was fitted to the data with up to a maximum of two estimated knots using WinBUGS 1.4.3. This was presumed the best empirical description of the data. The posterior distribution of the fits of the E_{max} and linear models were then compared to the spline and the level of visual agreement between them assessed. The above diagnostics are compared with simple binning.

Results and discussion:

For all designs the proposed diagnostics performed at least as well or better than simple binning. In case of design 1 where both the covariate and event space are balanced then random binning and simple (conventional) binning are the same and provide good diagnostic features. In the case of designs 2 and 3 random binning and simplified Bayes marginal model plots were superior in assessing the model fit when compared to simple binning. In the case of simple binning examples were seen where the wrong model was preferred and also where the correct model would have been completely discounted as an acceptable descriptor of the data. For the completely unbalanced scenario (design 3) there were cases where the simplified Bayes marginal model plots provided superior discriminatory ability to random binning. In all cases for design 3 random binning was superior to simple binning.The main limitation of simplified bayes marginal plots are that they require additional computation. The above diagnostics have been tested for fixed effects models but can be extended to mixed effects models.

Conclusion:

Simple binning fails to provide either the ability to consistently identify the correct model or the ability to identify model deficiencies when the study design is unbalanced. Random binning and the Bayes marginal model plots provid good visual assessment of model performance.

Reference:

[1]. Pardoe I, Cook D R. A Graphical Method for Assessing the Fit of a Logistic Regression Model; The American Statistician.2002, 56(4): 263-272.

Willem de Winter Integrating a Model for Weight Change into the Mechanism-Based Model for Type 2 Diabetes

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Background: Obesity and weight gain, caused by an imbalance between energy intake and energy expenditure, play a primary role in the development of type 2 diabetes mellitus. Excessive fat storage, especially intra-abdominally, causes loss of insulin sensitivity in liver, fat and muscle tissues. Initially, this reduced insulin sensitivity is compensated by increased insulin secretion, but in many patients the beta-cells cannot keep this up indefinitely, leading to elevated blood glucose and overt diabetes. Because of this close interplay between body weight regulation and the disease processes underlying type 2 diabetes, most antidiabetic agents also affect body weight and fat storage, either by increasing or reducing it. This may have important consequences for the long-term effects of a compound on disease progression and cardiovascular clinical outcomes.

Objectives: To develop a mechanism-based, integrated model of type 2 diabetes disease progression and body weight change that allows the estimation of the direct effects of antidiabetic treatment on glucose homeostasis and disease progression, as well as its indirect effects via body weight change.

Methods: The mechanism-based disease progression model for type diabetes [1] is integrated with an in-house developed turn-over model for body weight change based on the energy flux balance equation [2]. The models are implemented in NONMEM VI on phase III data comparing topiramate 96 and 192 mg to placebo in obese diabetic patients.

Results: The models provide adequate descriptions of the data. Because the patient population was typically early in the disease, the differential equation for HbA1c in original diabetes disease progression model [1] is modified to take account of the relatively larger contribution to HbA1c formation of post-prandial glucose excursions. An issue to be resolved were the different time-scales of the physiological processes represented in the model: changes in the glucose-insulin homeostasis take place in a matter of minutes, whereas changes in HbA1c and body weight occur over weeks or months. Therefore, in the original diabetes model [1], the differential equations for fasting plasma glucose and insulin are reduced to their steady-state solutions. The added value of integrating the weight change model into diabetes disease progression model is evaluated.

Conclusions: Type 2 diabetes mellitus is disorder not only of glucose homeostasis, but also of lipid metabolism and storage and as such tightly linked to body weight regulation. This is highlighted by the fact that cardiovascular disease is the primary cause of death among type 2 diabetics. In this light, the model presented here can be seen as a further step towards a full, comprehensive disease model of type 2 diabetes and its long-term clinical outcomes.

References:

[1] De Winter et al. (2006) A mechanism-based disease progression model for comparison of long-term effects of pioglitazone, metformin and gliclazide on disease processes underlying Type 2 Diabetes Mellitus. J. Pharmacokin Pharmacodyn, Vol. 33-3, pp. 313-343.

[2] E.g. Chow CC, Hall KD (2008) The Dynamics of Human Body Weight Change. PLoS Comput Biol 4(3): e1000045. doi:10.1371/journal.pcbi.1000045

William Denney Modeling and Simulation for Determination of the Therapeutic Window of MK-2295: a TRPV1 Antagonist

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Objectives: MK-2295 is a potent TRPV1 (transient receptor potential vanilloid subfamily, member 1; also known as VR1) antagonist currently in clinical development for chronic pain. The therapeutic window and the dose to maintain plasma concentrations within that therapeutic window were determined with the goal of determining a dosing regimen that would allow safe, efficacious administration.

Methods: Population pharmacokinetic (PK) and PK/pharmacodynamic (PK/PD) analyses were performed using NONMEM VI based on data from five clinical trials with approximately 182 subjects treated with drug and/or placebo. A 2-compartment PK model with covariates for age and gender was developed to describe the MK-2295 PK. A series of PK/PD models was developed which related MK-2295 concentration to markers of on-target and undesired activity: core body temperature (CBT, standard E_{max} with diurnal variation), capsaicin-induced dermal vasodilation (CIDV, competitive E_{max}), warmth sensation threshold (WS, standard E_{max}), and hot water bath hand withdrawal time (HWT, Weibull time to event with a standard E_{max} as the scale parameter).

Results: The EC_{50}s for CBT and CIDV, both markers for MK-2295 on-target activity, were 69.9 and 57.9 nM, respectively. The EC_{50}s for WS and HWT were 267 and 292 nM. While effects on HWT strongly suggest on-target activity, effects of MK-2295 on WS may reflect undesired activity. PK/PD simulation indicated that thermal sensitivity was highly correlated with other target engagement measures (CBT and CIDV) and thus it was impossible to identify a dosing regimen of MK-2295 that was predicted to be efficacious yet also devoid of risk for burn injury.

Conclusions: Modeling and simulation suggested that it is not possible to decouple the loss of temperature sensitivity from the on-target effects of MK-2295. Such modeling efforts can greatly inform decision making.

References:

[1] Van der Schueren J, et al. (2007a) MK-0974, an oral CGRP antagonist, inhibits capsaicin-induced vasodilation in the human skin. Basic Clin Pharmacol Toxicol 101 (Suppl 1): 33.
[2] Szallasi A, et al. (2007) The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. Nature Drug Discovery: 6.

Robert Kalicki Modeling of Red Blood Cell (RBC) Lifespan (LS) in a Hematologically Normal Population

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Objectives: Recently, Cohen et al[1] published an original work focusing on the effect of RBC LS heterogenicity on formation of glycosylated hemoglobin (HbA1c). An individual approach using a cubic fit was performed to describe the decay of biotin-labelled RBC over time. The aim of this work was to reanalyse the data using a more physiological model, based on a finite RBC LS and random destruction rate (RDR)[2], and taking into account the IIV as a basis for the development of future models which will be applied in the HbA1c modelling area.

Methods: Biotin-labelled RBC survival–Time profiles from 6 diabetic and 6 non-diabetic subjects1 were first digitalized using two different softwares (TechDig and xyExtract Graph Digitalizer). For each time record the average of both digitalized values was taken providing a satisfactory precision (mean SD of 0.4% units). Different models taking into account the finite RBC LS with or without a random destruction rate were fitted to the data using NONMEM VI: (i)zero-order decay; (ii)combined zero-first order decay; (iii)transit compartment model; (iv)transit compartment model with RDR. The RDR-Time profile was further investigated. Both estimates of LS and RDR, as well as the optimal number of transit compartments (NCOMP), were evaluated. The slope-intercept residual error was used.

Results: Overall, transit compartment models showed a better performance compared to zero and zero-first order decay models. The addition of an overtime linearly increasing RDR did considerably further improve the fit. The mapping of the NCOMP and OFVs values permitted to determine the optimal NCOMP for the simple transit compartment model (NCOMP=12, OFV=345.6, LS=91.8 d). Whereas for the extended model with RDR, the optimal NCOMP could not be established because of an intrinsic NONMEM limitation in the NCOMP (NCOMP=29, OFV=272.3, LS=103, RDR=0.209%/d). However, the mapping of the OFV showed an asymptotic profile with insignificant gain when increasing the NCOMP. No significant difference of estimated parameters could be found between diabetic and non-diabetic subjects.

Conclusions: Our preliminary work confirms the presence of both mechanisms (lifespan and RDR) responsible for the natural elimination of RBC. The implementation of the transit compartment model using the maximum allowed number of compartments with RDR linearly increasing over time showed to be superior and needs to be considered in future.

References:
[1] Cohen RM, Franco RS, Khera PK et al. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. Blood. 2008; 112(10): 4284-4291.

[2] Berlin N.I., Waldmann T.A., Weissman S.M. Lifespan of Red Blood Cell. Vol. 39. Metabolism Service, General Medicine Branch, National Cancer Institute, Bethesda, Maryland.

Ron Keizer Modeling of hypertension in response to anti-angiogenic therapy

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Objectives: Hypertension is a common toxicity for anti-angiogenic drugs targeting the VEGF pathway, such as tyrosine kinase inhibitors (e.g. sorafenib [1]) and monoclonal antibodies (bevacizumab [2]). In most cases, hypertension can be controlled by dose reductions, dose delays, or prescription of antihypertensive therapy. Our aim was to construct a general pharmacokinetic-pharmacodynamic (PK-PD) model for hypertension toxicity following treatment with anti-angiogenic agents. This model may guide clinical interventions and provide treatment recommendations for this compound and other drugs in this class.

The novel multiple tyrosine kinases inhibitor E7080 has shown anti-tumor activity in preclinical testing [3,4] and phase I clinical trials. [5-7] Although generally well tolerated in phase I clinical studies, commonly observed toxicities with E7080 were hypertension and proteinurea. From data collected in these phase I trials a PK-PD model was developed describing the increase in BP in response to exposure with the drug. Using simulations, we evaluated several intervention options for management of hypertension toxicity.

Methods: Plasma concentration and blood pressure (systolic: BP_{sys}, diastolic: BP_{dia}) data were obtained from 67 patients enrolled in a two-center phase I study, investigating qd dosing of E7080 at increasing dose levels. BP data were recorded weekly, over a mean period of 21 weeks (range 1-77 weeks). PK and BP data were modeled sequentially with NONMEM software, using the FOCE-I method. The PK model was developed previously, and consisted of a two-compartment model, combined zero- and first-order absorption, and linear elimination. Several models for BP, baseline BP, and drug effect on BP were evaluated including effect-compartment models and indirect effect models or combined effects. [8] Prescription of anti-hypertensive (AH) medication was accounted for in the model as a negative effect on BP using ‘defined daily dose equivalents' (DDDE), i.e. the ratio of daily dose/defined daily dose, cumulative over all AH medications. Model fits were evaluated using the likelihood ratio test, individual plots and visual predictive checks.

Using the final model and parameter estimates, several simulation studies were performed evaluating interventions for management of hypertension. Simulations were performed for 500 patients. To be able to estimate precision, this was repeated 500 times with parameter sets drawn from the full covariance matrix obtained for the final model. In the simulation studies, efforts were made to mimic the clinical protocol as best as possible: when presented with hypertension in the clinic, the BP measurements were repeated at least 2 times during the next hour(s). This was implemented in the intervention model used in the simulations by averaging multiple drawn observations on each occasion when hypertension occurred, assuming that 50% of the variation in BP was due to inter-day variability and 50% to inter-measurement variability.

Results: The final BP model consisted of two separate indirect-effect models for BP_{sys} and BP_{dia}. Baseline BP_{sys} and BP_{dia} were estimated at 126 and 77 mmHg (RSE <5%) respectively, with 10% (RSE 12%) inter-individual variability (IIV) for both BP_{sys} and BP_{dia}, and 70% (RSE 15%) correlation between systolic and diastolic baseline. Input rate for the indirect effect model was 0.35 $mmHg.hours^{-1}$ (RSE 20%) for both BP_{sys} and BP_{dia}. The effect of E7080 plasma concentration on the input rate of the indirect effect PD model was 0.497 (RSE 21%) and 0.88 (RSE 13%) ng^{-1}.ml for BP_{sys} and BP_{dia} respectively, leading to an approximate similar absolute effect size (in mmHg). IIV on drug effect was estimated at 72% (RSE 40%) for BP_{sys} and 26% (RSE 50%) for BP_{dia} input rates, with a correlation of 42% (RSE 62%) between them. The effect of AH medication on BP input rates could not be estimated separately for BP_{sys} and BP_{dia}, and was 0.036 per DDDE for both. The overall exponential residual error in BP was 12.9% (RSE 3 %), with 53% (RSE 3%) correlation between systolic/diastolic errors.

