15th Basel Modeling & Simulation Seminar

Please note that there is something new for the poster presentation: the "Poster Blitz". During the poster blitz, a presenter will be given ONE MINUTE (or less, not more) to summarize his/her poster – and to make it attractive to the audience.

Monday/Tuesday, September 9th/10th, 2019
UKBB, Auditorium 2. Stock
Spitalstrasse 33, 4056 Basel

Register here

How to Extrapolate from Adults to Pediatrics? (Day 1)

Is Machine Learning more than a Buzzword? (Day 2)

This year's Basel M&S Seminar has two main topics. On the first day, we discuss how we can leverage literature data, pharmacometric and physiology-based modeling & simulation to extrapolate from adults to pediatrics. On the second day, we exchange views on machine learning (ML) and its relationship to pharmacometrics.

Day 1: Monday, Sep 9th 2019, 13:00-17:45

13:00	**Registration (please arrive no later than 13:15 for badge collection)**	
13:30	**Opening and Welcome**	Marc Pfister
13:35	**Session 1 Pediatric Research & Drug Development**	Chair: Cheikh Diack
13:35	Consider developmental pharmacology and clinical aspects in pediatric research	**Johannes van den Anker** **Tamara van Donge** UKBB/University of Basel
14:05	Extrapolation in pediatric drug development Opportunities and lessons learned	**Bruno Reigner** Roche
14:35	An industry perspective on extrapolation in pediatric drug development: A quantitative approach to assess similarity of adult and pediatric efficacy.	**Günter Heimann** Novartis
15:05	**Poster Blitz and Coffee Break**	**Jean-Louis Steimer**
16:00	**Session 2 Extrapolation**	Chair: Andreas Krause
16:00	Prediction of human PK and pharmacological active dose by PB-PK/PD	**Ruben De Kanter** Idorsia
16:30	Leverage literature and real world data to extrapolate from adults to pediatrics	**Pascal Chanu** Genentech / Roche
17:00	Special interactive session	**Andreas Krause**
	The multiple-peak phenomenon in pharmacokinetics	**Andrea Henrich** Idorsia **Guillaume Baneyx** Novartis
17:45	**Closing Remarks**	Andreas Krause

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(Access Map)

Day 2: Tuesday, Sep 10th 2019, 08:30-12:30

08:30	**Registration (please arrive no later than 08:45 for badge collection)**	
09:00	**Session 3 Pharmacometrics & Machine Learning – A Happy Couple?**	Chair: Olivier David
09:00	What is machine learning (ML)? Should I care?	**Marc Vandemeulebroecke** Novartis
09:30	How to think about ML as a pharmacometrician?	**Oliver Sander** Novartis
10:00	Pharmacometrics and machine learning: a happy couple or enemies for life?	**Julia Vogt** ETH Zurich **Gilbert Koch** UKBB/University of Basel
10:30	**Coffee Break**	
11:00	**Session 4 Applications in Precision Medicine**	Chair: Marc Pfister
11:00	Applying optimal control to compute optimal individualized dosing regimen in pediatrics	**Freya Bachmann** UKBB/University of Constance
11:20	Utilize big data to detect Alzheimer's disease earlier and facilitate precision medicine	**Grazia Frontoso** Google
11:40	Who responds to treatment? Integration of M&S and ML to advance precision medicine	**Cheikh Diack** **Francesco Brizzi** Roche
12:00	Panel discussion	**All**
12:30	**Closing Remarks**	Marc Pfister

ABSTRACTS DAY 1


JOHANNES VAN DEN ANKER

Dr. John van den Anker is a pediatric clinical pharmacologist and the Eckenstein-Geigy Distinguished Professor of Pediatric Pharmacology at the University Children's Hospital Basel, Switzerland. He is the immediate Past President of the American College of Clinical Pharmacology and the European Society for Developmental Perinatal and Paediatric Pharmacology, is funded by NICHD and SNF and has published over 400 peer reviewed papers in the area of pediatric and neonatal pharmacology.


TAMARA VAN DONGE

Tamara van Donge obtained her Master Degree in BioPharmaceutical Sciences at the University of Leiden in 2017. At the beginning of 2018 she started a joint PhD collaboration with Roche and the University Children`s Hospital Basel. Her main research concerns the effect on hepatic and renally cleared drugs in neonates and infants.

