

PAGE2012 Oral Abstracts

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Joachim Grevel Panel Discussion: Modelling and Simulation and the Regulatory Process

Moderator: Joachim Grevel. Panel composition: Terry Shepard, Gerard Pons, Peter Milligan, Mick Looby, Leon Aarons, Nick Holford.

This discussion will recapture a recent workshop at the EMA (December 2011) and promote a future collaboration between modellers working in drug development and assessors of the regulatory agencies.

The six panel members were asked to prepare answers to the following questions in order to jumpstart a lively discussion:

1. Why is the concept of the target concentration not guiding drug development during all clinical phases? And why are regulators not asking for the corresponding dosing target to guide therapy?
2. How does one rationally select a dose in the absence of having characterised a dose response?
3. If the likelihood of an informative p-value is small (limited evidence), which alternative approach can provide sensible inferences to guide the approval of new medications?
4. Model-based reasoning is currently only accepted by regulators in cases such as paediatrics where the classic approach ($p < 0.05$) is impractical. What can the modelling community do in order to increase the regulatory acceptance of their work in all types of submissions? Should we just wait for new guidances?
5. It was suggested at the EMA/EFPIA meeting that the EMA would try to increase its capabilities to assess modelling and simulation work. What are EMA's concrete plans and how can EFPIA help?

Bruno Bieth Model-based analyses for pivotal decisions, with an application to equivalence testing for biosimilars

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Objectives: In a drug development context, non-linear mixed effects models (NLME) are routinely used for exploratory analyses. These methods are very powerful but their appropriateness relies on the correctness of the model assumptions. The strict regulatory standards applied during phase III favor the use of analysis methods which are assumption-free, but often less powerful. The objective behind the present work was to use an NLME analysis in a pivotal phase III setting, to take full advantage of the substantial improvement in power, whilst at the same time maintaining the strict regulatory standards for phase III as much as possible.

Methods: The principle of our approach is illustrated in the context of biosimilar equivalence in rheumatoid arthritis, using the American College of Rheumatology 20% (ACR20) response criterion as primary study outcome. The planned model-based analysis would proceed as follows. To prevent against model misspecification, a set of several candidate models is pre-specified to describe the expected time course of ACR20 response. The models considered in this application were of Markov type [1]. Since the study aims to demonstrate equivalence between the originator product and the biosimilar, a key modeling outcome is the mean response rate difference between the two groups at primary end-point. We rely on model averaging [2] to combine the individual model estimates. A confidence interval for the model average estimate can be derived using bootstrap and this confidence interval can serve for formal equivalence testing.

Results: The proposed model-based test was evaluated through simulations and compared to the classical equivalence test based on end-point data only. Operational characteristics, such as type 1 error and power, were of particular interest. This investigation was performed under a range of simulation models and scenarios. Type 1 error appeared to be controlled under the simulation scenarios investigated. The gain in power with the model-based test was substantial compared to the classical equivalence test.

Conclusions: While those simulation results are promising, initial feedback from European health authorities suggested that further work should be undertaken to evaluate the performances of the proposed approach. In particular, the absence of theoretical results to justify type 1 error control appears to be a critical concern deserving careful consideration.

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Sylvain Goutelle A unified in vivo modeling approach for quantitative prediction of the impact of gene polymorphism and drug interactions on drug exposure

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Objectives: We propose a unified approach to predict in vivo variation in drug exposure due to gene polymorphism or drug-drug interactions (DDI). An application to drugs metabolized by cytochrome 2C19 (CYP2C19) is presented.

Methods: The approach is based on frameworks proposed by Ohno [1] and ourselves [2] for drug interactions and gene polymorphism, respectively. The metrics used is the ratio of altered drug AUC*, which may be caused by gene polymorphism or drug interaction, to reference AUC measured in patients with no mutation or no interaction (AUC^*/AUC , denoted R_{AUC}). For CYP2C19 gene polymorphism, prediction of the R_{AUC} is based on a model with two parameters: the contribution ratio of the drug CR (fraction of oral clearance dependent of CYP2C19), and the fraction of activity FA of allele combinations (relative activity of CYP2C19 in mutants compared with wild-type extensive metabolizers). For drug interactions, the two-parameter model includes CR of the victim drug and the inhibition ratio of the inhibitor (IR) which is a measure of inhibitor potency.

First, initial estimates of CRs and FAs were obtained from the literature, for 30 CYP2C19 drug substrates and 5 genotypes. Then, these values were used to predict R_{AUC} which were compared with observed R_{AUC} from another set of published data (external validation). Third, all data from step 1 and 2 were used to estimate posterior distributions of CRs, FAs, and AUCs by using Bayesian orthogonal regression in the Winbugs software. For drug interactions, previously estimated CRs and published data were used to estimate IRs of 10 inhibitors, by use of similar Bayesian approach. Final estimates of R_{AUC} were compared with observed values from all genotype and DDI published studies.

Results: Published data were available for 111 (drug, genotype) and 23 (victim drug, inhibitor) pairs. The mean prediction errors of R_{AUC} were -0.142 and -0.60, while the mean absolute prediction errors were 0.58 and 1.02 for genotype and DDI data, respectively. Overall, only 5 out of 134 predicted R_{AUC} were outside the 50-200% range of observed R_{AUC} .

Conclusions: This approach showed good predictive performance. It also provides unpublished prediction of R_{AUC} corresponding to rare genotypes (e.g., ultrametabolizers *17/*17) and DDI for 30 drugs metabolized by CYP2C19, including the widely prescribed proton-pump inhibitors and clopidogrel.

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France Mentré Launch of the new journal 'CPT: Pharmacometrics & Systems Pharmacology'

France Mentré, Lena Friberg, Piet Van der Graaf

The American Society for Clinical Pharmacology and Therapeutics (ASCPT) and Nature Publishing Group are pleased to announce the upcoming launch of a brand new publication: CPT: Pharmacometrics & Systems Pharmacology.

Piet van der Graaf, PhD, PharmD, Pfizer, will serve as editor-in-chief of CPT:PSP. The following individuals have been appointed as Associate Editors: Lena Friberg, PhD, Uppsala University; Steve Duffull, PhD, University of Otago; France Mentré, MD, PhD, Université Paris Diderot; Marc Gastonguay, PhD, Metrum Research Group; Paolo Vicini, PhD, Pfizer Global Research and Development; Douglas Lauffenburger, PhD, Massachusetts Institute of Technology; Amin Rostami, PharmD, PhD, University of Manchester; and Don Mager, PharmD, PhD, University at Buffalo, SUNY.

This group of editors represents and reflects the scientific and demographic diversity of CPT:PSP. Collectively, the editorial leadership of CPT:PSP will be advocates for the journal, responsible for selecting high-quality content for publication.

CPT:PSP, which is owned by ASCPT, and is an official journal of the American Society of Pharmacometrics (ASoP), will be published as an online-only, Open Access journal by Nature Publishing Group (NPG) and will provide a unique international forum for scientists in the pharmacometrics and systems pharmacology space. CPT: Pharmacometrics & Systems Pharmacology will publish advances in quantitative methods as applied in pharmacology, physiology, and therapeutics in humans with a common focus on the application of these two areas on drug discovery and development.

Together, the CPT: Pharmacometrics & Systems Pharmacology editorial leadership, ASCPT, ASoP, and NPG look to further define and shape the fields of pharmacometrics and systems pharmacology as applied to drug development.

CPT:PSP will officially launch in the Summer of 2012 with the online submission site opening on May 21 and the first issue expected to publish in the Fall. As an Open Access journal, all CPT:PSP content will be made freely available worldwide immediately upon publication.

Additional information on CPT:PSP, including the journal's Aims and Scope, is available at www.nature.com/psp.