Simulations showed that continuous dosing of E7080 at the maximum tolerable dose (MTD) of 25 mg qd without AH medication, would result in an increase of 16.2 / 17.7 mmHg (systolic/diastolic, RSE 20%) for a typical patient, with half of the increase attained within 2.5 weeks. At this dose level, dose limiting hypertension (defined as an increase of ≥20 mmHg in BP_{dia}, corresponding to CTC grade ≥2) would be expected in 56.7% (RSE 15.2%) of the patients. In patients that developed hypertension, BP_{dia} could be reduced by a median 2.6 mmHg (RSE 84%) after 12 weeks of treatment with AH medication at 1 DDDE. Intensification of AH therapy to 2 DDDE when hypertension could not be controlled sufficiently, could reduce BP_{dia} by 4.8 mmHg (RSE 39%). This resulted in 63.7% and 68.8% (RSE 13%) of patients respectively being able to continue treatment with E7080. The effect of a dose reduction to 50% of the MTD (12.5 mg/day) resulted in a median decrease of 7.0 mmHg (RSE 29.3%), resulting in 82.1% (RSE 7%) of patients being able to continue treatment.

Conclusions: A PK-PD model was developed that was able to capture the effect of daily treatment with E7080 on BP, which showed a clear exposure-response relation. We were able to account for the use of anti-hypertensive medication in the model. Using simulations we evaluated several interventions for management of hypertension toxicity. Data from upcoming studies with different regimens, will aid in defining the relationship between exposure and hypertension and the effects of AH therapy in more detail. Incorporation of a model to describe proteinurea toxicity is currently ongoing, which may allow further treatment optimization. The current model will aid in further clinical development of E7080, and can serve as a template model for analyzing hypertension toxicity in treatment with this class of drugs.

References:

[1] D.A. Sica, "Angiogenesis inhibitors and hypertension: an emerging issue," *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, vol. 24, Mar. 2006, pp. 1329-31.
[2] M.A. Cobleigh et al., "A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer," *Seminars in oncology*, vol. 30, Oct. 2003, pp. 117-24.
[3] J. Matsui, et al., "E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition," *International journal of cancer. Journal international du cancer*, vol. 122, Feb. 2008, pp. 664-71.
[4] J. Matsui et al., "Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase," *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, vol. 14, Sep. 2008, pp. 5459-65.
[5] K. Yamada et al., "Phase I dose escalation study and biomarker analysis of E7080 in patients with

advanced solid tumors," *J Clin Oncol*, vol. 26, May. 2008.
[6] J. Nemunaitis et al., "Phase I dose-escalation study of E7080, a multikinase inhibitor, in patients with advanced solid tumors," *J Clin Oncol*, vol. 26, May. 2008.
[7] H. Glen et al., "A phase I dose finding study of E7080 in patients (pts) with advanced malignancies," *J Clin Oncol (Meeting Abstracts)*, vol. 25, Jun. 2007, p. 14073.
[8] N.L. Dayneka, V. Garg, and W.J. Jusko, "Comparison of four basic models of indirect pharmacodynamic responses," *Journal of pharmacokinetics and biopharmaceutics*, vol. 21, Aug. 1993, pp. 457-78.

Fran Stringer Genotyped versus phenotyped dosing to account for UGT polymorphism of the novel PPAR agonist sipoglitazar

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Objectives: Sipoglitazar, a novel orally available PPAR agonist with activities for PPAR α, δ and γ is metabolised through UGT. A polymorphism of the UGT enzyme was observed to result in a wide distribution of clearance for the same dose. The compound has a narrow therapeutic window therefore limiting exposure. The relative merits of prospective initial dose selection by genotype assignment *versus* retrospective dose selection by a TDM approach were assessed by population analysis of Phase I and II data.

Methods: A population PK model was developed using 3 small Phase I studies. The model was first used to predict the exposure in an additional large Phase I trial in 524 patients to characterise the genotype distribution. External model validation was performed using two Phase II trials with trough sample collection. The model was implemented in NONMEM and the distribution of the exposure resulting from the genotype was explored using the $MIX routine to evaluate the proportion in each genotype.

Results: The model developed using the 3 smaller Phase I trials was not able to accurately predict the exposure distribution of the genotype in the larger Phase I study. Therefore, the model was updated using the latter data and validation was confirmed using the 2 Phase II studies. The 3 small Phase I studies were shown to underpredict the variability associated with the clearance of the 3 different genotypes through the validation provided by the larger study. Updating the model by combining the Phase I studies resulted in a more accurate prediction of the genotype distribution in the Phase II data.

Conclusion: Use of a genotype approach was considered as a viable method to dose selection. However, population PK analysis showed this approach would result in over exposure in the poor metaboliser (PM) patients. Exploration of a TDM approach through simulation indicated that a smaller number of PM would be over exposed. These results become critical and rate limiting when considering the correct dosing approach for the PM group. Modeling and simulation has demonstrated that following a genotype approach from a small population in this case was not able to accurately predict with sufficient precision the exact distribution of the clearance associated with PM group. This could have resulted in the over exposure of PM patients and resulted in a potential safety risk.

David Ternant Model-based optimization of rituximab dosing regimen in follicular non-Hogdkin lymphoma

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Objectives: Rituximab has dramatically improved the survival of patients with non-Hodgkin lymphomas (NHL) but currently used dosing regimen should be optimised. However, the concentration-effect relationship of rituximab has never been described by pharmacokinetic-pharmacodynamic (PK-PD) modeling, precluding the use of simulation to test new dosing regimens. The aims of this study were to:

- develop a PK-PD simulation model of rituximab in follicular NHL (FL);
- quantify the benefit of new dosing strategies of rituximab in FL patients for rituximab monotherapy and R-CHOP treatments;
- design clinical trials where the optimal dosage for rituximab would be investigated.

Methods: A model describing the relationship between rituximab concentrations and progression-free survival (PFS) was developed using data extracted from the pivotal study, which evaluated 151 relapsed/resistant FL patients. The influence of *FCGR3A* genetic polymorphism onthe efficacy of rituximab in FL, which was quantified using data from 87 relapsed/resistant FL patients [1,2]. The predictive performance of the model was analysed using two independent data sets: a study which evaluated rituximab combined with chemotherapy (R-CHOP) in 334 relapsed/resistant FL patients [3] and a study which evaluated rituximab monotherapy in 47 asymptomatic FL patients with known *FCGR3A* genotype [4]. Several dosage strategies, including rituximab maintenance, were tested for rituximab monotherapy and R-CHOP. The benefit of a rituximab dose adjustment according to *FCGR3A* was investigated.

Results: For R-CHOP, observed and model-predicted PFS at 24 months were 0.50 and 0.48, respectively for the observation arm, and 0.62 and 0.59, respectively for the rituximab maintenance arm [3]; for rituximab monotherapy, observed and predicted PFS at 24 months were 0.67 and 0.63, respectively for *FCGR3A*-V/V patients, and 0.41 and 0.36, respectively for *FCGR3A*-F carriers [4]. The optimal dosage was 1500 mg/m2 in cure period and 2250 mg/m2 for maintenance. Because of a high difference in PFS between VV patients and F carriers, a dosage adjustement for rituximab according to the *FCGR3A* genotype is not feasible.

Conclusions: Our model provides a satisfactory prediction of PFS at 24 months. The results support the benefit of a dose increase of rituximab in FL, which should be confirmed in controlled clinical trials. In these trials, 230 to 470 patients should be included.

References:

[1] Berinstein NL et al. Ann Oncol, 1998
[2] McLaughlin P et al. J Clin Oncol, 1998
[3] van Oers et al. Blood, 2006
[4] Cartron et al. Blood, 2002

Vladimir Vainstein Targeted drug delivery by gemtuzumab ozogamicin: mechanism-based pharmacokinetic model for treatment strategy improvement and prediction of individual responses.

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Objectives: In this work, we present the analysis of a general mechanism-based PK model for a conjugated mAb-based drug using experimental and clinical data of Gemtuzumab Ozogamicin (GO) interactions with leukemic blasts. GO is a anti-CD33 monoclonal antibody conjugated to chemotherapeutic agent calicheamicin. The main objectives of the study were, firstly, to evaluate individual parameter values of blast-drug interactions in AML patients and determination of their relative significance for the response to treatment, and, secondly, to propose optimized strategies of GO combined with other cytoreductive chemotherapeutics for future clinical trials.

Methods: We implemented a general mechanism-based PK model of monoclonal antibody-target cell population interaction to the data from relapsed AML patients who participated in phase II clinical trials of GO monotherapy [1,2,3]. All computer simulations were run on a PC computer with Matlab 7.0 software. Peripheral blood was drawn at 0, 3 and 6 hour points after initiation of a 2-hour intravenous infusion of GO at a dose of 9 mg/m^2. Additionally, AML193 cells were incubated in vitro with various GO doses for 15, 60, 180 and 360 minutes. Patients' blasts and AML193 cells were examined by flow cytometry to determine numbers of free and GO-bound CD33 molecules on the cell surface. Efflux of GO from leukemic blast cells was previously estimated using dye efflux essay [3]. The resultant data were used for estimation of the PK model parameters in the population individual patients. The model allowed for estimation of the intracellular drug content, as a surrogate for drug efficacy. Different GO treatment schedules were then simulated.

Results: In vitro data on AML193 cells enabled determination of CD33-GO association and dissociation rates. Forty seven of 276 patients who participated in the GO clinical trial had both data on drug efflux and CD33 saturation and therefore could be analyzed by the model to determine parameters of CD33 production and internalization rates of free and bound CD33. The model can successfully retrieve the differences in blood concentration profiles of GO in the leukemic patients during the first versus the second infusions as well as to estimate non-invasively the leukemic blast burden. Parameter sensitivity analysis show that low blast burden, intermediate CD33 antigen production rate, and low drug efflux are key characteristics that determine high intracellular GO exposure according to model calculations, all other parameters being much less influential. Moreover, even a modest blast burden reduction may significantly increase intracellular GO exposure and allow reduction in the dose of GO.

EORTC-GIMEMA AML-19 Trial (published at 2008 ASH meeting) showed that the reduced GO dose (6 mg/m2) is effective, as well as administration at days 1 and 7 is more efficacious than at days 1, 3 and 5. These results match fully our model simulations, constituting additional line of its validation.

Conclusions: Our results suggest that GO efficacy could be enhanced when used after the leukemic tumor burden was lowered, e.g by alternative cytoreductive agents. Furthermore, the presented model proposes optimization of GO administration schedule as verified in an independent clinical trial. Additionally, we suggest that estimation of CD33 production and drug efflux in blasts of individual AML patients can better define the population with the most susceptible disease.

References:

[1] van Der Velden *et al.* Targeting of the CD33-calicheamicin immunoconjugate Mylotarg (CMA-676) in acute myeloid leukemia: in vivo and in vitro saturation and internalization by leukemic and normal myeloid cells. Blood 2001;97:3197-204

[2] van der Velden *et al.* High CD33-antigen loads in peripheral blood limit the efficacy of gemtuzumab ozogamicin (Mylotarg) treatment in acute myeloid leukemia patients. Leukemia 2004;18:983-8

[3] Walter, R.B. *et al.* CD33 expression and P-glycoprotein-mediated drug efflux inversely correlate and predict clinical outcome in patients with acute myeloid leukemia treated with gemtuzumab ozogamicin monotherapy. Blood 2007;109:4168-70.

Nathalie Gobeau Comparison of different tools for the optimization of a pediatric clinical trial

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Objective: compare the features, ease of use and results of three publicly available pieces of software (PFIM version 3.0 (1), POPT version 3.0 (2) and PopED version 2.08 (3)) for optimizing a pediatric clinical trial.

Methods: A pediatric clinical trial is planned primarily to characterize the steady-state pharmacokinetics (PK) of a drug under development in children aged 1 month to 16 years old. The design is a fixed 3-step dose up-titration study. Three different tools (PFIM, POPT and PopED) were employed to optimize the sampling times in order to limit the number of samples. The optimization was undertaken based on the assumption that the PK in children was described by a population PK model previously developed in adults, scaled by weight. Due to the different features of the optimization tools, the problem was set up differently to take into account the varying PK parameters with age/weight: optimization per weight category in PFIM; optimization per age category in POPT with 3 competing models between a population with respectively minimum, median and maximum weight; optimization per age category in POPED assuming a uniform weight distribution. The performance of the designs obtained were compared with a 21 samples design initially proposed by the clinicians via simulations as described in Hooker et al. (4).

Results: The number of sampling times could be reduced from 21 to 6 per patient with a total number of patients of 48 without compromising the estimation of the PK parameters. The optimized times designs obtained with the different optimization tools were similar; the main differences between the tools were found to be the implementation of the problem. The performance of the optimized design via simulations, expressed in terms of Relative Mean Square Error (4), was found to be acceptable compared to the one obtained with the rich sampling design.