Consider developmental pharmacology and clinical aspects in pediatric research

The main goal of pediatric clinical pharmacology is to understand developmental changes and optimize care in neonates, infants, children, and adolescents. After birth, the neonate is subject to rapid physiological changes related to the transition from intrauterine to extrauterine life. In addition, maturational processes affecting the pharmacokinetics (PK) and pharmacodynamics of administered drugs occur. Incorrect dosing in neonates and young infants can not only result in short-term complications, but can also have a negative impact on the long-term development of these infants. As a consequence, it is of importance to characterize these physiological changes and describe the corresponding consequences related to maturation in preterm and term neonates. Pharmacometric modeling together with model-based simulations can help us to characterize relevant physiological changes and their effects on drug exposure and response throughout childhood. By presenting two cases, we will highlight the importance of understanding physiological changes as well as the impact of modeling and simulation on dosing simplification. There is currently an unmet need to enhance knowledge on age-dependent changes of kidney injury biomarkers in pediatrics. Creatinine-based parameters for monitoring kidney function are not reliable for early detection of kidney injury, particularly tubular damage. We discuss challenges and opportunities in the design and conduct of clinical biomarker studies in infants and children. In addition, with the use of modeling and simulation we have been able to evaluate complex and empirically established dosing recommendations for drugs such as methadone in neonates. Simulations that accounted for developmental PK changes indicated that a simplified, shorter methadone dosing strategy might maintain target exposure to control withdrawal symptoms in preterm neonates. Such a dosing strategy will not only reduce the risk of measurements errors related to complex dosing schedules, but also decreases the number of interventions in these preterm patients.


BRUNO REIGNER

Dr. Bruno Reigner is Head of Clinical Pharmacology-Established Products at Hoffmann- La Roche Ltd. in Basel. He is chairman of the Clinical Pharmacology Pediatric Working Group and member of the Pediatric Extrapolation Working Group. Both Working Groups have an advisory role to Project Teams. He has been involved in numerous pediatric programs, from the development of plans up to pediatric filings/approvals.

Extrapolation in pediatric drug development: Opportunities and lessons learned

The goal of the presentation will be to share knowledge and experiences in pediatric drug development in a large pharmaceutical company. The focus will be on extrapolation of efficacy because regulatory authorities have now created a framework to make this topic the most important emerging opportunity to streamline or accelerate pediatric development programs. This opportunity comes as well with challenges and several case study examples will be presented to illustrate the concepts and share real life successes and lessons learned. Recommendations will include the importance of forming cross-functional teams to address the multiple components of extrapolation in pediatric drug development.


GÜNTER HEIMANN

Günter Heimann received his degree (Diplom) and his PhD in Mathematics from the Universität Hamburg in Germany in 1985 and 1989, respectively. Günter started his career as a statistician in the pharmaceutical industry in 1989 in Berlin, working in different roles for Schering AG. From 1998 Günter worked for Pfizer in the UK, initially as an internal consultant in the Statistical Research Centre, and, since 2001 as the Head of Clinical Statistics in Sandwich. In March 2004 Günter joined Novartis in Basel as the Global Head of Early Development Biostatistics. From July 2010 Günter was responsible for the Statistical Modelling department within Modelling and Simulation, and in 2015 he took on the role as Unit Head for the Oncology Pharmacometrics unit. Since 2017 Günter supports pediatric drug development within Biostatistics and Pharmacometrics at Novartis.

An industry perspective on extrapolation in pediatric drug development: A quantitative approach to assess similarity of adult and pediatric efficacy

Guenter Heimann, Inga Ludwig, Sebastian Weber, Thomas Dumortier

Recruitment of patients into pediatric studies is difficult and slow, and traditional fully powered pivotal trials are prohibitive.

For indications and drugs where the disease progression in children is similar to that in adults, and where the pharmacology of the drug is similar to that in adults, one may fully extrapolate efficacy from adults to children. Often, however, there is not yet enough evidence to apply full extrapolation. In these cases one may want to apply a partial extrapolation approach, and one needs to collect some efficacy data from children to demonstrate that the adult and the children efficacy are similar.