***Fabrizio Benedetti* The neurobiology of placebos**

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Objectives: The placebo effect has evolved from being thought of as a nuisance in clinical and pharmacological research to a biological phenomenon worthy of scientific investigation in its own right. The study of the placebo effect and of its negative counterpart, the nocebo effect, is basically the study of the psychosocial context around the treatment and the patient, and it plays a crucial role in the therapeutic outcome [1,2].

Methods: In recent years, different types of placebo effects have been analyzed with sophisticated biological tools, such as neuropharmacology, neuroimaging, and single-neuron recording from awake subjects, that have uncovered specific mechanisms at the anatomical, physiological, biochemical and cellular level.

Results: Most of our knowledge about the neurobiological mechanisms of the placebo effect comes from the field of pain, whereby different neurotransmitters have been found to be involved, such as endogenous opioids and endocannabinoids in placebo analgesia [3] and cholecystokinin in nocebo hyperalgesia [4]. In addition, dopamine has been found to play a role as well, with an activation of dopamine receptors in the nucleus accumbens in placebo analgesia and their de-activation in nocebo hyperalgesia. Recent findings suggest that some of these mechanisms are also present in other medical conditions, like Parkinson's disease, in which placebos induce dopamine release in the striatum and changes of neuronal activity in the thalamus, subthalamus and substantia nigra [5].

Conclusions: This recent research has revealed that these placebo-induced biochemical and cellular changes in a patient's brain and body are very similar to the biochemical changes induced by drugs. This new way of thinking may have profound implications both for clinical trials and for medical practice [6].

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Jakob Ribbing Literature Model for FEV1 in COPD Trials – Separating the Dynamic Components of Placebo Effect, Disease Progression and Interacting Drug Effects

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Objectives: In chronic obstructive pulmonary disease (COPD) the forced expiratory volume in one second (FEV1) is the most important biomarker for lung function, and is used for dose selection.[1] The objective of this work was to develop a longitudinal model for FEV1 based on literature (summary level data) on COPD trials, to quantify placebo effect and disease progression, as well as treatment effects and their interaction in combination treatment.

Method: Criteria for inclusion were a) randomised, blinded COPD maintenance trial b) including treatments class: LABA, LAAC, ICS or PDE4i c) FEV1: troughs were used when available. Pre-study-drug measurements occurring after administration of a short-acting bronchodilator (post SABD) were otherwise used. Background therapy was generally allowed and any interaction was handled by drug-drug interaction models. Estimation was performed in NONMEM.

Results: The database included 87 studies, totalling 59775 patients across 228 treatment arms (including 72 placebo arms). These trials reported 1080 FEV1 values, each representing the mean in an arm, at a certain time during the study. Study durations ranged: 1 week to 4 years. The final structural model included components which described the baseline and the time course for: a) placebo response b) disease progression and c) drug effect. The drug-effect model included separate estimates for 13 compounds and described dose-response where possible. Drug interactions were estimated for the combination LABA+LAAC as well as for LABA or LAAC measured post SABD. An anti-inflammatory agent (ICS or PDE4i) in combination with a direct bronchodilator (LABA or LAAC) provided efficacy as the sum of the two mono components. Random inter-study variability (ISV) was included in all four structural components and in addition inter-arm variability in baseline. Important covariates were identified.

Conclusion: This exercise a) consolidated relevant information across compounds, in terms of efficacy, dose-response and time course for onset of drug-effect b) positions each published trial result into a broader evidence based context and c) illustrates the impact of PD interactions and other covariates.

Furthermore our FEV1 model will be developed to predict exacerbations, providing predicted trough FEV1 even for trials that only measured FEV1 post SABD. This is an important efficiency gain since the late phase exacerbation trials require thousands of patients and at least one year duration.

Reference:

[1] Outcomes for COPD pharmacological trials: from lung function to biomarkers. M. Cazzola et al. Eur Respir J 2008; 31: 416-468.

Thomas Eissing A physiologically-based PK/PD model to capture population variability for diabetes research and automatic blood glucose control

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Objectives: Realistic in-silico models of the glucose metabolism can provide invaluable information to improve diabetes management and research and the development of automatic control strategies for diabetes. Existing in-silico models (reviewed in [1]) already provide a powerful tool, e.g. [2] approved by the FDA for pre-clinical testing, but do not provide the mechanistic and structural detail at molecular and organ levels necessary to integrate heterogeneous data that can drive fundamental research in diabetes. We here present the methods necessary to close this gap.

Methods: A coupled PBPK/PD model of glucose metabolism, including glucagon, was developed on a high level of mechanistic detail using PK-Sim® and MoBi® [3, 4]. Mechanistic models of both insulin receptor dynamics and subcutaneous insulin absorption were integrated to capture variability in insulin action on a molecular level and to accommodate for the application of commercial insulin analogs. A detailed description of the GI-Tract for oral absorption allows the simulation of meal and glucose absorption and can be extended for the study of oral anti-diabetic agents. The established model can be extrapolated to populations, be it adults, children or elderly [5] to capture the variability of glucose metabolism. The different modules as well as the multi-scale model were parameterized using literature, e.g. [6], and in-house data and will be further tested in clinical trials.

Results: The model is able to describe different standard scenarios including clamp studies, the response to intravenous and oral glucose tolerance tests as well as complete clinical trials, both, with healthy subjects and subjects with type 1 diabetes. It can be individualized based on physiological data and patient history (e.g. bodyweight or total daily dose of insulin). The high level of mechanistic and structural detail allows to capture some of the intra-individual variability generally compensated by a time-variant correction of insulin sensitivity. The modeling framework allows to generate virtual diabetic populations or individualized models for support in pharma R&D of diabetes and for the evaluation of automatic glucose control within integrated systems [7].

Conclusion: Overall, the PBPK/PD model provides a powerful basis to the medical scientific, pharmaceutical and device R&D community for the testing and validation of novel diabetes treatment strategies on virtual diabetes populations.

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Maria Kjellsson Predicting late-phase outcome from early-phase findings using a Model-Based Approach – Application to Type 2 Diabetes Mellitus

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Objectives: Predicting late-phase outcome from early-phase findings is increasingly being used to inform decisions in drug development. However, if the biomarker in early-phase is different from late-phase this bridging is more challenging. In this work, we present a model-based bridging approach for type 2 diabetes mellitus (T2DM) as an example of drug development programs where different biomarkers are used in phase 1 (meal test provocation tests) and phase 2 (HbA1c levels) for efficacy assessment.

Methods: Two previously developed semi-mechanistic models were used; an integrated glucose and insulin (IGI) model [1-2] predicting glucose and insulin concentration after meal test provocation experiments and an integrated glucose-red blood cell-HbA1c (IGRH) model [3] predicting the time-dependent change in HbA1c levels from the average glucose concentration (C_{g,av}) and life-span of red blood cells. Study and drug specific parameters of the IGI model were estimated using data from a phase1 study in 59 diabetic patients receiving placebo or a glucokinase activator (GKA) for one week with repeated meal test challenges. From this adapted IGI model, C_{g,av} was simulated according to a phase2 study design and used in the IGRH model to predict the HbA1c response. This bridging approach was validated by comparing the predicted relative change in HbA1c to the actual outcome of the phase 2 study.

Results: The re-estimated parameters of the IGI model and the GKA drug effect parameters were in good agreement with previously reported parameters [2]. The main trend in relative change in HbA1c over time was reasonably well captured except for two dose arms. Using only the point estimates of mixed-effects parameters with the residual error under-estimated the variability seen in the study. Including the uncertainty in the parameters improved the predictions.