Conclusions: The optimization software tools tested were found to be useful in helping reduce the number of samples in a pedicatric clinical trial. The main difference between the tools was the implementation of the problem. As for non-linear models in general, the search of optimal designs require appropriate prior knowledge of the PK parameters to make the optimal designs valuable. For that very reason, the pediatric PK model is being refined using parameters estimated using a Physiologically-Based PharmacoKinetic (PBPK) model.

References:
[1] http://www.pfim.biostat.fr/
[2] http://www.winpopt.com/
[3] http://poped.sourceforge.net/
[4] Hooker, A. C., Foracchia, M., Dodds, M. G., and Vicini, P., "An evaluation of population D-optimal designs via pharmacokinetic simulations," Ann Biomed Eng, Vol. 31, No. 1, 2003, pp. 98-111.

Joakim Nyberg Population optimal experimental design for discrete type data

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Objectives: Models with discrete type data are increasingly used in the field of drug development, especially to model pharmacodynamics.

To increase the efficiency in various stages in drug development, optimal experimental design has been used [1]. This approach is built upon the Cramer-Rao inequality that states that the inverse of the Fisher Information Matrix (FIM) is a lower bound of the uncertainty of the parameters in a model, given a specific design. Optimal design has extensively been used to optimize different type of continuous repeated measurements with mixed effect models but little research has been done on optimizing mixed effect models with repeated discrete type data. Nestorov et al [2] did optimize over a categorical model but without random effects and Ogungbenro et al [3] presented a method for calculating the sample size and power with random effects models but dependent on the distribution of the data.

The aim of this investigation is to develop and investigate methods for optimizing mixed effects models with discrete type data independent on the underlying data distribution using the Laplace approximation and Monte Carlo techniques using the optimal design software PopED [4,5].

Methods: Two models were used in this exercise. A dichotomous model with the probability of having response that was dependent on the dose, e.g. a high dose increased the probability of having a response. Inter individual variance was assigned to the parameter in an additive way with a variance of 0.1. This variance gives rise to ~25% difference in the probability for the response/non-response for 95% of the individuals with a low dose. The design contained 50 individuals with 30 observations each. However the 30 observations were split into 3 doses with 10 observations each. One dose (10 obs.) was fixed to a placebo dose and the other two doses were optimized between 0-1 units.

The second model that was investigated was a count model with a dose effect on the variance of the Poisson distribution. The Poisson variance was dependent of a baseline parameter with a random effect, a $Dose_{50}$ parameter and the dose. The baseline had an exponential random effect with a CV of ~32%. The design had 20 individuals with 90 observations each, again split into 3 dose levels (30 obs/dose) and 30 observations were fixed to a placebo dose. Similar to the dichotomous model the remaining two doses were optimized between 0-1 units.

To calculate the Fisher information matrix (FIM) for these types of models, two different approaches were considered: 1) Approximate the likelihood with the Laplace approximation or 2) calculate the exact likelihood with Monte Carlo (MC) integration techniques. Calculating the likelihood enables computing of an observed FIM, i.e. a FIM dependent on a certain set of data. Further the expectation of the observed FIM is calculated with Monte Carlo integration over all data. To be able to have stable numerical derivatives and stable design optimization the sampling technique reused the samples from

the first iteration (similar to the technique presented in Kuhn and Lavielle [6]). The code performing the FIM calculation was implemented in PopED as a penalty function and the random search and line search (with default settings) in PopED was used for the design optimization. The optimization criteria used was D-optimal (optimizing the determinant of FIM). Latin Hypercube (LH) sampling was used in the MC calculation of the likelihood to speed up and stabilize the likelihood calculation. The number of LH samples differed between the different models but was between 40-200 individual samples. The FIM was calculated both using the expectation of the gradient product of the first derivative of the ln likelihood with respect to the parameters as well as the expectation of the negative 2nd order derivative of the ln likelihood with respect to the parameters.

NONMEM [7] was used to investigate the uncertainty (covariance) by stochastic simulation and re-estimation (SSE). This was done by doing 1000 SSE and calculating the uncertainty from the parameter estimates. Numerous investigations of different observed FIM, calculated with NONMEM and the MATRIX=R option, was compared to the observed FIM with the same data calculated by PopED with either Laplace or MC.

Results: The likelihood approximation and calculation with 1) and 2) were successfully implemented and further the observed FIM and the FIM was computed. Slight differences between the exact likelihood and the Laplace approximation were observed. As an example; the -2 ln likelihood for a specific data set with the dichotomous model: 1631.912 (NONMEM), 1631.912 (PopED Laplace) and 1631.877 (PopED MC with 100 000 samples).

The observed FIM for both models showed similar results with NONMEM's R-matrix compared to the Laplace approximated observed FIM and the MC integrated observed FIM calculated with PopED. Further the FIM calculated with Laplace and MC was similar to the covariance calculated with NONMEM. However, a lower bound was observed, e.g. the sum of CV(%) for the parameters in the dichotomous model: 83.8% (NONMEM SSE), 80.3% (PopED Laplace) and 80.5% (PopED MC).

The D-optimal design (PopED Laplace) for the dichotomous model was found to have 10 more observations for the placebo dose than the original design and the last 10 observations were placed at 0.50 units. This gave a determinant of the FIM = 5.91E+05. The D-optimal design for PopED MC had also 10 observations at the Placebo dose but the last 10 observations were placed at 0.44 units with a determinant of the FIM = 6.00E+05.

The D-optimal design for the count data model was estimated to two high doses of 1 unit with both PopED Laplace and PopED MC. The determinant of the optimal design was |FIM|= 5.4E+07 and 6.0E+07 for Laplace PopED and Laplace MC respectively.

Calculation of the FIM with either first derivative of the likelihood with respect to the parameters or the 2nd order approach showed similar results but was dependent of the number of samples used to calculate the expectation of FIM over data.

Conclusions: A method for calculating optimal designs for discrete data mixed effects models was implemented. This method could be used for any type of model with a user specified likelihood that need a high order approximation to the likelihood (2nd order or exact).

The Laplace approximated likelihood showed similar results as the MC integrated likelihood. However, the optimal design differed for the dichotomous model between the Laplace approximation and the MC

method. This difference was due to the approximation of the likelihood which indicates that the method of calculating the likelihood might be important.

The predicted covariances from the method also seemed to agree well with the covariances obtained with simulation and estimation. The largest difference was seen in the expected uncertainty of the random effect. The difference was very minor (a few CV(%)) and is expected because the Cramer-Rao inequality is a lower bound of the imprecision.

References:

[1]. Mentré, F., A. Mallet, and D. Baccar, *Optimal design in random-effects regression models.* Biometrika, 1997. **84**(2): p. 429-442.

[2]. Nestorov, I., Graham, G., Duffull, S., Aarons, L., Fuseau, E., Coates, P. (2001). *Modeling and stimulation for clinical trial design involving a categorical response: A phase II case study with naratriptan.* Pharm. Res. 2001 **18**(8): p. 1210-1219.

[3]. Ogungbenro K. and L. Aarons. *Sample Size Calculations for Population Pharmacodynamic Experiments Involving Repeated Dichotomous Observations*. J. Biopharm. Stat. 2008. **18**(6): p. 1212-1227.

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

[5]. PopED, version 2.08 (2008). http://poped.sf.net/.

[6]. E. Kuhn, M. Lavielle. *Maximum likelihood estimation in nonlinear mixed effects models.* Comput. Statist. Data Anal. 2005. **39**(2): p. 187-201.

[7]. NONMEM Users Guides, (1989-2006). Beal, S.L., Sheiner L.B., Boeckmann, A.J. (Eds.) Icon Development Solutions, Ellicott City, Maryland, USA.

Robert Bauer Improvements and New Estimation Methods in NONMEM 7 for PK/PD Population Analysis

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Objective: To demonstrate NONMEM 7's improvements and additional estimation methods for population analysis

Methods: The NONMEM 7 software has been significantly upgraded to meet the demands of population PK/PD modeling needs. The classical NONMEM algorithm first order conditional estimation method (FOCE) has been improved by reducing the occurrence of computational errors that result in abnormal termination, and allowing users to specify gradient precision, which improves the efficiency of optimization and increases the incidence of successful completion of the problem. In addition, exact likelihood Monte Carlo algorithms for non-linear mixed effects optimizations have been incorporated, such as importance sampling expectation maximization (EM) [1], and Markov chain Monte Carlo (MCMC) stochastic approximation EM (SAEM) [2]. A three hierarchical stage MCMC Bayesian method using Gibbs and Metropolis-Hastings algorithms is also available [3,4]. All set-up parameters for these new methods may be specified in the standard NMTRAN control stream file format. NONMEM 7 has the ability to handle more data file items, longer labels, and initial parameters may be expressed in any numerical format. Output files that are readily transferred to post-processing software are also produced, and the number of significant digits reported may be specified by the user. Diagnostic results such as inter-subject and residual variance shrinkage, conditional weighted residuals, Monte Carlo assessed exact weighted residuals, and normalized probability distribution errors [2], are also outputted. The source code has been upgraded from Fortran 77 to Fortran 95, and the internal precision of all variables involved in computation have been increased to 15 significant digits (double precision). Error handling of multiple problem runs have been improved to allow continuation despite abnormal termination of a given problem, and there is interactive control of NONMEM 7 batch processes.

Results: Three examples of simulated data sets were created to test NONMEM 7's EM and Bayesian algorithms. The first example consisted of a simple two compartment PK problem with few data points per subject. The second example was a two compartment first-order and receptor-mediated clearance PK and indirect response PD model, with 46 population parameters, variances/covariances, and intra-subject error coefficients to be estimated, requiring numerical integration of three mass transfer differential equations. NONMEM 7 population parameter estimates from these data were very similar to the expected values. In the third example, estimation performance of the Monte Carlo EM methods were compared to that of the FOCE method using data simulated for a two compartment model with first-order input from the depot compartment into the central compartment and zero-order input directly into the central compartment. Between subject variability was estimated for all parameters including the rate or duration of the zero-order input. Out of 100 replicate data sets, none of the FOCE analyses resulted in successful completion of both the estimation and covariance steps. For the Monte Carlo EM methods, successful completion of both steps occurred for 88% or more of the problems. Comparison

of objective function values indicated that FOCE generally failed to achieve the minimum value based on comparisons with the EM methods.

Conclusions: The additional analysis methods, and expanded format of control stream input files and output files in NONMEM 7 provide users with a flexible, powerful, and accurate tool for population analysis of PK/PD models.

References:

[1] Bauer, RJ. *Technical Guide on the Population Analysis Methods in the S-ADAPT Program*, Appendix H, Version 1.56.
[2] Lavielle, M. *Monolix Users Manual* [computer program]. Version 2.4. Orsay, France: Laboratoire de Mathematiques, U. Paris-Sud; 2008.
[3] Benet, Racine-Poone, and Wakefield. MCMC for non linear hierarchical models. In: Markov Chain Monte Carlo in Practice. W.R. Gilks et al., Chapman & Hall (1996), chapter 19, pp 341-342.
[4]Gilks, Richardson and Spiegelhalter. Introducing Markov chain Monte Carlo. In: Markov Chain Monte Carlo in Practice. W.R. Gilks et al., Chapman & Hall (1996), chapter 1, pp 5-8.

julie bertrand Model-based tests to detect gene effect in pharmacokinetic studies

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Introduction

Pharmacogenetics studies the relationship between the interindividual variability and variations in DNA sequence of proteins involved in mechanisms of drug absorption, distribution, elimination and effect [1]. Indeed, single nucleotide polymorphisms (SNPs) can change the amino acid sequence of proteins or else alter gene splicing, transcription factor binding, or the sequence of non-coding RNA. Pharmacogenetic information is more and more considered during the development process and the clinical use of a drug to realize the concept of personalized medicine. In this work we consider a biallelic SNP which leads to three possible genotypes all the more unbalanced when the mutant allele is rare.

In pharmacogenetic studies, concentrations data are mainly analysed using non-compartmental methods followed by a one-way analysis of variance (ANOVA) on the individual parameters of interest. More sophisticated approaches based on NonLinear Mixed Effects Models (NLMEM) have also sometimes been used with various approaches to test pharmacogenetic information. Preliminary screening is usually performed using ANOVA on the individual parameters estimates [2] followed by a stepwise model building approach with the likelihood ratio test (LRT) [3]. As an alternative approach, a global Wald test can assess whether estimates for the genetic effect are significant [4].

As in NLMEM the integral in the likelihood has no analytical form, specific algorithms are needed to estimate the model parameters and their standard error (SE). The two most widely used methods, first order (FO) and first order conditional estimation with interaction (FOCE-I), linearize the model function and are implemented in the NONMEM software [5]. The more recent stochastic EM algorithm (SAEM) avoids the linearisation step and is implemented in the MONOLIX software [6].