In principle, our extrapolation approach consists of three steps: (1) the adult data are used to develop a model which links exposure and baseline risk factors to clinical outcome or surrogate markers, (2) the model is then used to predict the clinical outcome of the pediatric study conditional on observed exposure and covariates, and (3) the predicted outcome is then compared to the observed outcome to validate the model. Successful validation serves as supportive evidence to justify partial or full extrapolation.

In this talk, we use three real (but anonymized) examples, were extrapolation was or is applied, to explain the three steps listed above in more detail. We will discuss some aspects of model selection and validation for step (1). For step (2), we propose to simulate (from the adult model) a predictive distribution for the outcome of each of the n pediatric patients separately (conditional on the exposure and risk factors), rather than to obtain a predictive distribution for the overall pediatric study outcome. We will explain how this helps in step (3) to compare observed with predicted.

RUBEN DE KANTER

Ruben de Kanter works at Idorsia (former Actelion research) as a modeling & simulation scientist within preclinical DMPK. Before he was working at Solvay (now Abbott) in the Netherlands and before that at Pharmacia (now Pfizer) in Italy. He is a DMPK project leader specializing in PBPK combined with PD modeling.

Prediction of human PK and pharmacological active dose by PB-PK/PD

Extrapolation from in vitro data to clinical PK and active predicted dose. PB-PK/PD was used as an integrated approach to include various properties, such as logD, pKa, plasma protein binding, potency on target and metabolic stability to be able to select a drug candidate out of a class of structurally related compounds. Target engagement was extrapolated from other drugs on the market, using PK/PD analysis.


PASCAL CHANU

Pascal Chanu has a Pharm.D., he started modeling with drug monitoring during hospital residency. He joined Roche M&S group in 2003 as a postdoc and grew professionally up to Disease Area M&S expert. He moved to consultancy working for Pharsight (now Certara) in late 2008. He is back to the Roche group since 2016, working in the gRED Clinical Pharmacology - M&S group, supporting Genentech projects. Outside of work, he likes gardening, cooking for his family and playing tennis.

Leverage literature and real world data to extrapolate from adults to pediatrics

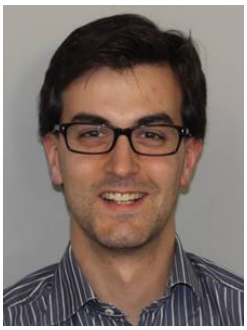
Background: C.E.R.A. indicated in Chronic Kidney Disease adult patients to correct and maintain hemoglobin (Hb) levels is approved in Europe and US since 2007; pediatric development is ongoing. A 20-week open-label Phase II study (NH19707) of intravenous (IV) C.E.R.A. in patients aged 5–17 years was conducted and data collected was analysed with adult data. Objectives were to determine the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of C.E.R.A. in a broad population, to simulate treatment outcomes of C.E.R.A. administered IV and subcutaneous (SC) in pediatric patients and compare them to NH19707 data and Real World Data (RWD).

Methods: PK and Hb data from 63 pediatric patients were pooled with 400 adult patients IV and SC data and analysed using models previously developed in adults. Simulations of treatment outcomes with C.E.R.A. administered IV and SC were performed. Assumptions on SC bioavailability in pediatric patients were based on previous darbepoetin data. Model inferences were challenged versus RWD obtained in 158 pediatric patients receiving C.E.R.A. SC (N=126) or IV (N=32) from registries maintained by the International Pediatric Dialysis Network (IPDN, www.pedpd.org).

Results: The adult PK and PK/PD models adequately described the pediatric data and indicated a similar exposure-response relationship in both populations. C.E.R.A. doses were adjusted to Hb levels during the simulation process to reflect clinical practice; simulated Hb levels matched observations. Furthermore, simulated median monthly C.E.R.A. doses following Hb stabilization were 105 µg (95% prediction interval 72–159 µg) for SC and 84 µg (60–123 µg) for IV, in good agreement with those reported in the IPDN registry: 100 µg and 80.4 µg, respectively.

Conclusion: The PK/PD characteristics of C.E.R.A. are similar between adult and pediatric populations. Simulations of clinical outcomes in accordance with clinical trial data and RWD provided sufficient clinical evidence to support pediatric plans optimization subsequently approved by FDA and EMA.