Conclusions: Using a model based approach allowed to predict reasonably well Phase 2 HbA1c response from effect on glucose and insulin observed in Phase I

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Franziska Schädeli Stark Semi-physiologic population PKPD model characterizing the effect of bitopertin (RG1678) glycine reuptake inhibitor on hemoglobin turnover in humans

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Objectives: Bitopertin, a glycine reuptake inhibitor in development for the treatment of schizophrenia, selectively inhibits the glycine transporter type 1 (GlyT1), which is localized on pre-erythrocytes in addition to being expressed in the CNS. A reduced glycine uptake leads to a dose dependent decrease of hemoglobin (Hb) synthesis in animals and humans. A semi-physiologic PKPD model of bitopertin hematological effect in red blood cells (RBC) has been developed as a tool to estimate the long term risk of anemia due to GlyT1 inhibition.

Methods: The hematological effect of GlyT1 inhibition was studied in 62 healthy subjects treated with placebo, 10, 30, or 60 mg bitopertin daily for 120 days. Hb, RBC, and mean corpuscular Hb (MCH) data were collected during treatment and 120 days follow-up. A semi-physiologic population PKPD model taking into account the Hb and RBC turnover has been developed in NONMEM 7. Two parallel chains of four transit compartments sharing the same transit rate constant but with their own production rates represent RBC and MCH turnover. Since blood Hb is the cumulative product of RBC*MCH in all compartments, the model was fit simultaneously to the MCH and RBC data. The drug acts as an inhibitory Emax model on MCH production rate (i.e. Hb synthesis), with individual AUC_{ss} estimates driving the effect. Hb decrease triggers a feedback to increase the RBC production rate.

Results: A dose-related decrease of MCH in RBC over time was observed, which was reversible after treatment discontinuation. The RBC start to increase due to feedback after about 4 weeks at 30 and 60 mg. All observed data were well predicted. Estimates of Hb synthesis rate (0.96 pg/cell/day), RBC production rate ($0.04 * 10^{12}$ /L/day) and RBC life span (124 days) are in line with expected physiological values. A 12 % lower RBC production rate was estimated for females, resulting in lower baseline RBC and Hb values. The model predicts that a nadir of Hb decrease is reached after about one RBC life span, followed by a plateau of effect at slightly higher levels when the steady-state of the hematological system, including feedback reaction, is reached. The model predicts a typical Hb decrease of 14 % at nadir for the 60 mg dose, and less than 10 % for 20 mg.

Conclusions: The semi-mechanistic PKPD model will be a useful tool to characterize the hematological effect of bitopertin in the target population, to predict the risk of anemia and to support Hb monitoring guidelines for patients treated with bitopertin.

James Yates Applying mechanistic pharmacokinetic-pharmacodynamic models (PKPD) to describe the growth and inhibition of xenograft tumours in rats and mice by targeted anti-cancer agents.

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Objectives: Measurement of tumour volume over time could mask a range of changes due to underlying biology and treatment. Simeoni et al [1] published a mathematical model with drug-concentration induced cell damage, and transit-compartments to empirically describe populations of cells undergoing stages of cell damage and death. The model involves a number of assumptions: All healthy cells are equally susceptible to drug treatment at all times; drug action is linearly related to drug concentration; drug action causes cell damage and death. Ribba et al [2] recently demonstrated the utility of a mechanistic model that characterizes the tumor xenograft in terms of non-hypoxic, hypoxic, and necrotic cells and the drug action on these sub-populations of cells. We will illustrate several modeling examples of how a more mechanistic model can be developed.

Methods: We have adapted the models to be more mechanistic by incorporating features that describe: (1) the utility of biomarkers as a driver for growth inhibition; (2) multiple mechanisms of drug action on sub-populations of cells. We also extend the models to incorporate the spatial features of a tumor in an attempt to better describe the tumor micro-environment. Pharmacokinetic, biomarker and tumor growth data for example compounds have been used to demonstrate the utility of these mechanistic models. Structural identifiability analysis [3] was applied to check that parameters are estimable. Example data sets were then analysed to demonstrate the utility of the model.

Results: The model is identifiable and the parameters are practically identifiable. Incorporating non-linearity between drug exposure, biomarker response, and tumor growth inhibition allows observed differences between dosing schedules to be explained. Using a biomarker as the driver for tumor growth inhibition provides a more meaningful surrogate for pharmacological action, particularly in the situation where biomarker response to drug is significantly delayed compared to the pharmacokinetics. Modeling multiple mechanisms of action on sub-populations of cells can allow an accurate representation of the drug effect on the disease biology.

Conclusions: We demonstrate that adding mechanistic features to a descriptive model of drug-induced tumor growth inhibition makes it more representative of the disease biology and drug action. The model also could potentially be used for translation to the clinic from pre-clinical data.

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***Ben-Fillippo Krippendorff* Relationship between the dose of therapeutic antibodies and the inhibition of cytoplasmic and nuclear growth factor signalling**

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Objectives: Inhibition of growth factor signalling is a promising strategy in cancer treatment because of the importance of such signals for proliferation, survival and resistance to chemotherapy. We have investigated how different physiological processes contribute to the relationship between the dose of a therapeutic antibody and the inhibition of cellular signalling. We therefore built a multi-level PK/PD model to relate the dose of an intravenously administered anti-EGFR antibody to the inhibition of intracellular growth factor signalling in cancer cells.

Methods: First, we built a pharmacokinetic model for different therapeutic antibodies on the market targeting the EGFR. The model follows the idea of target mediated drug disposition (TMDD), but we extended the concept by including intracellular receptor trafficking and the competition of the drug with endogenous receptor ligands. The final model allows the translation of a dose of administered antibody into the percentage of receptor molecules inhibited during the time of the treatment. Second, we built a cellular model to follow the effect of changes in EGFR activity from the cell surface to ERK in the nucleus. ERK is a key protein, downstream of the EGFR, controlling the expression of genes involved in proliferation and survival.

Results: To evaluate the multi-level PK/PD model, we compared our model predictions with experimental data of zalutumumab (2F8), an IgG1 antibody against the EGFR that inhibits tumor growth in xenograft models and has shown promising results in phase I/II clinical trials. The predicted time-courses of the drug concentrations showed a good agreement for high, medium and low doses (40 mg/kg, 20 mg/kg and 2 mg/kg). We then validated the cellular part of the model by using an imaging cytometer to quantify phosphorylated epidermal growth factor receptor (EGFR) and double phosphorylated Erk1/2 in individual cancer cells.

The decomposition of the different levels of drug treatment suggests that the overall response to a therapeutic antibody against the EGFR can be described by (i) a nonlinear relationship between the dose and receptor inhibition (ii) a nonlinear processing of the receptor signal by the MAPK cascade, and (iii) linear signal amplification by nuclear import processes of Erk.

Conclusions: Extending pharmacokinetic models to the cellular level by incorporating in vivo and in vitro data allows the prediction of the cellular effect of different drug doses.

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Mélanie Wilbaux Population K-PD joint modeling of tumor size and CA 125 kinetics after chemotherapy in relapsed ovarian cancer (ROC) patients

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Objectives: Ovarian cancer remains the leading cause of gynecologic cancer deaths. CA125 is used as a serum marker of epithelial ovarian cancer. Although lacking of specificity, it may be used to predict tumor burden after chemotherapy and before surgery. The aim of this work is to externally validate a population semi-mechanistic model of CA125 and tumor size kinetics.

Methods: Patients: 535 ROC patients from the CALYPSO trial, a randomized phase III study comparing 2 platine-based regimens (Carboplatin-Paclitaxel vs Carboplatin-Pegylated Liposomal Doxorubicin) were analyzed. Median of 10 CA125 concentration values and 4 tumor size observations per subject were available. 2/3 of patients were randomized to a learning dataset for model building; 1/3 to validation dataset for the external validation.