Aims

The aim of our work was to evaluate by simulation the three tests described above, ANOVA, LRT and Wald, in terms of type I error and power. We studied different estimation algorithms, we proposed type I error correction by means of permutation and we further investigated the impact of the design on the performances of these tests. We applied our conclusions to investigate the influence of SNPs on indinavir pharmacokinetics in HIV patients from the COPHAR2-ANRS 111 trial [7] and on concentrations of a drug under development (drug X) and its active metabolite.

Simulation study

a) Simulation settings

The concentrations were simulated using a one compartment model at steady state with first order absorption (k_a), first order elimination (k), a diagonal matrix for the random effects and a proportional error model [8]. The model and parameters used for simulation came from a preliminary analysis without covariates of the indinavir concentration data from the COPHAR2-ANRS 111 trial. The genetic framework was inspired from the ABCB1 gene coding for the P glycoprotein found on the main physiological barriers. We simulated a diplotype of SNP_1 (C and T the wild and mutant allele, respectively) and SNP_2 affecting the drug bioavailability through the volume of distribution (V/F) The diplotype distribution mimicked that of exon 26 and exon 21 of the ABCB1 gene yielding for SNP_1 unbalanced frequencies of 24%, 48% and 28% respectively for CC, CT and TT genotypes.

b) Influence of the estimation algorithm

Under the null hypothesis of no gene effect (H_0), 1000 data sets were simulated with a design of N=40 patients and n=4 samples (inspired from the COPHAR2-ANRS 111 trial) and 1000 with the same sampling pattern but N=200 patients. Under the alternative hypothesis with a gene effect (H_1), we simulated 1000 data sets with the N=40/n=4 design. Each of the three tests was applied to detect the effect of the SNP_1 polymorphism. The type I error and the power of the tests were evaluated using FO, and FOCE-I implemented in NONMEM version V and SAEM implemented in MONOLIX version 2.1.

FOCE encountered many more convergence problems than FO whereas SAEM achieved convergence on all data sets. The ANOVA maintained a type I error close to the nominal level for both designs with all algorithms. The Wald test and the LRT obtained slightly inflated type I error on the N=40/n=4 design with both SAEM and FOCE-I. This inflation was corrected on the design N=200/n=4 for both tests with SAEM while only for the LRT with FOCE-I. The linearisation in the FO algorithm led to very poor performances of both the Wald test and the LRT.

c) Type I error correction

To correct type I error inflation of the Wald test and the LRT when N is small (40) we compared the approach by means of simulations and its non parametric alternative, the permutation test. We analyzed 200 data sets under H_0 and 200 data sets under H_1 for the design N=40/n=4. On the 200 data sets, the type I error and the power are estimated first using the theoretical threshold and then applying a threshold obtained from simulations or permutations. We used SAEM and FO but not FOCE-I to limit computing times and numerical difficulties.

Both correction approaches provided a type I error close to the nominal level with FO or SAEM. However, the corrected power for the Wald test and the LRT were much lower using FO than with SAEM. Indeed, we observed with FO a high correlation between the estimation errors of the parameter of the gene effect and their estimates, this relationship led to decreased values of the Wald statistic and therefore reduced the power to detect a genetic polymorphism effect. This pattern was not observed using SAEM. Permutations of the genotypes vector could not overcome limitations of the estimation method.

d) Influence of the design

In 2007, the EMEA has stated that pharmacogenetic studies should include a satisfactory number of patients of each geno- or phenotype in order to obtain valid correlation data [9]. Therefore, in a third

step, we considered two other designs with a larger number of subjects but different blood sampling strategies as four sampling on each patient would no longer be practical. A design optimized using the PFIM software [10], N=80/n=2 sorted in four groups and a combined design, N=20/n=4 plus N=80 with only a trough concentration. These two designs involved the same total number of observations as the original design with 40 patients, to allow proper comparisons between designs [11]. In front of the results obtained previously, the estimation was performed only with the SAEM algorithm.

ANOVA kept a correct type I error estimate but its power was lowered when there was high shrinkage (N=100/n=4,1). The Wald test and the LRT had significantly increased type I error in the two designs. Yet, the inflation remained moderate as all the type I errors were below 10%. The design N=80/n=2 provided the best performances; as it had both the lowest estimation errors on the gene effect coefficients and the highest power among the three designs with a total of 160 observations.

Applications

a) Influence of five SNPs on indinavir pharmacokinetics in the COPHAR2-ANRS 111 trial

We analysed the concentrations of forty patients collected after two weeks of treatment at 1, 3, 6 and 12 hours following administration. For each patient, genotypes are obtained for ABCB1 exon 26 and 21, *CYP*3A5*3, *CYP*3A5*6 and *CYP*3A4*1B polymorphisms along with demographic covariates. We modelled the pharmacokinetics of indinavir using SAEM in MONOLIX version 2.1. We performed a screening on the EBE using ANOVA followed by an ascending selection based on LRT. In front of the previous results, as the number of patients is limited, we then performed a backward selection using a LRT by permutation [12].

A one-compartment model with first-order absorption and elimination best described the indinavir concentrations. The eight patients *1B/*1B for *CYP3A*4 gene had an absorption rate decreased by 70% compared to *1A/*1B or *1A/*1A genotypes (0.5 versus 2.1, P=0.04).

b) Influence of the *CYP*2D6 polymorphism on the pharmacokinetics of the drug X and its active metabolite

We analysed the pharmacokinetic profiles of ninety patients collected after four weeks of treatment at 1, 3, 6 and 24 hours following administration. Concentrations were measured for both the parent drug and its active metabolite. For each patient, genotypes are obtained for the *CYP*2D6 polymorphism. We modelled jointly the concentrations of drug X and its active metabolite using SAEM in MONOLIX version 2.4. We performed a screening on the EBE followed by an ascending selection based on LRT. As the design of the study was rather rich, we did not perform a correction using permutations.

In the final model, the volumes of the parent drug and the metabolite were set to be equal and the decrease of bioavailability with the dose was taken into account. Through a first pass effect, 14% of the dose formed directly the metabolite and this metabolite was partly back-transformed into the parent drug. Between patients variabilities were estimated on all parameters with the exception of the metabolization and back-transformation clearances while correlations were observed between the absorption constant rate, the volume of distribution and the elimination clearance of the metabolite. The CYP2D6 polymorphism was found to influence the pharmacokinetics of the molecules.

Conclusions

For test of gene effects in pharmacokinetic studies analysed with NLMEM, we recommend using an ANOVA on the individual parameters as this method showed, in our simulation setting, the best performance in terms of type I error whatever the estimation method even in designs with some shrinkage. If one still wants to perform Wald test or LRT and construct a global model, we promote the use of permutation tests on designs with unbalanced genotypes and/or small number of subjects. A more recent estimation method, as the SAEM algorithm, shows better properties and is easier to apply for permutation tests because it ensures reasonable computing time and meets with no numerical difficulties on repeated data sets.

References

[1] EMEA. ICH topic E15 definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories. Technical report, EMEA, 2008.
[2] D Hirt, F Mentré, A Tran, E Rey, S Auleley, D Salmon, X Duval, JM Tréluyer and the COPHAR2-ANRS Study Group. Effect of CYP2C19 polymorphism on nelfinavir to M8 biotransformation in HIV patients. Br. J. Clin. Pharmacol., 65:548-57, 2008.
[3] Y Yamasaki, I Ieiri, H Kusuhara, T Sasaki, M Kimura, H Tabuchi, Y Ando, S Irie, JA Ware, Y Nakai, S Higuchi, and Y Sugiyama. Pharmacogenetic characterization of sulfasalazine disposition based on NAT2 and ABCG2 (Bcrp) gene polymorphisms in humans. Clin. Pharmacol. Ther., 84:95-103, 2008.
[4] D Li, W Lu, JY Zhu, J Gao, YQ Lou, and GL Zhang. Population pharmacokinetics of tacrolimus and CYP3A5, MDR1 and IL-10 polymorphisms in adult liver transplant patients. Clin. Pharm. Ther., 32:505-515, 2007.
[5] L Sheiner and S Beal. NONMEM Version 5.1. University of California, NONMEM Project Group, San Francisco, 1998.
[6] M Lavielle. MONOLIX (MOdèles NOn LInéaires à effets miXtes). MONOLIX group, Orsay, France, 2008. http://software.monolix.org/index.php.
[7] X Duval, F Mentré, E Rey, S Auleley, G Peytavin, M Biour, A Métro, C Goujard, AM Taburet, C Lascoux, X Panhard, JM Tréluyer, D Salmon. Benefit of therapeutic drug monitoring of protease inhibitors in HIV-infected patients Depends on PI used in HAART Regimen - ANRS 111 trial. Fund. Clin. Pharmacol., in press, 2009.
[8] J Bertrand, E Comets, and F Mentré. Comparison of model-based tests and selection strategies to detect genetic polymorphisms influencing pharmacokinetic parameters. J. Biopharm. Stat., 18:1084-1102, 2008.
[9] EMEA. Reflection paper on the use of pharmacogenetics in the pharmacokinetic evaluation of medicinal products. Technical report, EMEA, 2007.
[10] S Retout, E Comets, A Samson, and F Mentré. Design in nonlinear mixed effects models: optimization using the Fedorov-Wynn algorithm and power of the Wald test for binary covariates. Stat. Med., 26:5162-5179, 2007. http://www.pfim.biostat.fr/.
[11] J Bertrand, E Comets, and F Mentré. Properties of different tests to detect the effect of a genetic covariate on pharmacokinetic parameters using the SAEM algorithm for several designs. PAGE 17 [Abstr 1337], Marseille, France, 2008.
[12] J Bertrand, JM Treluyer, X Panhard, A Tran, S, E Rey, D Salmon-Céron, X Duval, F Mentré and the COPHAR2-ANRS 111 study group. Influence of pharmacogenetics on pharmacokinetic interindividual variability of indinavir and lopinavir in HIV patients (COPHAR2 - ANRS 111 trial). PAGE 16 [Abstr 1153], Copenhagen, Denmark, 2007.

Acknowledgments

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Nick Holford The Influence of the Time Course of CD4 and Viral Load on Clinical Outcome Events Before and During Antiretroviral Therapy

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Objectives: Mechanistic mixed effect models for HIV infection using CD4 cell counts and viral load (VL) are only practical for small data sets and short term follow up because of computational problems related to solving stiff differential equations. Existing models are from industrialized countries and even those purporting to show African HIV outcomes have been developed with data from the USA. Our objective has been to develop methods for describing the time course of CD4 and VL that can be used as predictors of clinical outcomes in HIV-infected patients in long term follow up settings in southern Africa.

Methods: CD4 and VL in HIV-infected patients can be described with empirical continuous functions of time before and after the initiation of antiretroviral therapy (ART). The parameters of a hazard function for clinical outcome events can be estimated using a combined Weibull and Gompertz baseline distribution with CD4, VL and ART as time varying explanatory factors.

Results: The simplest model describing CD4 used an exponential drop from baseline prior to ART. When ART is started a shallow sigmoid Emax model predicted the initial rapid rise and subsequent slow rise towards an asymptote. VL was essentially constant prior to ART and then fell exponentially. More complex models can be used for example to describe an initial slow decline before rapid loss of CD4 cells leading to ART. The hazard of death could be explained more by the time course of CD4 than by VL.

Conclusions: Prediction of survival in HIV-infected patients depends on time varying factors which are modified by ART. Survival analyses using only baseline characteristics are likely to be misleading about future events. Empirical mixed effect models for CD4 and VL offer a practical method for understanding time to event outcomes such as death, hospitalization, and treatment failure.

Acknowledgment: We are grateful to the patients who provided the data used to develop these methods and to our clinical collaborators at Madwaleni Hospital (Lynne Wilkinson,Tom Boyles, Richard Cooke) and Aid for AIDS (Michael Hislop, Leon Regensberg).

Matt Hutmacher Estimating Transformations for Population Models of Continuous, Closed Interval Data

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Objectives: The Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) is a self reported tool used in rheumatoid diseases. These clinical data have a closed interval range from 0 to 3, inclusive of the endpoints. Presumptively, the closed range vitiates the normality assumption for random effects. The standard Box-Cox transformation family mitigates these issues for positive open interval data, but is not appropriate for closed or semi-closed (closed on one end) interval data. Maintaining probability support for a model within the data range is difficult, and is noticeable when simulating data, since unrealistic (negative) data can be generated. We propose a general nonlinear mixed-effects approach to estimating transformations for longitudinal closed interval data (semi-closed interval data are a special case), for which a transformation family other than Box-Cox is required. Data with values on the range limits (endpoint data) are considered censored observations in the likelihood. This assumption is predicated on the transient nature (non-permanent) and incomplete effect of most drugs. The likelihood can be extended to account for 'inflation' of the endpoint data.

Methods: A case study is presented to introduce the transformation methodology. The model results are compared to an approach which uses shift parameters to translate the closed interval into an open one to facilitate transformation, and also to the model fitted to the original data. Simulation studies were performed to understand the properties of these approaches.