ANDREA HENRICH



GUILLAUME BANEYX

Andrea Henrich studied pharmacy at the Goethe University in Frankfurt (2007 - 2013, Prof. Jennifer Dressman among others) where she received her pharmacist's degree. Since May 2017, she works as a modeling and simulation scientist at Actelion/Idorsia. She holds a PhD from the department of clinical pharmacy and biochemistry in Berlin with Prof. Charlotte Kloft (PharMetrX scholarship, oncology PK/PD modeling in collaboration with Markus Joerger, 2013 - 2017).

Pharmacist with a specialization in PKPD modeling applied to drug development obtained from University of Paris 5. I joined the preclinical modeling group of Roche in Basel and worked on research topics including prediction of drug-drug interaction and assessment of tumor diffusion capabilities of anticancer agents. In 2014, I joined the pharmacometric department at Novartis to support both early and late clinical development of oncology projects.

Special interactive session: How to deal with the multiple-peak phenomenon?

The multiple-peak phenomenon is observed quite frequently: multiple concentration peaks occur after administration of a single dose. If the phenomenon occurs in entry-into-man studies, it poses particular challenges for extrapolation to multiple-dose administration. This session features two short presentations of case studies to introduce the topic and sketch possible models.

The aim of the session is to engage the audience in a discussion that might cover physiology, data collection, modeling, extrapolation from single- to multiple-dose administration, clinical aspects, and more. You are encouraged to "bring your own" (experiences).

ABSTRACTS DAY 2


MARC VANDEMEULEBROECKE

Marc Vandemeulebroecke joined Novartis in 2006. He has been supporting development programs in early and late phase across various disease areas, as statistician and pharmacometrician. Currently he is Global Group Head for Statistics in Dermatology. Marc holds a maîtrise in mathematics from the University Paris XI, a diploma in mathematics from the University of Münster, a PhD in mathematical statistics from the University of Magdeburg, and an MSc in PKPD modeling from the University of Manchester. He received the Gustav-Adolf-Lienert award from the German Region of the International Biometric Society (IBS). He co-authored various scientific publications and one R package. Marc's current interests include statistical graphics and machine learning.

What is machine learning (ML)? Should I care?

In this talk I will provide an introduction to machine learning and artificial intelligence. The talk is non-technical in nature; it will cover some basic definitions and taxonomy, a brief historical overview, and it will review major subtypes of machine learning applications. The goal of this talk is to provide an easy-access high-level overview of the field of machine learning and artificial intelligence, to demystify some of its fundamental concepts, and to highlight similarities and differences to more "classical" quantitative approaches.


OLIVER SANDER

Oliver Sander holds a degree in computer science and received a PhD in computational biology from the Max-Planck-Institute for Informatics in Saarbruecken, working on the molecular foundations of HIV drug resistance and cell entry. At Novartis he worked in pharmacometrics and statistics groups, spanning the therapeutic areas autoimmune disorders, infectious diseases, and ophthalmology.

How to think about machine learning as a pharmacometrician?

Renewed enthusiasm and promises by machine learning also touch pharmacometricians in different ways. Readouts based on machine learning might be used as input to pharmacometric methods, machine learning might be seen as a competitor, or as an additional “fit-for-purpose tool” in the pharmacometrician’s toolbox.

However, the breadth and complexity of methods can make it challenging to asses “fit-for-purpose”. How to avoid missing the forest for the trees, when thinking about forests and trees (or networks, or other machine learning methods)?

This talk will give an introduction to a few fundamental concepts in machine learning (e.g. performance assessment, regularization, and overfitting) and how these principles can help when coming into contact with machine learning methods as pharmacometrician.


JULIA VOGT


GILBERT KOCH

Julia Vogt is an Assistant Professor at the Department of Computer Science at ETH Zurich, heading the research group “Medical Data Science”. Before joining ETHZ in May 2019, she was an Assistant Professor at the University of Basel. She studied mathematics both at the University of Konstanz and at the University of Technology in Sydney, and she received her Ph.D. in computer science from the University of Basel. While one focus of her Doctorate was on developing new machine learning methods, she was also deeply engaged in collaborative biomedical applications. The main focus of her research is on linking computer science with medicine, with the ultimate aim of personalized treatment.