Model: A semi-mechanistic model was built to describe CA125 and tumor size kinetics after chemotherapy administration. The population analysis was performed with a nonlinear mixed effects model using Monolix 4.1.1. Selection of best model was achieved using criteria based on the likelihood, GOF plots and simulation-based diagnostics. External validation was done using the normalized prediction distribution errors (NPDE) from 2000 replications of the validation set.

Results: Since no drug concentration data were available, a KPD approach has been used for the kinetics of the drug effect. The KPD was described by 2 virtual compartments: 1 central compartment receiving the dose, and 1 transit compartment allowing for a delayed drug effect. Tumor kinetics was dependent on the treatment effect, acting as an inhibitor of tumor growth. CA125 production rate was linked to tumor size variations. CA125 and tumor size kinetics in ROC patients after chemotherapy were properly fit over a 500 days period. NPDEs, calculated on validation dataset, did not deviate from a standard normal distribution, which lead to conclude that the model and population parameter distributions are correct. On the validation dataset tumor size could be adequately predicted using only CA125 levels and model parameters estimated on the learning dataset.

Conclusion: Our semi-mechanistic model is the first to link tumor size and CA125 kinetics to cytotoxic treatment in ROC patients receiving chemotherapy. External validation showed the predictive ability of this model. Modeled CA125 kinetics will be used to compare treatments and to derive predictors of tumor burden dynamics and tumor resectability.

***Ekaterina Gibiansky* PK/PD modeling and optimization of eltrombopag dose and regimen for treatment of chemotherapy-induced thrombocytopenia (CIT) in cancer patients**

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Objectives: To characterize the time course of platelet counts (PLC) following eltrombopag administration, an oral thrombopoietin receptor agonist, in cancer patients receiving carboplatin/paclitaxel (CP), and to optimize eltrombopag dose and regimen for patients receiving CP.

Methods: Of 172 patients undergoing chemotherapy with CP every 21 days, 125 also received 50, 75 or 100 mg eltrombopag for 10 days following each CP administration, and 47 received placebo. Nonlinear mixed effects modeling was used to develop the PK/PD model of PLC reduction due to chemotherapy in patients receiving placebo and to describe the effect of eltrombopag on PLC. Proposed models employed a bone marrow precursor production compartment with first- or zero-order proliferation rate that did or did not depend on PLC, differing number of transit/maturation compartments, and a circulation compartment [1,2]; CP decreased the precursor production rate while eltrombopag increased it. CP concentrations were not collected and were described using a KPD approach [3]. Individual predictions of eltrombopag concentrations were computed using an earlier developed PK model [4]. After visual predictive check evaluation, the final model was used to simulate various eltrombopag dosing regimens with dosing before and after CP.

Results: PLC were described by a 4-compartment model (with thrombopoiesis parameters equal to those in healthy subjects [2]) where carboplatin [5] and eltrombopag affected zero-order production of platelet precursors. Carboplatin lowered production linearly with dose, more with each cycle, decreasing it by 18.1 to 31.4% at 536 mg of carboplatin (median dose in cycle 1) in cycles 1 to 8, respectively. Eltrombopag stimulated production, linearly with concentration, less with each cycle, increasing it 133 to 37% at 7 mg/mL of eltrombopag concentration (median average concentration at steady state at 100 mg dose) in cycles 1 to 8, respectively, compared to CP alone. Simulations indicated that eltrombopag started 5 days before CP and continued 5 days after in each cycle minimizes the reduction and fluctuation of PLC. Eltrombopag dose should be increased across cycles to overcome the impact of CP, and higher starting doses are required in patients with low baseline PLC.

Conclusions: The developed semi-mechanistic PKPD model described the opposing effects of CP and eltrombopag on PLC, and was used to optimize eltrombopag dose and regimen selection in patients receiving eltrombopag for the treatment of CIT.

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Thomas Dorlo Translational pharmacokinetic modelling and simulation for the assessment of duration of contraceptive cover after use of miltefosine for the treatment of visceral leishmaniasis

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Background & Objectives: Miltefosine is currently the only oral drug available for the treatment of visceral leishmaniasis (VL), a neglected tropical parasitic infection. It has been adopted in national VL elimination programmes in India, Bangladesh and Nepal, but its widespread use and roll-out into rural clinics is severely hampered by its potential teratogenicity [1]. Foeto- and embryotoxicity have been shown in rabbits and rats. Therefore, use during pregnancy is strictly dismissed and contraceptive cover both during and after treatment is recommended in women of child-bearing potential.

Duration of post-treatment contraceptive cover in females remains a point of debate: most guidelines recommend either 2 or 3 months of post-treatment contraceptive cover, based on simple extrapolations of the initial elimination half-life [2]. However, miltefosine can be detected in plasma until at least 5 months post-treatment and the post-treatment contraceptive cover period could be extended accordingly [3]. Currently, various shortened miltefosine regimens for VL are being evaluated [4]. Nevertheless, uncertainty about the length of contraception to use for these shorter regimens strongly impedes their implementation. Unfortunately, previous pharmacokinetic (PK) data are not available for women of child-bearing potential because of exclusion from previous clinical trials.

This study aimed at providing a more scientific and rational approach to suggest durations of contraceptive cover after the use of various miltefosine regimens based on conversion and translation of dosing data from preclinical reproductive toxicity studies in animals and simulation of human PK data using a unique comprehensive anthropometric dataset of an historical cohort of Indian VL patients.

Methods: Anthropometric data for female VL patients of child-bearing potential were selected from a large demographic dataset from Médecins Sans Frontières (MSF dataset), collected between 2007 and 2009 from Vaishali District, Bihar State, India.

Simulations and estimations were performed using NONMEM VII and R. An open two-compartment model with first-order absorption and elimination from the central compartment, estimated and validated from previous miltefosine PK data [5], was used for Monte Carlo simulations. To account for body size, allometric scaling of clearance (0.75) and volume of distribution (1) by fat-free mass was applied, which was previously evaluated over a wide range of

body sizes [5]. Concentration-time curves after miltefosine treatment for 5, 7, 10 & 28 days (2.5 mg/kg/day) were simulated using the demographic data from the MSF dataset (n=465). Simulations were repeated 100 times.

The no observed adverse effect level (NOAEL) of miltefosine in animal reproductive toxicity studies was determined from available literature. This NOAEL in rats was translated to a total human dose equivalent using available anthropometric data and Boyd's formula for body surface area [6]. A human reproductive safety threshold exposure limit (RSTEL) for miltefosine was defined as the median predicted miltefosine exposure ($AUC_{0-\infty}$) following administration of the NOAEL human dose equivalent in Indian females of child-bearing potential. To account for any unknown between-species differences in sensitivity to reproductive toxicity, the RSTEL was divided by a default animal-to-human uncertainty factor of 10 [7].

The 'unprotected' residual exposure to miltefosine after end of the post-treatment contraceptive cover period (EOC) until infinity ($AUC_{EOC-\infty}$) was determined in the individual simulated PK curves for the different miltefosine regimens. Different periods of post-treatment contraceptive cover were considered (1, 2, 3 and 4 months). The individual $AUC_{EOC-\infty}$ was compared to the RSTEL and the probability for simulated Indian female VL patients of child-bearing potential of having an exposure exceeding the RSTEL was calculated.

Results: PK data were simulated for 465 selected treated Indian female VL patients of child-bearing potential with a median (IQR) age, weight and BMI of 25 (16-31) yrs, 38 (34-42) kg and 17.3 (15.8-18.8) kg/m², respectively. The median (90% PI) times until the simulated plasma PK curves reached the current lower limit of quantitation (LLOQ; 4 ng/mL [8]) were 158 days (103-216 days), 176 days (119-235 days), 196 days (139-255 days) and 258 days (201-318 days), for the 5, 7, 10 and 28 day miltefosine regimen, respectively.