Results: Posterior predictive distributions of selected statistics indicated that only the proposed methodology maintains simulated data within the feasibility range. Simulations with the model fitted to the original scale indicates that setting data outside the closed interval to the range endpoints induces estimation bias, and this bias increases with the quantity of data set to the endpoints. Further, using arbitrary shift parameters can induce unpredictable biases. These biases also increase with greater amounts of data near the range endpoints. Such biases yield biased predictions of the population mean on the original scale.

Conclusions: A general likelihood-based approach is proposed for closed interval data. The approach is principled in that it restricts the probability support to the feasible data range, and does not suffer from biases induced by selection of arbitrary shift parameters.

References:

[1] Box GEP, Cox DR. An analysis of transformation. Journal of the Royal Statistical Society, Series B 1964; 26(2):211-252.
[2] Carroll RJ, Ruppert D. Transformation and Weighting in Regression. Chapman & Hall: London, 1988.
[3] Boik RJ, Todd C. Response transformations in repeated measures and growth curve models.

Communications in Statistics - Theory and Methods 2000; 29(4):699-733.
[4] Gurka MJ, Edwards LJ, Muller KE, Kupper LL. Extending the Box-Cox transformation to the linear mixed model. Journal of the Royal Statistical Society, Series A 2006; 169(2):273-288.
[5] Moulton LH, Halsey NA. A mixture model with detection limits for regression analysis of antibody response to vaccine. Biometrics 1995; 51(4):1570-1578.
[6] Olsen MK, Schafer JL. A two-part random-effects model for semicontinuous longitudinal data. Journal of the American Statistical Association 2001; 96():730-745.
[7] Aranda-Ordaz FJ. On two families of transformations to additivity for binary response data. Biometrika 1981; 68(2):357-363.
[8] Berk KN, Lachenbruch PA. Repeated measures with zeros. Stat Statistical Methods in Medical Research 2002; 11(4):303-316.
[9] Oberg A, Davidian, M. Estimating data transformations in nonlinear mixed effect models. Biometrics 2000; 56(1):65-72.

Celine Marielle LAFFONT A new exact test to globally assess a population PK and/or PD model

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Objectives: Standardised predictions errors are provided by most software (WRES in NONMEM; PWRES in MONOLIX) and are widely used as a diagnostic tool in routine [1]. They can be calculated in several ways which are more or less accurate [2,3], but their main limitation is that they come from the theory of linear models and do not apply to non-linear models [2]. In that context, new metrics on observations have been proposed [2,4]. Normalised prediction distribution errors (NPDE) represent a major improvement as they do not rely on any approximation of the model and are uncorrelated within an individual [2]. However, absence of correlation does not imply data independence (unless individual *vectors* of observations are Gaussian, which is barely the case for non-linear models). It results that, while NPDE actually follow a $N(0,1)$ distribution at each observation time, their joint distribution is not standard Gaussian. Our objective is thus to develop an exact test that overcomes this issue of data dependence and allows to globally assess a population PK/PD model.

Methods: As for NPDE [2], we calculate for each individual *i* the vector of standardised predictions errors (U_i) using the expectations and full variance matrix estimated empirically over K simulations. We use a random projection method (see [5] for an application) that allows an easy analysis of dependent data. Briefly, we project U_i on random directions drawn from a uniform distribution on the unit sphere. We then use these projections to perform a global test and propose an easy diagnostic graph that does not require a subjective interpretation: the QQ "ring" plot. Our test compares, using the sup-norm, the empirical distribution of projected U_i with their distribution under the null hypothesis (H0). Simulation studies were performed with different PK or PK/PD models, under H0 and several alternative hypotheses (H1), to evaluate the level and power of the test. The performances of our test were compared with those of Kolmogorov-Smirnov test applied to NPDE, WRES and PWRES (population mean predictions) for a $N(0,1)$ distribution, under H0 and H1 (NPDE only).

Results: Our test showed very good performances both in terms of type I error and power. The performances of NPDE were also good but revealed insufficiencies for highly non-Gaussian models. In agreement with previous work [2], the performances of both WRES and PWRES under H0 were very poor.

Conclusions: We have developed an exact test for evaluation of population models. Its good theoretical properties were confirmed by several simulation studies using different PK and/or PD models. We also propose a very innovative graph as a global diagnostic tool.

References:
[1] Brendel K et al. Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? A survey of the literature from 2002 to 2004. Clin Pharmacokinet 2007; 46:221-234.

[2] Brendel K. et al. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. Pharm Res 2006; 23:2036-2049.
[3] Hooker AC et al. Conditional weighted residuals (CWRES): a model diagnostic for the FOCE method. Pharm Res 2007; 24:2187-2197.
[4] Mentré F and Escolano S. Prediction discrepancies for the evaluation of nonlinear mixed-effects models. J Pharmacokinet Pharmacodyn 2006; 33:345-367.
[5] Cuesta-Albertos JA et al. The random projection method in goodness of fit for functional data. Computational Statistics & Data Analysis 2007; 51:4814-4831.

Benjamin Ribba Estimating the kinetic parameters of vascular tumor growth models to optimize anti-angiogenesis drugs delivery

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Objectives: Optimizing the delivery of anti-angiogenesis drugs requires the development of relevant drug-disease models of vascular tumor growth. We aim to characterize the dynamic of tumor growth and angiogenesis - the process of intra-tumoral blood vessel formation - in xenografted mice by means of mixed-effect modeling techniques.

Methods: Subcutaneous xenografts of human colorectal HT-29 and HCT-116 cells were implanted in athymic mice. Two diameters were recorded for each animal every 2−3 days and tumor volume was calculated. Mice were sacrificed at different times and tumors were analyzed by means of histochemistry techniques. Blood vessel surfaces and diameters, as well as percentage of necrotic tissue and proliferation index were assessed. Monolix 2.4 [1] was used to estimate the parameters of the mixed-effect models.

Results: Tumor dimension data coming from 29 mice (15 bearing HT-29 cancer cells and 14 bearing HCT-116) representing 314 observations were analyzed separately. A 5-parameters model combining an early exponential growth phase followed by a power-law better fitted the tumor volume data than the usual 3-parameters modified-Gompertz model [2]. The gain Akaike information criteria was -53.8. Tumor diameter data were also analyzed by means of a new model combining a logistic growth coupled to an exponential growth. Population and individual predictions depicted, for some mice, a transient deceleration in tumor growth.
The analysis of the relationship between the tumor growth behavior and histochemical data showed that only the percentage of necrotic tissue could be associated to the switch in tumor growth velocity. Based on these results, we developed a mechanistic model composed by a system of three ordinary differential equations to describe vascular tumor growth in xenografted mice.

Conclusions: Using mixed-effect modeling techniques, we showed that a structural model combining an exponential growth followed by a power-law may be more relevant than the classical modified-Gompertz model to fit tumor growth volume data. Analyzing tumor diameters led us to propose a mechanistic model of tumor growth and the process of angiogenesis. Monolix software and SAEM were necessary to correctly identify the different parameters of this complex mechanistic model. We are presently using this model to optimize the delivery of anti-angiogenesis drugs Sunitinib in combination with chemotherapy FOLFIRI in xenografted mice.

References:
[1] Kuhn E, Lavielle M. Maximum likelihood estimation in nonlinear mixed effects models. Comp Stat Data Anal. 2005. 49(4):1020-38.

[2] Simeoni M, Magni P, Cammia C, et al. Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. Cancer Res 2004;64:1094-101.

Birgitte Rønn Maximum likelihood estimation in nonlinear mixed effect models: Adaptive Gaussian Quadrature by sparse grid sampling

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Objectives: Compartment models for PK population modeling are often nonlinear mixed effect models (NLME) with normal distributed random effects and residual error structure. The parameters may be found by maximum likelihood estimation, but the log-likelihood function for such models involves an integral, that can not be solved, but has to be approximated. Adaptive Gaussian Quadrature (AGQ) is an approximation of high accuracy [1], but unfortunately the computing costs grow exponentially with the dimension of the random effects. We suggest reducing the growth in cost to be proportional to the dimension of the random effect vector by following the formulation of Smolyak's rule for sparse grid sampling found in [2].

Methods: In NLMEs calculation of the log-likelihood function involves a *d*-dimensional integral that usually cannot be solved explicitly (*d* is the dimension of the random parameter). Different approximation methods to the integral have been implemented and AGQ has been shown to be precise, but requires intensive computations. For one-dimensional random effects the integral can be approximated by evaluating the non-linear integrand in m points which are roots in a polynomial of certain degree. However, multiplication of the one-dimensional rule with *m* points and *d*-dimensional random effect requires function evaluation in m^d points. Smolyak developed a tensor product based method of multiplying one-dimensional grids to higher dimensions. A low-order version of this method requires function evaluation in $(2d+1)$ points and gives exact results for normal integrand multiplied by any polynomial of degree 3 or less.

The algorithm is implemented in R, taking censoring problem into consideration, e.g. concentrations observed to be below LLOQ. The method has been tested on literature data on Theophylline [3] and Indomethacin [4]. A small simulation study has been conducted to investigate the accuracy of the suggested method and compare it with ‘full' AGQ.

Results: The sparse grid sampling AGQ resulted in parameter estimates similar to the results obtained with full AGQ. The simulation study revealed that for the considered compartment models both methods results in good approximations for the integral, resulting in similar parameter estimates.

Conclusions: The sparse grid AGQ is a less computational intensive but equally reliable as the full AGQ approximation for maximum likelihood estimation of parameters in NLMEs under normal circumstances.

References:
[1] Pinheiro, J. C. and Bates, D. M. (1995). Approxmiations to the log -likelihood function in the

nonlinear mixed-effects model. Journal of Computational and Graphical Statistics 4(1):12-35.
[2] Gertner T. and Griebel, M. (2003) Dimention Adaptive Tensor Product Quadrature. Computing 71. 65-87.
[3] Boekmann, A.J., Sheiner, L.B. and Beal, S.L. (1994). NONMEM Users Guide: Part V, NONMEM Project Group, University of California, San Francisco.
[4] Kwan, K.C., Breault, G.O., Umbenhauer, E.R., McMahon, F.G. and Duggan, D.E. (1976). Kinetics of indomethicin absorption, elimination and enterophetic circulation in man, Journal of Pharmacokinetics and Biopharmaceutics 4:225-280.

Radojka Savic A new SAEM algorithm for ordered-categorical and count data models: implementation and evaluation

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Objectives: Analysis of categorical and count data from clinical trials using mixed effect analysis has recently become the method of choice. However, algorithms available for parameter estimation, including LAPLACE and Gaussian quadrature, are associated with certain limitations, including bias in parameter estimates. This is a consequence of multiple approximations of the likelihood integral, whose impact is amplified when the proportion of response categories are skewed- for ordinal data, and when models accounting for under- or over dispersion of individual variance compared to the mean are applied, in case of count data. Additionally, the more quadrature points used to approximate likelihood integral, the longer the analysis runtime [1, 2]. The SAEM algorithm has proven to be a very efficient and powerful tool in the analysis of continuous data [3]. The aim of this study was to implement and investigate the performance of a new SAEM algorithm for discrete data.

Methods: A new SAEM algorithm was implemented in MATLAB for estimation of both, parameters and the Fisher information matrix. Stochastic Monte Carlo simulations followed by re-estimation scenarios similar to those used in previous studies to investigate properties of other algorithms were employed. For ordered categorical data, the proportional –odds model was explored using six different scenarios with varying parameter values. For count data, a single scenario was used to explore six different probability distribution models, (i.e., Poisson, Zero-inflated Poisson, Generalized Poisson, Poisson with Markovian Features, Poisson with a mixture distribution for individual observations and Negative binomial models). Performance of the algorithm was assessed by computing the relative bias (RB), root mean square error, and assessing the CPU time of the analysis. The accuracy of standard errors (SE) estimates was assessed as an absolute distance (AD) between actual and empirical relative SEs.

Results: For proportional-odds model, RB was < 8.13 % for all scenarios explored, including ones with skewed distributions of response categories. For count data models, RB was < 4.13 % for all models studied including ones accounting for over- or under-dispersion. Estimates of standard errors were close to the empirical SEs, with AD < 5.8% , for all explored scenarios. The longest CPU time out of all studied models was for the analysis of the Negative binomial model taking 40s for parameter estimation and 37s for SE estimation.

Conclusions: The SAEM algorithm was extended for analysis of ordered categorical and count data with extensions to the Hidden Markov Model. It provides accurate estimates of both, parameters and standard errors. The estimation is significantly faster compared to other algorithms. The algorithm will be implemented in Monolix 3.1, (beta-version available in July 2008).