The NOAEL miltefosine dose in rats (0.6 mg/kg/day p.o. for 10 days [2]) corresponds with a total dose of 35.42 mg/m² in rats, which was converted to a total human dose equivalent of 45 mg. The median (90% PI) simulated $AUC_{0-\infty}$ following administration of this dose in the selected Indian female VL patients was 245 $\mu\text{g}\cdot\text{day}/\text{mL}$ (140-467 $\mu\text{g}\cdot\text{day}/\text{mL}$). Applying an animal-to-human safety factor of 10, a human RSTEL was derived of 24.5 $\mu\text{g}\cdot\text{day}/\text{mL}$.

Median (90% PI) 'unprotected' miltefosine exposure after the end of contraception use ($AUC_{EOC-\infty}$) was e.g. for the 28 day regimen 54.50 (22.92-125.74), 8.74 (3.08-25.19), 4.11 (1.37-12.52) for 1, 2 and 3 months contraception, respectively. Probability of 'unprotected' supra-threshold ($>\text{RSTEL}$; $>24.5 \mu\text{g}\cdot\text{day}/\text{mL}$) miltefosine exposure was very low ($<0.2\%$) for a post-treatment contraceptive cover period of 4 months for the standard 28 day regimen and 2 months for the 5, 7 and 10 day miltefosine regimen. One month post-treatment contraception resulted in substantial probability of $>\text{RSTEL}$ exposure for all regimens: 4.30%, 18.2%, 54.6% and 93.6%, for the 5, 7, 10 and 28 day regimen, respectively. The currently advised 2 months contraception (28 day regimen) led to 5.42% probability of having $>\text{RSTEL}$ miltefosine exposure.

Discussion & Conclusion: The design of clinical teratogenic risk management-programs for drugs exhibiting reproductive toxicity in preclinical studies is problematic. Finding the optimal contraceptive cover is ethically imperative: too long a period may be economically not favourable and lead to adherence problems, while too short a period may increase the risk at congenital malformations. Recommended periods of post-treatment contraception are often based on the bioanalytical LLOQ, lacking any rational physiological and PK considerations. To our knowledge, this is the first study providing rational suggestions for contraceptive cover for a teratogenic drug based on animal-to-human dose conversion. To assess adequacy of contraceptive cover the probability of post-contraceptive supra-threshold miltefosine exposure was linked to the environmentally induced fraction of overall congenital malformation incidence ($\sim 0.2\%$) [9,10]. Our

results indicate that, for the standard 28 day miltefosine regimen, post-treatment contraceptive cover may be extended from the currently advised 2 months to a period of 4 months. For the shortened regimens, 2 months may be sufficient, which has important implications for the implementation of these regimens in the developing world.

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Sebastian Ueckert Application of Item Response Theory to ADAS-cog Scores Modelling in Alzheimer's Disease

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Objectives: The challenges in the development of new therapeutic agents for Alzheimer's Disease (AD) become apparent through the high number of failed late phase trials [1]. Despite an increasing interest in biomarkers, cognition remains the primary regulatory accepted clinical outcome. The most frequently used test, ADAS-cog, consists of a broad spectrum of tasks that test different components of cognition [2]. The total ADAS-cog score is obtained by rating a subject's performance in each of the subtests and summing up the resulting subscores to yield an overall assessment. In turn, pharmacometric models traditionally describe Alzheimer's disease progression using this summary score [3,4]. An alternative approach, explored in this work, is to model each subscore separately and link the model subcomponents to a common unobserved variable "cognitive disability". In psychometrics, this method is used to study the sensitivity of items in standardized educational tests, and the approach is referred to as item response theory (IRT) [5]. The aims of this work were a) to develop an IRT model for ADAS-cog scores, b) to compare the performance of a longitudinal model using item level or summary data and c) to apply optimal design to the selection of the most informative battery of tests in a given population.

Methods

1 ADAS-cog IRT Model

Baseline ADAS-cog assessments with item level data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) [6] and the Coalition Against Major Diseases (CAMD) [7] databases were used for this part of the project. The resulting dataset used in this work consisted of 2651 subjects from 7 studies with a total of 152313 baseline observations. For each subtest of the cognitive assessment, depending on the nature of the arising data, a binary, count or ordered categorical model was developed, describing the probability of a failed test outcome as a function of the latent cognitive disability. All parameters considered as characterizing the individual test item were expressed as fixed effects, whereas the cognitive disability was modeled as a subject specific random effect. The model performance was evaluated through comparison of observed and simulated data for each item.

2 Longitudinal Model Comparison

Based on the accessibility of study protocol information, one study from the CAMD database was selected for a complete longitudinal analysis. The available data consisted of the placebo arm of an 18-month AD trial with a total of 322 patients and 7 ADAS-cog assessments per patient. The basic longitudinal model, without covariates, published by Ito et al. (3) was applied to a) the summary ADAS-cog score and b) the hidden cognitive disability variable. The model adequacy was assessed through visual predictive checks on both item and summary levels and parameter precision was

evaluated through a posterior predictive check of the mean ADAS-cog score at baseline and the mean annual change in ADAS-cog.

3 Optimal Test Design

Based on the developed IRT model, the Fisher information for estimating a patient's cognitive disability was calculated for each item in the ADAS-cog test. The test items were ranked by information content within a mild cognitively impaired (MCI) and a mild AD (mAD) patient population. Furthermore, the additional amount of information added to an ADAS-cog assessment through incorporation of additional components ("delayed word recall" and "number cancellation" [8]) were evaluated in both populations.

Results

1 ADAS-cog IRT Model

The final ADAS-cog IRT model consisted of 39 binary, 5 binomial, 1 generalized Poisson and 5 ordered categorical submodels with a total of 166 parameters. Simulations from the individual models were in excellent agreement with the observed data. All but one estimated characteristic curves for the test items were well defined with a low failure probability for healthy subjects and high failure probability for severely impaired patients. Only the characteristic curve for the task "state your name" was essentially flat.

2 Longitudinal Model Comparison

Without re-estimation of the item specific parameters, the IRT model described the longitudinal nature of most of the test subcomponents satisfactorily. The introduction of study specific parameters for 2 of the 4 investigator-rated items significantly improved the description of the observed data. Another significant improvement was the introduction of Markov effects for test items repeated across occasions. On visual predictive checks, no difference between the prediction intervals obtained with the summary score model and the IRT model was observed, however the 95% confidence interval of both the mean baseline score and the annual change was narrower with the IRT model.

3 Optimal Test Design

The information content ranking of the subcomponents in a classical ADAS-cog assessment differed between the two patient populations. For the MCI population the word recall component was most informative, while for the mAD population the orientation component carried most information. Similarly, there was an apparent difference in the relative amount of information added by including the delayed word recall and number cancellation components. With the additional components, the information content of the complete ADAS-cog assessment increased by 78% in the MCI population compared to only 35% for the mAD population.

Conclusions: Utilizing IRT, the information available in clinical trial databases can be used to characterize the relationships between the individual items of a cognitive assessment. The resulting mathematical description can serve as a platform for future trials with the advantages of a) a more exact replication of the score distribution, b) an implicit mechanism for handling missing information, and c) the ability to easily combine data from different ADAS-cog variants. Parameter estimates obtained through application of the IRT model to longitudinal clinical trial data were more precise than the ones obtained through a summary score-based model, indicating a higher probability to detect changes due to a drug effect. Another feature demonstrated in this work is the capability to quantify the information content of the individual components of a cognitive assessment and the possibility to adapt a cognitive assessment specific to the patient populations' degree of disability. A population specific test would not only be more sensitive to changes due to disease progression or drug effect, but also reduce the assessment time and thus burden for the

patient. In addition, IRT also allows combination of different cognitive assessments, like the mini-mental state examination (MMSE), into one common pharmacometric model. Many of the benefits of using item-level models are not exclusive to AD, but can easily be extended to other disease areas where summary scores constitute an important clinical measure, e.g. in Parkinson's disease or rheumatoid arthritis.

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Oliver Ackaert A hidden Markov model to assess drug-induced sleep fragmentation

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Objectives: Drug-induced sleep fragmentation can cause sleep disturbances either via their intended pharmacological action or as a side effect. The characterization of the circadian sleep pattern by EEG following drug exposure has improved our understanding of the mechanisms, leading to sleep disturbance, and their translatability across species. EEG shows frequent transitions between specific sleep states leading to multiple correlated sojourns in these states. We have quantitatively compared sleep disturbance in rats induced by a new chemical entity (NCE) and an active comparator methylphenidate using a Markov modeling approach. The original data and analysis have been published previously [1] and are presented at this meeting for further discussion.

Methods: The effects of methylphenidate and the NCE on sleep were determined on 2 cohorts of rats (n=6-8 per group) in a placebo controlled cross-over design. EEG and EMG signals were recorded during 12h post dosing and sleep state (REM, NREM and WAKE) was determined using sleep stage discriminator. It was decided to consider 2 vigilance states: WAKE and SLEEP, obtained by merging REM and NREM. The time spent in each of the states was binarized, using a cut-off point of 2.5 min. A hidden Markov model was developed to analyse in NONMEM this dense and continuous data taking dependency between observations and misclassification errors into account. It was assumed that placebo and these drugs could either accelerate or decelerate the transitions between sleep states. The predictive performance was assessed by simulations and a receiver operating characteristic (ROC) curve.

Results: The hidden Markov model predicted the data well with a low probability of misclassification and a good predictive performance. Methylphenidate and NCE both showed sleep disturbance by promoting wakefulness in a dose dependent manner with methylphenidate being 5 times more potent than NCE. Methylphenidate exhibits its effect by inhibiting the transition between sleep states, while the NCE stimulates this transition, suggesting a potential different mechanism of action for both compounds.

Conclusion: This model can be used to quantify differences in sleep fragmentation and provides insight into the nature of the underlying mechanism of action of drug inducing sleep fragmentation. As a result this hidden Markov modeling approach can be applied to screen NCE's early in development for their possible effects on sleep fragmentation.

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Chee Ng Novel Hybrid Artificial Neural Network-Nonlinear Mixed Effect Model Modeling Approach for Population Data Analysis in Model-based Drug Development

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Background and Objectives: A potential limitation of current model-based drug development (MBDD) approach is that integration of the knowledge from observed data into population model can be incomplete (incomplete learning) due to computing hardware/software limitation and lack of biological understandings. This resulted in biased model prediction that may lead to inefficient drug development strategy. Artificial neural network (ANN) is a powerful function mapping tool and any well-behaved multivariate functional relationships can be implemented exactly with ANN. Therefore, it is hypothesized that ANN can be used to detect/correct the deficiency of the population model developed with nonlinear mixed-effect model (NLME) and improve the model prediction throughout the MBDD process. The objective of this study is to develop a novel hybrid ANN-NLME modeling approach for population data analysis in MBDD.

Methods: The developed ANN-NLME method consists of a three-layer fully connected feed-forward ANN with Bayesian regularization and NONMEM FOCE. A MATLAB program was written to integrate the ANN with NONMEM for data analysis. Three simulated dataset/scenarios were used to assess the performance of the ANN-NLME (FOCE) (Table 1). The complete model was used to simulate population data. Three different models including 1) complete model with NONMEM FOCE (C), 2) Incomplete model with NONMEM FOCE (IC), and 3) Incomplete model with ANN-FOCE (IC-ANN), was fitted to the simulated data and then results were compared.

Table 1: Scenarios for Model Comparison

Scenarios	Complete Model	Incomplete Model
A	2-compartment PK	1-compartment PK
B	2-compartment PK IgG model with time-dependent inhibitory effect of anti-IgG antibody on PK of the low dose group	2-compartment PK
C	PK-PD model with two interacting PD pathways (I and II)	PK-PD model with a pathway I

Results/Conclusion: The ANN was able to detect/correct the model deficiency and improve the prediction of the model with incomplete information (Table2). To my best knowledge, this is the first reported hybrid ANN-NLME modeling approach for population data analysis. This novel approach that combines the powerful mapping function of ANN with flexibility of NLME method may serve as an excellent computational platform for developing highly predictive population model to support decision making in MBDD.

Table 2. RMSE of Model Prediction. (Lower=Better)

Scenarios	IC	IC-ANN	C
A	0.223	0.104	0.094
B	0.373	0.178	0.095
C	0.238	0.119	0.095

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William Denney N-dimensional Likelihood Profiling: An Efficient Alternative to Bootstrap

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Objectives: Bootstrap is the reference method for obtaining robust estimates of the confidence intervals (CI) of model parameters and simulation estimates. However, bootstrapping requires significant computational resources with typically ≥ 1000 iterations (each taking approximately the same CPU time of a single run) and ≥ 30 independent subjects to provide 95-99% CI. [1] The objective of this work is to develop a time effective alternative to bootstrapping: N-dimensional Likelihood Profiling (NLP) is proposed here as the extension of log-likelihood profiling [2-3] to multiple dimensions with applications analogous to bootstrapping.

Methods: The basis of NLP is integration of the log-likelihood surface with regions defining the deviation from normality. The method iteratively estimates the n-dimensional log-likelihood by adaptive sampling of the surface and refining regions in areas of large uncertainty until the changes are below a user-provided tolerance. At completion, a parametric probability surface is provided to the user with confidence intervals on each estimated parameter. This parametric surface can be sampled with algebraic integration for further model simulation (similar to a bootstrapped VPC). The algorithm logical steps are:

- 0) Initialize with multivariate normal surface assumption
- 1) While $\Delta \int \chi^2(\log\text{Lik}(\theta)) d\theta > \text{tol}$
- 2) Choose new θ for refinement
- 3) Estimate $\log\text{Lik}(\theta)$

Where θ is the vector of model parameters; $\log\text{Lik}$ is the log-likelihood as a function of model parameters; χ^2 is the p-value from the chi-squared distribution for the given log-likelihood relative to the model minimum; and tol is the user-selected tolerance.

Results: Simulated PK and PD datasets allowed estimation of the likelihood surface using NLP with ≥ 10 -fold reduction in the computational time compared to bootstrap (using 1% as tolerance); when a high number of dimensions are required for uncertainty estimates, the efficiency approaches parity with bootstrapping. Results were similar to bootstrapped estimates when examined visually and bootstrapped points outside an estimated confidence region.

Conclusions: In a variety of PK and PD model examples, NLP provides excellent agreement with bootstrapping in model simulation confidence intervals using NONMEM 7.1.2 FOCE-I. NLP markedly decreases computation time relative to bootstrapping.

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Gilbert Koch Modeling of delayed phenomena in PKPD by delay differential equations of lifespan type

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Objectives: Delayed phenomena are common in PKPD modeling. Traditionally, transit compartments (TC) based on ordinary differential equations (ODE) are applied to handle delays and further also used to describe populations, e.g. cells, see [1] or [2]. We investigate the relationship between TCs and delay differential equations (DDE) of lifespan type, see [3]. Our aims are to rewrite TCs by a lifespan approach in order to reduce the amount of physiological non-interpretable stages, to apply DDEs for populations and, in general, to handle delays with DDEs. We present two applications and theoretical results.