References:

[1] Jonsson, S., Kjellsson, M.C.and Karlsson, M.O., Estimating bias in population parameters for some models for repeated measures ordinal data using NONMEM and NLMIXED. J Pharmacokinet Pharmacodyn, 2004. 31(4): p. 299-320.

[2]Plan, E.L., et al. Maximum Likelihood Approximations: Performance in Population Models for Count Data. in PAGE. 2008.

[3]Kuhn E., Lavielle M., Maximum likelihood estimation in nonlinear mixed effects models. Computational Statistics and Data Analysis, 2005. vol. 49, No. 4, pp 1020-1038.

Diane Wang Standardized Visual Predictive Check – How and When to used it in Model Evaluation

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Objectives: PK/PD modeling is increasingly used in drug development, and model evaluation has become an important component in the modeling process to confirm model adequacy. The objectives of the present study were to examine the performance of Visual Predictive Check (VPC), a commonly-used model evaluation method, in evaluating PK/PD models with different properties, to illustrate the situations where VPC may not be applicable, and to propose Standardized Visual Predictive Check (SVPC) for evaluating PK/PD models for which VPC is inadequate.

Methods: The PK/PD datasets ("observed" data) were simulated with pre-defined models under two common scenarios. One scenario is a nonlinear PK/PD model with subjects receiving different doses of drug (e.g. body weight-based dosing). The other is a PK/PD model with covariate effects (e.g. age as a covariate for clearance). These datasets were then fitted with the corresponding true models (pre-defined models) and the alternative (false) models. VPC and SVPC were conducted for both true and false models, respectively, and their performances were compared. SVPC was performed by plotting against time the percentile of each observation in the dataset in relation to its 1000 simulated observations derived from the true and false models.

Results: In both of the aforementioned situations, VPC failed to distinguish between the true and the alternative models. Specifically, VPC suggested model inadequacy for the true model in case of nonlinear PK/PD with different doses, and it indicated model adequacy for the false model in case of PK/PD with covariate effects. However, SVPC distinguished correctly the true and false models in both scenarios.

Conclusions: Although being used more and more frequently, VPC may be inadequate for model evaluation in many cases, such as nonlinear PK/PD models with different doses and PK/PD models with covariate effects (unless the covariates can be conveniently stratified). VPC is only applicable in situations where dose normalized PK/PD profiles for all subjects are expected to be the same when Ωs and σs are all set to 0. However, SVPC can be used in all situations.

Billy Amzal Population TK/TD for chemical risk assessment and drug safety: the cadmium example

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Background: Population pharmacokinetic/pharmacodynamic (PK/PD) models have been largely developed and used in the context of drug development for a number of purposes,including the optimisation of dose regimens and the risk analysis of acute toxicity. These models are often based on dedicated clinical trials. On the other hand, very few models have been used to evaluate chronic or long term adverse effects such as population toxicokinetic/toxicodynamic (TK/TD) models particularly in the context of quantitative risk assessment in humans. In contrast to PK/PD models, TK/TD models developed for chronic exposure in humans can often only be based on epidemiological data.

Objectives: In this work, we illustrate how similar modelling approaches can be used in pharmacological and toxicological contexts, emphasizing their specificities and similarities. In the context of toxicological risk assessment of chemicals, population TK and dose-response models (TD) can be developed and linked together in order to evaluate a "safe dose" ("health-based reference value") for a given population. For this purpose, assessment and integration of population variability based on aggregated epidemiological data is a key element to perform a sound quantitative risk assessment.

Methods: The recent health risk assessment of Cadmium in food performed by the European Food Safety Authority (EFSA), illustrates the whole process of TK/TD model-based risk assessment. From a systematic review and Bayesian meta-analysis of scientific literature on cadmium renal effects, a populated Hill dose-effect model was built and the benchmark dose method implemented. The TK assessment involved the comparison of a 8-compartment toxicokinetic model and a one-compartment population TK model, based on a cohort study of 680 Swedish women, over a 20-year-long period.

Results: For cadmium renal effects, β_2-microglobulinuria was the most commonly reported biomarker. The dose-effect model showed that a urinary cadmium level above 1 μg/g creatinine leads to an excess risk of 5% for the Caucasian population of being with β_2-microglobulinuria above the critical cut-off of 300 μg/g creatinine. The TK model showed that a food intake of about 2.5ug/kg body weight and per week would prevent 95% of the Caucasian population from being above the threshold of 1 μg/g creatinine of urinary cadmium.

Conclusion: The modelling tools used in the pharmacological context could be applied to a toxicological context for the risk characterization of a contaminant for human health. Similarly, some toxicological risk assessment tools such as benchmark dose models or meta-analysis of epidemiological data could also be used for pre- or post-market drug safety evaluation in a pharmacological or pharmaceutical set-up.

Andrew Hooker Time to Event modeling of dropout event in clinical trials

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Background: Dropouts can greatly affect the outcome of clinical trials and a proper understanding of the dropping-out mechanisms is critical for the correct interpretation of the outcomes of clinical trials. Among the different reasons for dropout are the lack of efficacy, the occurrence of unwanted effects and that the exposure-response parameter estimates can be inappropriate in presence of non-random dropouts.

Objectives: 1) To develop a parametric time-to-event model for dropout investigating the potential effect of both efficacy and PK as significant covariates; 2) To develop a joint model accounting for PK/efficacy and dropout [1]

Methods: Drop out data from two clinical trials (in the neuroscience therapeutic area) were analyzed using a parametric time to event model. Several parametric descriptions of the hazard function were evaluated (exponential, Gompertz, Weibull including a cure rate term). Treatments (i.e., placebo, test drug, and active comparator), PK and clinical endpoints were investigated as potential covariates. The parameters were estimated maximizing the joint likelihood using the laplacian approximation as implemented in NONMEM VI. Model selection was based on the log-likehood ratio test; in addition visual predictive checks (VPC) were used to evaluate model performance using simulated vs non parametric estimates of survival (Kaplan-Maier plots). Finally, a joint model including efficacy and/or PK and time to event data was attempted.

Results: The Weibull model including a cure rate term was the best model to describe the dropout data. Time to Event analysis on dropouts showed a significantly higher drop-out rate for the test drug (approximately 40%) compared to both placebo and active comparator (24 and 22% , respectively). Overall PK exposure (AUC) during treatment was not found to be a significant covariate to explain the probability of drop-out in the test drug arm. Results including the efficacy as covariate showed a great improvement in the objective function suggesting that lack of efficacy was one of the main reason of drop out.

Conclusions: The effect of drop out event is critical and needs to be properly considered in the development of PK and PK-PD models. Parametric time to event models are suitable for this description. All this should be properly implemented before embarking in clinical trial simulation work.

References:
[1] Hu C, Sale M. A joint model for nonlinear longitudinal data with informative dropout. *J Pharmacokinetic Pharmacodynamic* 2003; 30:82-103.

Chuanpu Hu Confirmatory Phase III Population Pharmacokinetic Analysis

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Objectives: An important objective in population pharmacokinetics analysis is to assess covariate influence. Results from covariate assessments may be used to guide potential dosing adjustment or drug labeling. The commonly used extensive exploratory approach may contain certain biases [1] that can lead to unwarranted dosing adjustments. Recently, we proposed a confirmatory approach aimed for regulatory submission purpose [2]. We herein provide refinements to the proposed approach, and apply it to several more case scenarios to gain further experience with the performance of this approach in contrast to the exploratory approach with phase III clinical trial data.

Methods: A pre-specified primary analysis is proposed based on phases I/II data and the phase III study design, together with two sensitivity analyses similar to [2]. Confidence intervals of covariate effect estimates were proposed as the means for assessing dosing adjustment needs, and refinements of time-adjustment were considered for the linear-model sensitivity analysis. The sensitivity analyses aimed to address potential concerns associated with the primary analysis, which may include misspecification of base and covariate models as well as the lack of robustness due to dosing/sampling time inaccuracies. The approach was applied to several phase III analyses covering different situations of small molecule and therapeutic protein, as well as different sample sizes.

Results: Differences between the proposed confirmatory approach and the exploratory analyses varied, in part depending on sample sizes and the amount of explorations. However, differences in main covariate effects between both approaches were usually small, which was consistent with both theoretical predictions and practical expectations. The proposed confirmatory approach provided a clearer understanding of the uncertainties embedded in the conclusions. The analysis time was also substantially shortened because the amount of exploration was vastly reduced.

Conclusions: The confirmatory approach provides a method that is more accurate in statistical theory, and also gives better understanding of uncertainties and robustness from practical considerations. It is relatively easy to implement with appropriate pre-planning prior to the analysis.

References:

[1] J. Ribbing and E.N. Jonsson. Power, selection bias and predictive performance of the population pharmacokinetic covariate model. Journal of Pharmacokinetics and Pharmacodynamics 2004; 31:109-134.
[2] C. Hu and H. Zhou. An improved approach for confirmatory phase III population pharmacokinetic analysis, Journal of Clinical Pharmacology, 48: 812-822, 2008.

Andreas Kuttler A 3D Computational Model Of Cerebrospinal Fluid Dynamics For Predictive Biosimulation

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Objectives: With approximately 130,000 new cases per year globally, spinal cord injury (SCI) is a global epidemic [1] involving males between the age of 16-30 in 82% of case. While there is no cure for SCI, several new therapies targeting the spinal cord are in development. Drugs targeting spinal cord function, most notably local anesthetics and opioids, are typically administered into the cerebrospinal fluid (CSF) in the spinal canal by lumbar intrathecal injection or infusion. To optimize drug administration and distribution at a target site of pharmacologic action, a precise understanding of the anatomy and physiology relevant to intrathecal drug delivery is needed.

Methods: We developed a 3D computational fluid dynamics model of the spinal canal, based on actual geometry reconstructed from MRI data and dynamics controlled by transient Navier-Stokes equations. The driving forces for fluid transport (pulsating blood flow in the cranium and breathing) are modeled based on literature data [2,3]. These numerical investigations provided detailed quantitative data on CSF flow in the canal, allowing prediction of local differences in fluid dynamics (e.g., distribution of velocity profiles and flow direction over time). The simulated velocities are in good agreement with the velocities measured by phase contrast magnetic resonance imaging at five additional cross-sections [4].

Results: The pulsating nature of the fluid flow together with the specific geometry of the spinal canal results in convective transport of injected drug molecules. Because of these effects, even large molecules like monoclonal antibodies with a low molecular diffusion rate get distributed though not in a spatially homogenous manner. Virtual marker fluid analysis show reduced transport in some of the transition zones (e.g., T9/T10). We simulated the biodistribution of compounds in the CSF as a function of time and space, intrathecal injection site, and infusion modes, volumes and rates. The determined local transport velocities are in the same range as those measured by CSF radionuclide scintiphotography using radiolabeled human serum albumin [5,6].

Conclusions: Using modeling tools based on first principles of biophysics, transport phenomena as they occur in the spinal canal may be analysed in detail. By providing a framework for appropriate integration of population clinical data into a dynamic system physiology platform, this technology allows for the simulation of different clinical scenarios to support decision making, turning model based-drug development to reality.

References:

[1] www.campaignforcure.org
[2] Alperin, N.; Sivaramakrishnan, A.; Lichtor, T.: Magnetic resonance imaging-based measurements of cerebrospinal fluid and blood flow as indicators of intracranial compliance in patients with Chiari malformation, Neurosurg 103 46-52, 2005

[3] Lee, R.R.; Abraham, R.A.; Quinn, C.B.: Dynamic physiologic changes in lumbar CSF volume quantitatively measured by three-dimensional fast spin-echo MRI, Spine 2001;26:1172-1178
[4] Yallapragada, N.; Alperin, N. : Noninvasive mapping of the spinal canal hydrodynamic complaince using bond graph technique and magnatic resonance imaging , Bioengineering Conference, June 2003, Florida
[5] Ashburn, W.L.; Harbert, J.C.; Briner, W.H.; Di Chiro, G.: Cerebrospinal Fluid Rhinorrhea Studied With Gamma Scintillation Camera, Journal Of Nuclear Medicine, vol.9, no.7
[6] Di Chiro, G.; Hammock, M.K.; Bleyer, W.A.: Spinal Descent Of Cerebrospinal Fluid In Man, Neurology 26: 1-8, January 1976

Brian Anderson Are Children Small Adults?