Methods: We applied DDEs of the form

$$x'(t) = f(t, x(t), x(t-T)) \text{ with } x(s) = \varphi(s) \text{ for } -T \leq s \leq 0$$

for PKPD modeling. In contrast to ODEs, such models consists of an explicit delay parameter $T > 0$ and uses information from the past in the term $x(t-T)$. In DDEs of lifespan type the parameter T describes the mean lifespan of individuals in a population.

Results: Our main theoretical result is that the totality of all objects of TCs with arbitrary initial values converges to a DDE of lifespan type, see [3]. As a consequence one can substitute TCs by DDEs and also vice versa. In a first application we rewrote the TC structure of a standard tumor growth model (see e.g. [1] or [2]) by DDEs. The resulting model has exactly two states, one for proliferating cells and one for dying tumor cells, see [3]. The second application dealt with arthritis development where increased cytokine concentration drives strongly delayed bone destruction, see [4]. We directly applied DDEs of lifespan type to characterize this large delay and the PKPD model results in just three pharmacological meaningful states. Finally, we will characterize four typical structures of PKPD models by DDEs from a theoretical point of view.

Conclusions: DDEs of lifespan type are a serious alternative to traditional TCs of length n because the number of states to describe delays or populations reduces to exactly one. Further DDEs open the route to introduce information from the past of pharmacological processes into a PKPD model.

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***Aris Dokoumetzidis* Lumping of compartments**

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Interest in simplification of large mechanistic mathematical models of biological systems which are usually described by differential equations, has increased in recent years as Systems Biology is growing. Often model reduction techniques are borrowed from Petroleum Science where simplification of particularly large models of thousands of chemical reactions is widely used. In the field of Pharmacokinetics, simplification of large models has been considered mainly for Whole Body Physiologically Based Models (PBPK), while the potential of bridging the gap between the bottom-up, knowledge driven, systems biology models and the top-down, data driven models of empirical PK-PD, sounds intriguing.

The main approaches for model simplification are elimination of states and reactions (or flows) and lumping of states or compartments. While lumping can be any linear or indeed nonlinear transformation of the states of the original model to new, fewer in number states, a special case called proper lumping, allows a clear physical interpretation of the reduced model since each state of the original model contributes to a single state of the reduced model. The main question of any lumping algorithm is to determine exactly which states are to be grouped together. Also one of the main problems of model reduction is that it produces models which are valid locally in the parameter space and therefore robustness of a reduced model is crucial.

In this presentation an introduction on lumping will be discussed with emphasis on pharmacokinetics with relevant examples.

Jin Jin Model-Based Meta-Analysis for the Efficacy and Safety of Paclitaxel in Cancer Patients

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Objectives: Meta-analysis of integrated literature data can help to maximize our learning from the past and to optimize ongoing drug development. This project aims to quantify the effect of paclitaxel (PAC) dose and regimen on efficacy and safety using data from published trials. To our knowledge, this is one of the earliest attempts of model-based meta-analysis of literature data in oncology.

Methods: A literature database with PK, efficacy, and safety of PAC mono-therapy in cancer patients was developed based on thorough literature search. Meta-analysis was conducted for the objective response (OR) and overall survival (OS) in patients with metastatic breast cancer (MBC) as efficacy endpoints, and the incidence of neutropenia in all patients as safety endpoint. Percent of patients with OR or with \geq Grade 2 neutropenia were modeled as a function of dose, regimen, and other covariates using logistic regression. Relative risk of OS was modeled as a function of dose, regimen and other covariates using proportional hazard model. A mixed-effects modeling approach accounting for inter-trial variability was used (S-Plus v6.2).

Results: The PAC database includes 49 trials with 95 arms and contains trial-level data for 4256 patients. Average PAC dose ranges from 44 to 130 mg/m²/wk with once-every-3-weeks (Q3W) or once-a-week (QW) regimen. Dose-response relationship was established for both efficacy (%OR, n=3070 in 29 MBC trials; or median OS, n=2749 in 15 MBC trials) and safety (%neutropenia, n=1886 in 24 trials). Model predicted that an increase of PAC dose from 60 to 90 mg/m²/wk QW (180 to 270 mg/m² Q3W) may increase the %OR from 30.5% (25.3-36.2%, 95% CI) to 40.0% (34.9-44.8%), and median OS from 11.1 (7.2-17.8) months to 20.6 (13.1-32.2) months in MBC patients. Of special note, %OR and median OS best correlated with average PAC dose in mg/m²/wk regardless of Q3W or QW regimen, while %neutropenia best correlated with administered dose in mg/m². These results implied PAC efficacy was driven by overall exposure, while safety was driven by C_{max} (i.e. for the same total dose, QW may show the same efficacy with better tolerability relative to Q3W).

Conclusions: The effect of PAC dose and regimen on clinical efficacy and safety was quantified by model-based meta-analysis integrating literature data from multiple trials. These analyses can be used to guide trial design and interpretation for PAC as control agent or as combination therapy with new anti-cancer agents.

Yasunori Aoki A practical algorithm for practical parameter identifiability analysis

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Objectives: When constructing a mathematical model in biology, we often face the problem of parameter identifiability. As the reliability of predictions based on a parameterized mathematical model depends on the reliability of the estimated parameters, being able to identify the parameters based on the experimental data is crucial. Thus parameter identifiability analysis is an essential stage in model building and designing experiment. We aim to conduct this identifiability analysis by finding multiple sets of parameters that are consistent with the experimental data. If these multiple parameter values are well-constrained, then we can say the parameter is most likely identifiable, and otherwise it is not identifiable. Although this approach to identifiability analysis is known to be reliable, its existing implementation in the Monte Carlo method is known to be computationally intensive and often considered to be impractical.

Methods: Conventionally, multiple sets of parameters that are consistent with the experimental data are found one-by-one using a local optimization algorithm such as the Levenberg-Marquardt method. We propose a new algorithm for parameter identifiability analysis by modifying the Cluster Newton method for parameter identification presented in [1], which simultaneously finds multiple sets of consistent parameters, hence reducing the computation time significantly.

Results: We have conducted numerical experiments using three finitely-parameterized systems of ordinary differential equations models in biology: an influenza viral kinetics model, an HIV viral kinetics model, and a three-step biochemistry pathway model. We have observed that our algorithm reliably estimates parameter identifiability at 1/10th to 1/50th the computational cost of the conventional Monte Carlo simulation.

Conclusions: With the proposed algorithm, parameter identifiability analysis of nonlinear mathematical models can be done significantly faster than using the Monte Carlo simulation, and gives more robust result than the local linearization-based identifiability analysis using the Fischer Information matrix. As parameter identifiability can be used for experimental design evaluation, we wish to incorporate the proposed algorithm into an optimal experimental design workflow in the future.

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Anne-Gaëlle Dosne A strategy for residual error modeling incorporating both scedasticity of variance and distribution shape

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Objectives: Implement a new error modeling strategy including dynamic transform both sides [1,2] with dynamic scedasticity (dTBS) and t-distributed residuals in NONMEM. Evaluate these methods with respect to their type I error rate when using likelihood ratio test for model building, practical estimation properties and improvement in fit to real data.

Background: Maximum likelihood estimation in non-linear mixed effects modeling is based on the assumption of normally distributed residuals. Violations of this assumption can cause bias in parameter estimates and invalidate the likelihood ratio tests (LRT). In this work, two error models relaxing the normality assumption are presented: (1) a t-distributed residual error model to account for heavy tailed residuals and (2) a power error model ($y_{\text{obs}}=y_{\text{pred}}+y_{\text{pred}}^{\lambda} \epsilon$) combined with a Box-Cox transformation of both dependent variable and model prediction (dTBS). Estimating shape and scedasticity dTBS parameters λ and ζ can correct for skewness in the residual error distribution and allow for non-linear relationships between the residual error magnitude and individual predictions.