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Growth and development are two major aspects of children not readily apparent in adults. Age is commonly lumped into neonates (<6 weeks age), infants (6 weeks-1 year) and children (>1 year) with age described as postnatal (PNA) or postmenstrual (PMA). Growth and development interact in ways that are not necessarily easy to determine from observations because they are quite highly correlated. (1) Tod has identified three major covariates (size, maturation, organ function) for paediatric PK and suggested standardisation for size before incorporating factors for maturation and organ function.(2) Size can be standardised for clearance in a 70 kg person using the allometric ¾ power model.(3, 4) Remifentanil, a drug cleared by hydrolysis, can be modelled in all age groups by simple application of this model using a standardized clearance of 2800 mL.min-1 for a 70 kg person.(5) Fat mass (6) contributes to overall body size and may have an indirect influence on both metabolic and renal clearance.(7) Allometry alone is insufficient to predict clearance in neonates and infants from adult parameters for most drugs; the addition of a model describing maturation is required. The sigmoid Emax has been found useful for describing this maturation process.(8) Propofol maturation may be described with a mature clearance of 1.83 L.min-1.70kg-1, a maturation half-time (TM50) of 44 weeks PMA and a Hill coefficient of 4.9.(9) Organ function also affects clearance and propofol clearance is reduced in neonates and infants after cardiac surgery.(6)

There are few data describing age-related PD changes. Those described appear to resolve during infancy (6 weeks-1 year PNA). Common examples include an increased sensitivity to the effects of neuromuscular blocking drugs in neonates (10), MAC changes of inhalational anaesthetics (11) and bronchodilator insensitivity (12)

Children are not small adults. Adults are BIG children and children are OLD babies.

References:

[1]. Meibohm B, Laer S, Panetta JC, et al. Population pharmacokinetic studies in pediatrics: issues in design and analysis. AAPS J 2005; 7:E475-87.
[2]. Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet 2008; 47:231-43.
[3]. West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science 1999; 284:1677-9.
[4]. Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet 2009.
[5]. Rigby-Jones AE, Priston MJ, Sneyd JR, et al. Remifentanil-midazolam sedation for paediatric patients receiving mechanical ventilation after cardiac surgery. Br J Anaesth 2007; 99:252-61.
[6]. Rigby-Jones AE, Nolan JA, Priston MJ, et al. Pharmacokinetics of propofol infusions in critically ill neonates, infants, and children in an intensive care unit. Anesthesiology 2002; 97:1393-400.

[7]. Rhodin MM, Anderson BJ, Peters AM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol 2009; 24:67-76.
[8]. Anand KJ, Anderson BJ, Holford NH, et al. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. Br J Anaesth 2008; 101:680-9.
[9]. Allegaert K, de Hoon J, Verbesselt R, et al. Maturational pharmacokinetics of single intravenous bolus of propofol. Paediatr Anaesth 2007; 17:1028-34.
[10]. Fisher DM, O'Keeffe C, Stanski DR, et al. Pharmacokinetics and pharmacodynamics of d-tubocurarine in infants, children, and adults. Anesthesiology 1982; 57:203-8.
[11]. LeDez KM, Lerman J. The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. Anesthesiology 1987; 67:301-7.
[12]. Stephenson T. How children's responses to drugs differ from adults. Br J Clin Pharmacol 2005; 59:670-3.

Willem de Winter Issues of size and scaling in comparative biology

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Johnson & Johnson

Issues of size, shape, form and function continue to intrigue and divide biologists. Ranging over seven orders of magnitude in mammals alone, body size represents the most conspicuous - and most easily quantified - source of variability between different organisms, as well as between different developmental stages within a single organism. In order to compare features of different organisms, therefore, size differences have to be taken into account through some scaling procedure.

Broadly speaking, there are two approaches to scaling for body size differences. One is to represent the size or dimension of the trait under study as a proportion of body size or some other, often functionally related trait in the same individual (e.g. femur length to tibia length, size of a brain part relative to the sizes of its major inputs). Such proportionally scaled measures of relative size are themselves unique, empirically measurable properties of a given individual organism, and as such their variability between organisms is readily amenable to functional interpretation.

The other approach, referred to as allometric scaling, is to measure the same trait in a broad sample of organisms and to regress the variability of its size or dimension against the variability in body size in the same sample (typically after a log-log transformation). The absolute dimension of this trait in any particular organism can then be evaluated relative to the expected dimension for that trait given its body size. In contrast to the proportional approach, however, such allometrically scaled dimensions are a property not only of the organism itself, but also of the sample of organisms against which it is scaled. This fact has important ramifications for both the empirical assessment of the allometric constants and for their functional interpretation. Some of these methodological issues, including choice of statistical regression procedures, (non-)independence of data points, selected sampling and dependence of allometric parameters on phylogenetic closeness, will be touched upon briefly.

A more fundamental issue with allometric scaling is its tendency to obscure the contribution of adaptation as a source of variability between species and developmental stages. In the allometric approach, the sheer magnitude of body size variation tends to swamp all other sources of variability, even if these carry much greater functional significance. Regardless of body size, however, every organism is the product of millions upon millions of years of adaptive evolution, tuning it in every aspect, every minute detail during every stage of its lifecycle, to its particular way of life in its particular environment. Moreover, in their natural environments, different organisms, but also the same organism at different developmental stages, face different sets of challenges and opportunities, are exposed to different predators, diseases or chemical substances, and can profit from different sources of shelter, food and protection. Therefore, body size alone can never be expected to fully explain, let alone predict, all functional differences between organisms. Previous work of the author on mammalian brain evolution will be shown to illustrate how decades of allometric research failed to uncover a wealth of adaptive variability in the functional organization of mammalian brains.

Naoto Hayashi Population PK of Sildenafil and PK/PD assessment of Exercise tolerability in children with Pulmonary Arterial Hypertension (PAH)

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Objectives: PAH is characterised by an increase in pulmonary vascular resistance, leading to right ventricular failure and, ultimately, death. Sildenafil a PDE5 inhibitor is approved for the treatment of adult PAH. Study A1481131 investigated the sildenafil use in children. Objectives were to assess the sildenafil PK and the peak oxygen consumption (pVO2) a cardio pulmonary exercise tolerance PD endpoint, which substitutes in children for the clinically frequently used 6 Minute-Walking-Test, only practical in adults. Final goal is to provide an optimal dosage for children.

Methods: PK data from this study was combined with previous adult data to explore the maturation process of the clearance covering neonate, children, and adult PAH patients. Using non-linear mixed effect modelling, a 1 compartment model with 1st order absorption and lag time was applied. The PK/PD analysis used pVO2 at baseline and end of treatment (16 wks) in conjunction with model predicted and individual PK exposure estimates

Results: PK samples from 173 children (1-17 years) and 207 adult patients were available. The relationship between body weight (BW) and oral clearance (CL/F) was well described by a sigmoid model with an intercept, reflecting the state and maturation process beyond the age of 1 year. Estimated model parameters were CLmax/F (57.8 L/h), CL0/F (13.9 L/h), slope (3.7), and weight at half CLmax/F (21.3 kg). CL increased 3 fold during 7 days after birth and showed a high correlation with BW [1] but BW or age didn't influence CL/F in adults.

Only 115 children (above 8 years) were developmentally able to perform the exercise test. A sigmoid Emax model described the relationship between average steady-state concentration (Cav,ss) and pVO2 increase. The maximal drug effect was estimated at 9.1%, a level considered to be clinically relevant. Cav,ss producing 90% of the maximal sildenafil response was estimated at 31 ng/mL. 48% of patients (plc: 20%) would meet a clinical responder criteria at the highest dose, defined as 10% improvement in pVO2. A dosage of 10 mg for children up to 20 kg, and 20 mg beyond is likely to achieve 85% of the maximum responder rate.

Conclusions: The integrated PK/PD assessment characterised the CL/F maturation (<4 fold change) from neonates to adult PAH patients as well an exposure range translating into a clinically meaningful response, which allowed to project a dose regimen expected to be efficacious in children with PAH.

References:
[1] Mukherjee A, Dombi T, Wittke B, Lalonde R. Population pharmacokinetics of sildenafil in term

neonates: evidence of rapid maturation of metabolic clearance in the early postnatal period. Clin Pharmacol Ther. 2009;85(1):56-63.

Michael Looby Elucidation of the optimal dosing scheme of an antiviral drug in children

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Objectives: Elucidate the optimal dosing scheme of Famvir in a pediatric population between 1 and 12 years

Methods: Very limited prior data pharmacokinetic data of famciclovir/penciclovir was available in children down to 6 years. Using a mixed effects analysis, this data was combined with available adult data to develop a population pharmacokinetic model which predicted the pharmacokinetics of penciclovir in both adults and children down to the age of 1 year. Using this model, studies were designed to assess the pharmacokinetics and safety of Famvir in pediatric patients with Varicella Zoster and Herpes Simplex virus infections. These studies were divided into two Parts A & B. In Part A, single doses of Famvir were administered to fully characterize the pharmacokinetics of pencicolovir and the relationship between systemic exposure and body-weight or age. The criterion for dose selection was to achieve similar penciclovir exposure in the pediatric- as in adult- population. The information collected in Part A was subsequently used to refine the Famvir doses for the 7-day multiple-dose safety Part B. The FDA endorsed the suggested approach.

Study design (Part A – Single dose pharmacokinetics): The model based analysis of the prior data determined the following characteristics as being optimal:

- Dose: 12.5 mg/kg if weight < 40 kg, otherwise 500 mg (adult dose).
- N = 52 (12 in the range 1 to <2 y, 24 in the range 2 to <6 y, 16 in the range 6 to 12 y)
- Up to 6 blood samples per child

A subsequent model based analysis of this data was used for ultimate dose selection.

Results: After an interim analysis in Part A, recruitment into this part could be terminated early due to success of prior predictions. Target 52; attained 41(at interim analysis) A model independent comparison of the exposure metrics of the pediatric population with the adult exposure envelop confirmed that the dosage algorithm (12.5 mg/kg) was successful in attaining exposure that lay within the adult exposure envelope. This correspondence provided an external validation of the model based predictions Nevertheless a trend was apparent in the pediatric data with exposure decreasing with age. This was expected given the linear scaling factor.

Using the newly generated data, the model was updated to simulate the dosing scheme that predicted penciclovir exposure across the pediatric population (age: 1 to 12 years, body-weight: 9 to > 40 kg) corresponding best to adults. Given the model, it is a straightforward task to test a whole range of possible dosing adjustment rules in silico. Finally, an 8-step dosing scheme with 50 mg dose steps was

selected as the best compromise between simplicity of dosing and accuracy of target exposure. This optimized dosing scheme was then used in the 7-day multiple dose safety Part B of the pediatric studies.

Conclusions:

- An innovative model based approach was used to design and analyse a pediatric study. Prior data was used to select a dosing scheme used in the initial part of the study.
- Confidence generated in the ability of this dosing scheme to attain adult exposures lead to the early termination of enrollement in the pharmacokinetic part of the trial. This was endorsed by FDA.
- With the new data in hand, it was possible to simulate a wide range of dosing schemes to determine the optimal dosing scheme.
- The final 8-step dosing scheme, endorsed by the FDA, was much simpler than the scheme used in the original study.

Software demonstration

Balaji Agoram A4S: a user-friendly PKPD simulation software for non experts

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Objectives: Effective communication of PKPD principles and results in a biomedical research environment remains a significant challenge [1], which can result in lack of buy-in and engagement from scientists outside the modelling and simulation communities. In our view, one of the barriers in this area is a lack of user-friendly tools which allow 'non experts' to use PKPD models without the need to develop technical skills and expertise in advanced mathematical principles and specialist software. The costs of large number of licenses for commercial software may also prevent large-scale distribution. One attempt to address this issue internally in our research organisation has resulted in the development of the A4S ('Accelera for Sandwich') software, which is a simple-to-use basic PKPD simulator targeted at biomedical researchers with little PKPD experience.

Methods: A4S was written in the MATLAB programming language and can run as a standalone tool in a standard Windows environment without the need for any additional software.

Results: A4S is entirely menu driven and takes the user in a step-wise manner through a complete PKPD simulation. A4S contains a range of 'standard' PK and PD models (including all NONMEM standard ADVAN PK models with the option to switch between different TRANS parameterisations), which can all be combined with each other. Some more 'advanced' models not available in other standard software as far as we are aware were also implemented, based on specific internal needs (for example mixed zero-and first order absorption and receptor kinetics). Most dosing regimen can be implemented for complex trial simulations. In addition, the software allows for stochastic simulations of either or both the PK and PD components of the model to explore parameter uncertainty/variability.

Conclusions: Within half a year of its rollout, A4S is increasingly being used by project scientists to (1)design preclinical PKPD experiments (2)explore PKPD models and (3)dose predictions. In addition, A4S has been used in educational workshops (both internally and externally), allowing participants with little or no prior PKPD experience to work on hands-on exercises with minimal need for software training.

References:
[1]Sheiner, T. PAGE 16 (2007) Abstr 1112 [www.page-meeting.org/?abstract=1112]

Balaji Agoram PulmoSim: A Physiologically-Based Mathematical Model Software Package to Predict Lung Retention and Inhaled Pharmacokinetics of Therapeutic Candidates

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Objectives: Retention within the lung tissue is widely believed to enhance the duration of action of inhaled therapeutics. However, the physicochemical factors that influence lung retention are not fully understood; hence rational design of potentially lung-retained inhaled molecules faces substantial hurdles.