Methods: The investigated error models were evaluated over a range of published PK and PD models. The results were evaluated with respect to improvement in model fit (OFV) and simulation properties compared to the published model. The type I error rate associated with additional residual error parameters was performed through stochastic simulation and estimation (SSE).

Results: Nominal type I error rates were not inflated when estimating dTBS or t-distribution parameters. Estimation of dTBS parameters was successful in all real data examples and lead to reasonable λ and ζ estimates. The OFV drop was significant in all cases and graphical improvement was observed in the distribution of IWRES-NPDE [3]. Estimation of dTBS parameters lead to changes in other parameter estimates as well as related parameter precision. Implementation of the t-distribution was successful in all real data examples and improved model fit in 75% of cases. Parameter estimates and precision were only slightly changed.

Conclusions: The use of dTBS and/or t-distribution models for the residual error provides a more flexible framework to characterize the distribution of the residual error. Both methods can improve model fit and relax modeling assumptions.

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Ron Keizer Extended NPDE diagnostics for the between-subject variability and residual error model

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Introduction: NPDEs allow comparison of each observation (DV) to its own predictive distribution based on simulation.[1] Thereby, NPDEs offers a model diagnostic tool, but it does not separate misspecification at the various levels of random effects. For diagnosis of misspecification of the between-subject (BSV) and residual error (RE) models, summaries of empirical Bayes estimates (EBE) and individual weighted residuals (IWRES) are commonly employed. However, these diagnostics are very sensitive to η - and ε -shrinkage.[2]

As extension and improvement to the above diagnostics, we propose to construct NPDE's for EBE and IWRES. These new NPDEs would have two main advantages:

- a) the decomposition of the NPDE diagnostic to the BSV model (EBE-NPDE), and the RE model (IWRES-NPDE)
- b) the proposed NPDE diagnostics would not be subjective to shrinkage

Objectives: To evaluate the ability of EBE-NPDE and IWRES-NPDE to diagnose model misspecification.

Methods: Calculation of the proposed NPDEs requires iterated re-estimation of EBEs (but not population parameter values) based on simulated data. Algorithms for this were implemented in PsN (versions 3.5.3 and up).[3] A previously developed model for a PK dataset (prazosin, n=65, 11 obs.) was used. Several misspecifications in the BSV model and the RE model were implemented, such as Box-Cox transformations and t-distributions vs normal distributions[4], and heteroscedastic vs homoscedastic RE models. DV-NPDE, EBEs, IWRES, EBE-NPDE and IWRES-NPDE were then calculated for the base model. The analysis was repeated at varying levels of shrinkage. Several diagnostic plots were evaluated for their diagnostic ability.

Results: IWRES-NPDE were more sensitive to detect misspecification in the RE model than DV-NPDE or IWRES, at both high and low levels of ε -shrinkage. EBE-NPDEs were able to detect misspecification of the η -distribution (Box-Cox transformed), which could not be detected using diagnostic plots of EBE or DV-NPDE, and were also informative in diagnosing appropriateness of covariance structure. Diagnostic plots for the NPDEs that were most informative included distribution plots, qq-plots, correlation plots, and plots of NPDE vs individual predictions.

Conclusion: EBE-NPDE and IWRES-NPDE offer valuable diagnostic tools, and allow decomposition of the NPDE-DV diagnostic to the BSV and RE level. The new NPDEs were more sensitive to detect model misspecification than the DV-NPDE or diagnostics based on EBE or IWRES.

Acknowledgements: This research was performed as part of the DDMoRe project

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Camille Vong Handling Below Limit of Quantification Data in Optimal Trial Design

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Objectives: The analysis of clinical trial data with classical statistical methods is often influenced by data below the limit of quantification (LOQ). Non-linear mixed effect models provide methods for using the information present in that data [1-3]. The aim of this work was to evaluate different methods of handling LOQs in Optimal Design (OD).

Methods: Six different methods were implemented in PopED [4]:

- D1: Ignore LOQ.
- D2: Non-informative Fisher information matrix (FIM) for median response below LOQ (FO) i.e. set the contribution to the FIM to zero if a design point gives a median response below LOQ.
- D3: Non-informative FOCE linearized FIM for individual response below LOQ i.e. set the individual contribution to the FIM to zero if a design point gives an individual response below LOQ.
- D4: Simulation & Rescaling i.e. Scale FIM with the probability of BLQ predicted from simulation.
- D5: Integration & Rescaling i.e. Scale FIM with the probability of BLQ calculated from the FO approximated joint density.
- D6: Calculation of FIM by integrating over simulated data with a joint likelihood for data above (normal likelihood) and below LOQ (M3 method) using the Laplace approximation.

Comparisons were performed using a 1-cmp IV bolus model with a standard design of 50 patients and 4 sample times per individual. Performance of D1-D6 was assessed for 5 LOQs (39, 42, 47, 51, 63% < LOQ). Predicted parameter relative standard errors (RSE) were compared to empirical RSEs obtained from multiple stochastic simulations and estimations (SSE) in NONMEM using the M3 method [2]. Optimizations using a 2-cmp IV bolus model with standard design of 200 patients and 5 sample times per individual were performed using the fastest methods. Resulting designs were assessed in terms of bias and precision from SSEs using the M3 method.

Results: Evaluated and SSE-derived RSEs for the 6 methods were in good agreement. Determinants of the FIM derived from Method D4-D6 in general were the closest to the empirical covariance obtained from SSEs. FIM calculation times relative to D1 were D2=1.27, D3=21115, D4=137, D5=7.99 and D6=37904. While optimizing with methods D1, D2, D4 and D5 for LOQs up to 70% censored data, D5 provided the most accurate and precise parameter estimates. Method D2 resulted in the least robust designs for estimation.

Conclusion: The use of OD methods anticipating BLQ data in planned designs allows better parameter estimations. For the scenarios investigated, method D5 showed the best compromise in terms of speed and accuracy.

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France Mentré Survey on the current use of optimal design approaches and the developments needed in adaptive optimal design for model based analysis performed amongst DDMoRe's EFPIA members

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Objectives: One objective of the DDMoRe project is to develop tools for adaptive optimal design using nonlinear mixed effect models (NLMEM). As a first step, a survey was conducted in the 10 EFPIA members of the DDMoRe project to identify current practices and perceived shortcomings.

Methods: The working group designed a survey that was sent to all EFPIA partners in October 2011. It was composed of two parts, part 1: state of the art on the use of optimal design methods in industry, part 2: requests for future developments in adaptive optimal design. Results were obtained in November 2011 from AstraZeneca, GSK, Lilly, Merck Serono, Novartis, Novo Nordisk, Pfizer, Roche, Servier, UCB Pharma.

Results: > Part 1 of the survey, investigating the current situation, showed that optimal design is being used by nearly all companies (9/10), mostly during phase 1 and 2 for PKPD. All currently available software (PFIM, POPED, PODES, POPT) are used, some companies using several. These approaches are used for a large variety of investigations, including design evaluation, design optimisation, power evaluation, dose/input optimisation, and for a wide variety of designs, including sampling windows or designs with several groups of elementary designs. The most common limitation was the need to change software when moving from estimation to design.

For Part 2, adaptive design is of high priority for most companies, with the following specific needs: (i) start from prior information, (ii) design optimisation after each new cohort, (iii) use stopping rules. New developments in design approaches should also have the following priorities: (i) handling data below quantification limit, (ii) design for discrete data and joint continuous/discrete models, (iii) handling continuous covariates, (iv) robustness across models.

Conclusions: This is the first survey of its kind performed in the pharmaceutical industry and it demonstrates the important role of optimal design in population PKPD. There is a clear need for further developments, especially for adaptive design and for discrete data in NLMEM.

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