The main aim of this work is to develop an *in silico* approach for designing lung retention. The specific objectives are: (1) integrate *in vivo* processes such as dissolution, retention, absorption, and systemic elimination of inhaled compounds quantitatively within a physiologically-based mathematical model with physicochemical determinants, (2) evaluate the model by comparing predictions of retention with experimental rat data for seven inhaled compounds and (3) create a user-friendly software package implementation of the model.

Methods: The model is based on a system of 15 ordinary differential equations describing drug dissolution, absorption across lung epithelium, lung tissue binding, systemic distribution and elimination processes. *In vitro* permeability and tissue binding data were generated for 7 small molecule compounds of widely different physicochemical characteristics and target mechanisms using Caco-2 systems and rat lung tissue. Plasma concentration data were also generated for these compounds in rats after intravenous (IV) and intratracheal (IT) solution dosing. Stochastic model simulations, accounting for uncertainty in model parameters such as permeability and tissue distribution, were performed to predict PK of IT compared to IV dosing. Retention of compound in the lung was assessed based on a visual examination of predicted lung and plasma IT PK profile compared to the IV profile. The model was implemented using MATLAB programming language.

Results: The model predictions were classified as either high or low confidence based on the width of predicted confidence intervals. Among high confidence predictions (5/7 candidates), all predictions of lung retention and lack thereof were accurate. Among low confidence predictions (2/7 candidates), 1 prediction of retention was accurate.

Conclusions: A mathematical model representing physiological processes during inhaled absorption has been developed and accurately predicts lung tissue retention in rats for the range of molecules tested. The model has the potential to substantially impact inhaled drug discovery and hence "inhalation by design" paradigm. The model has been implemented in a user-friendly software package and can run as a standalone application without additional software.

William Bachman PDx-Pop® 4 for NONMEM® 7

William J. Bachman
ICON Development Solutions

Objectives: PDx-Pop software provides an easy to use graphical user interface to expedite the iterative process of population pharmacokinetic modeling and analysis.

Results: New features available in PDx-Pop Version 4 - PDx-Pop 4 is fully compatible and synergetics with NONMEM 7:

1. Enhanced run options for multiple estimation method runs - stop and estimation method, skip to next estimation method, choice to display numerical iterations or not during the run.

2. Displays the real-time objective function versus iteration for all the new estimation methods (including Bayesian sampling history plots).

3. New diagnostic plots for the new methods (e.g. plots of automated multiple simultaneous Bayesian chain output).

4. New control stream wizard features to add NONMEM syntax for the new estimation methods.

5. Ability to use multiple cpu's on multi-processor systems for batched runs

Conclusions: The software has been updated and extended for NONMEM 7.

Caroline BAZZOLI New features for population design evaluation and optimization with R functions: PFIM Interface 3.1 and PFIM 3.2

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Objectives: To extend the graphical user interface version of PFIM for multiple response models and the R scripts version of PFIM to accommodate more complex models with parameters quantifying the influence of discrete covariates [1, 2]. The demonstration will show the features of these new versions.

Context: The R function, PFIM, has been developed as an efficient tool for design evaluation and optimization. It is based on the expression of the Fisher information matrix for nonlinear mixed effects models. Since 2003, several releases of PFIM have been proposed. Currently, two main versions are implemented in parallel: a graphical user interface package using the R software (PFIM Interface) and a R scripts version (PFIM). The latter requires knowledge in R programming but benefits of the latest methodological developments performed in our research team. PFIM Interface 2.1 has been proposed allowing both design evaluation and optimization but only for single response. The last release PFIM 3.0 includes the ability to deal with multiple response models [3]. Some improvements were added to both versions: the possibility to write the model under analytical form or differential equations system, the use of a library of "classical" pharmacokinetic models and the availability of the Fedorov-Wynn algorithm regarding the optimization step.

Methods / Results: We first detail the new PFIM Interface version 3.1 dedicated to design evaluation and optimization for multiple response models. This version incorporates the features that were previously released in version 3.0 of PFIM. Furthermore, the library of "classical" pharmacokinetic models has been completed by the three compartment models and a library of pharmacodynamic models is now available, supporting immediate response models (alone or linked to a pharmacokinetic model) and the turnover models. PFIM Interface 3.1 can handle either a block diagonal Fisher matrix, for a quick evaluation or optimization, or the complete one.
Then, we show the R scripts version PFIM 3.2. This version includes the same features in terms of model specification and development of the expression of the Fisher information matrix as in PFIM Interface 3.1. The key new feature of PFIM 3.2 is the computation of the Fisher information matrix for models including fixed effects for the influence of discrete covariates on the parameters, and the computation of the predicted power of the Wald test for a given distribution of a discrete covariate as well as the number of subjects needed to achieve a given power.
PFIM versions and extensive documentation are freely available on the PFIM website [4].

Conclusions: These new functions, PFIM Interface 3.1 and PFIM 3.2 will be demonstrated on several examples.

References:

[1] Retout S, Mentré F. Further developments of the Fisher information matrix in nonlinear mixed effects models with evaluation in population pharmacokinetics. *Journal of Biopharmaceutical Statistics*, 2003; 13(2):209-27.

[2] Retout S, Comets E, Samson A, Mentré F. Design in nonlinear mixed effects models: Optimization using the Federov-Wynn algorithm and power of the Wald test for binary covariates. *Statistics in Medicine*, 2007; 26(28):5162-79.

[3] Bazzoli C, Retout S, Mentré F. Fisher information matrix for nonlinear mixed effects multiple response models: evaluation of the first order linearization using a pharmacokinetic/pharmacodynamics model. *Statistics in Medicine*, 2009; in press.

[4] http://www.pfim.biostat.fr/.

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
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 and disposition of drugs in patients and specific subgroups of patients across different age ranges. The Simcyp models use experimental data generated routinely during pre-clinical drug discovery and development from *in vitro* enzyme and cellular systems as well as any relevant physico-chemical attributes of the drug and dosage forms.

The Simcyp Population-based ADME Simulator is particularly powerful tool in carrying out virtual clinical trials for recognition of covariates of PK and optimising early in man studies. 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 drug disposition 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 in 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 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, AstraZeneca, Daiichi-Sankyo, Eli Lilly, Johnson & Johnson PRD, Lundbeck, Novartis Pharma, Nycomed, Otsuka, Pfizer, sanofi-aventis, Servier, Takeda, UCB Pharma and Wyeth among others. The aim of the Consortium is to help members enhance the utilisation of information from pre-clinical development in the rational selection and design of *in vivo* studies. Value is added to decision-making processes by collaboration with regulatory bodies (the FDA, MPA, NAM, ECVAM) 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 and PBPK modelling from *in vitro* and physiochemical information in diverse populations including paediatric, obese, cirrhotic and renally impaired.

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

- 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 Pharm Stat. [Epub ahead of print].

- Jamei M *et al.* Population-based mechanistic prediction of oral drug absorption, The AAPS Journal, [Epub ahead of print].

- 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.

- Yang J *et al.* Cytochrome P450 Turnover: Regulation of Synthesis and Degradation, Methods for Determining Rates, and Implications for the Prediction of Clinical Drug Interactions. Current Drug Metabolism, 9(5), 384-394, 2008.

- 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.

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.

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The **BigNPAG** maximum likelihood nonparametric population adaptive grid modeling software runs in XP. The user runs the BOXES routine to make the 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, for the first time, 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].

References:

[1] Bustad A, Terziivanov D, Leary R, Port R, Schumitzky A, and Jelliffe R: Parametric and Nonparametric Population Methods: Their Comparative Performance in Analysing a Clinical Data Set and Two Monte Carlo Simulation Studies. Clin. Pharmacokinet., 45: 365-383,2006.
[2] Jelliffe R, Schumitzky A, Bayard D, Milman M, Van Guilder M, Wang X, Jiang F, Barbaut X, and Maire P: Model-Based, Goal-Oriented, Individualized Drug Therapy: Linkage of Population Modeling, New "Multiple Model" Dosage Design, Bayesian Feedback, and Individualized Target Goals. Clin. Pharmacokinet. 34: 57-77, 1998.
[3]. Bayard D, and Jelliffe R: A Bayesian Approach to Tracking Patients having Changing Pharmacokinetic Parameters. J. Pharmacokin. Pharmacodyn. 31 (1): 75-107, 2004.
[4]. Macdonald I, Staatz C, Jelliffe R, and Thomson A: Evaluation and Comparison of Simple Multiple Model, Richer Data Multiple Model, and Sequential Interacting Multiple Model (IMM) Bayesian Analyses of Gentamicin and Vancomycin Data Collected From Patients Undergoing Cardiothoracic

Surgery. Ther. Drug Monit. 30:67-74, 2008.
[5]. Jelliffe R: Estimation of Creatinine Clearance in Patients with Unstable Renal Function, without a Urine Specimen. Am. J. Nephrology, 22: 3200-324, 2002.

Marc Lavielle Analysing population PK/PD data with MONOLIX 3.1

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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. It converges in situations where other reference methods (NONMEM, nlme,...) do not.

A beta version of release 3.1 will be available on the MONOLIX website at the end of June 2009. This first version of MONOLIX 3 will contain many important features:

- A improved version of MLXTRAN (a NMTRAN-like interpreter) which allows to write complex models (ODEs defined models, count data and categorical data models, complex administrations, multiple compartments,...)
- 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)
- A basic library of count data and categorical data models
- Continuous and categorical covariate models,
- Constant, proportional, combined and exponential error models,
- Modelisation of the inter-occasion variability,
- 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 C++ ODEs solver package for user defined models (stiff models, linear models, delayed ODEs,...)

References:

[1] Delyon B, Lavielle M and Moulines E. *"Convergence of a stochastic approximation version of the*

EM algorithm", Annals of Statistics. 27, 94- 128, 1999.
[2] Kuhn E and Lavielle M. *"Maximum likelihood estimation in nonlinear mixed effects model"*, Computational Statistics and Data Analysis. 49, 1020-1038, 2005.
[3] Samson A., Lavielle M., Mentré F. *"Extension of the SAEM algorithm to left-censored data in non-linear mixed-effects model: application to HIV dynamics models"* Computational Statistics and Data Analysis, vol. 51, pp. 1562--1574, 2006.
[4] Lavielle M., Mentré F. *"Estimation of population pharmacokinetic parameters of saquinavir in HIV patients and covariate analysis with the SAEM algorithm"* Journal of Pharmacokinetics and Pharmacodynamics, vol. 34, pp. 229--49, 2007.
[5] Samson A., Lavielle M., Mentré F. *"The SAEM algorithm for group comparison test in longitudinal data analysis based in nonlinear mixed-effects model"* Stat. in Medecine, vol. 26, pp. 4860--4875, 2007.

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

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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

References:

[1] Hassan M, Brown RD, Varma-O'brien S and Rogers D. "*Cheminformatics analysis and learning in a data pipelining environment*". Molecular diversity 2006 Aug;10(3):283-99. PubMed
[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.

Daniel Weiner Phoenix NLME and Phoenix

Dan Weiner and Simon Davis
Pharsight Corporation

Objective: To demonstrate

- Phoenix NLME (beta) for nonlinear mixed effects modeling
- Phoenix Connect for supporting usage of NONMEM, SAS, S-Plus and SigmaPlot in Phoenix workflows

Results: Phoenix NLME is capable of fitting a wide variety of non-linear mixed effects models and datasets. Estimation methods include FO, FOCE (ELS and Lindstrom-Bates), Laplacian, adaptive Gaussian quadrature, naïve pooled and iterative two-stage as well as a sophisticated non-parametric algorithm. Support for covariate selection, model selection and model qualification (bootstrap and posterior predictive checks) is also provided. Results are generally comparable with NONMEM, but NLME often executes faster as its engines are parallelized. Results can be compared to NONMEM side-by side using Phoenix Connect.

Conclusions: Phoenix NLME (to be released later this year) and Phoenix Connect provide a powerful modeling and simulation environment for nonlinear mixed effects problems. Use of workflows facilitates efficiency via creation of report ready graphs and tables, and can be utilized on multiple datasets.

Justin Wilkins Census: NLME project management for NONMEM

Justin J Wilkins

NONMEM is a powerful tool for nonlinear mixed-effects modeling and simulation of pharmacometric data. However, it is a console-based application whose output does not lend itself to rapid interpretation or efficient management. Census is a comprehensive Windows-based project manager for NONMEM-produced data, providing detailed summary, comparison and overview of the runs comprising a given project, including the display of output data, post-processing of output, rapid diagnostic plots.

Census provides publication-quality diagnostic graphics through its integration with Xpose 4 and includes a direct interface to R. Simple run reports and comparisons may be generated as needed.

This session is intended to demonstrate the capabilities of Census and to solicit feedback from the pharmacometrics community at large. Census is open-source (written in Delphi Object Pascal) and free of charge; details may be found at http://census.sourceforge.net.