Gilbert is a Senior Research Fellow in the Pediatric Clinical Pharmacology Group at the University Children’s Hospital in Basel, Switzerland, and holds an Adjunct Professor position at the University of Buffalo, NY, USA. His research covers (i) modeling and simulation in neonates with a special focus on pre-terms, and (ii) improving pharmacometrics by applying advanced mathematical methods from other research areas. His goal is to support clinicians in decision making and consequently to improve individualized treatment for pediatric patients.

Pharmacometrics and machine learning: a happy couple or enemies for life?

Clinical studies often consist of a large number of patients, a plurality of individual patient characteristics, and longitudinal biomarker and disease progression measurements.

Machine learning (ML) analyzes such large data-sets based on patterns and inferences, and is therefore able to classify a newly diagnosed patient. ML is computationally efficient but is not based on pharmacological and biological assumptions. In contrast to ML, pharmacometrics modeling (PM) applies differential equations to characterize dynamical progression of drug concentration, disease status and other variables of interest, and is often build on mechanistic understanding of underlying time-dependent processes. However, the computational effort of PM e.g. to identify effects of patient covariates on the model parameters from data of large clinical studies can be tremendous.

In this study, we investigate bilirubin dynamics of 362 neonatal patients with a set of 44 covariates (demographics, laboratory values and clinical confounders) during their first days of life. We demonstrate how ML can predict the need for phototherapy for patients at risk and additionally show how ML can support PM in finding significant covariate effects on model parameters. It will be illustrated that ML and PM are no enemies and each method has its specific complementary advantages. Therefore, ML and PM are a happy couple to develop useful decision support tools for clinical application.


FREYA BACHMANN

Freya is a PhD student at the Department of Mathematics and Statistics at University of Konstanz. In collaboration with the UKBB, she applies techniques from optimal control theory and numerical optimization to PKPD models to compute optimal individualized dosing regimen.

Applying optimal control to compute optimal individualized dosing regimen in pediatrics

Providing the optimal dosing strategy of a drug for an individual pediatric patient is an important task in pharmaceutical sciences and daily clinical application. We developed and validated an optimal dosing algorithm (OptiDose) that computes the optimal individualized dosing regimen for PKPD models in substantially different scenarios with various routes of administrations by solving an optimal control problem (OCP).

The aim is to compute a control that brings the underlying system as closely as possible to a desired reference state by minimizing an objective function. In PKPD modeling the controls are the administered doses and the reference state can be the disease progression. Therefore, the objective function is quantifying the difference between a desired disease state and the actual state generated by a particular treatment which shall be minimized. Drug administration at certain time points gives a finite number of discrete controls, the drug doses, determining the drug concentration and its effect on the disease state. Consequently, we can construct a finite-dimensional OCP depending only on the doses and apply robust gradient-based descent methods from finite-dimensional optimization.


GRAZIA FRONTOSO

Grazia Frontoso is a Customer Engineer at Google Cloud in charge of supporting enterprise customers in Switzerland in digital transformation and Big Data analytics for the healthcare & life science sector. Before joining Google, she worked for several years as Software Product manager in risk management designing cloud solutions for regulated industries. She holds a PhD in physics and is passionate about the transformational power of technology.

Utilize big data to detect Alzheimer's disease earlier and facilitate precision medicine

Healthcare problems are becoming more and more data problems. From clinical trials and electronic health records to medical imaging, healthcare is an industry with an unprecedented amount of data. The total amount of DNA sequencing data is doubling every 7 months. Turning all those data into patient value is key.

Artificial intelligence has dozens of possible application areas, but healthcare stands out as a remarkable opportunity to benefit all of us. The talk will explore the potential of healthcare breakthrough innovation with artificial intelligence showing examples of personalized medicine and drug discovery. The project Baseline from Verily will also be presented. https://www.projectbaseline.com/


FRANCESCO BRIZZI


CHEIKH DIACK

Francesco Brizzi is currently a Roche Postdoctoral Fellow based in clinical pharmacology. The aim of his project is to develop a methodology to identify predictive markers of treatment response using big data collected as part of clinical data. Before joining Roche he has studied MORSE (Mathematics Operational Research Statistics Economics) at the University of Warwick, and obtained a PhD in Biostatistics from the University of Cambridge on developing novel Bayesian methods to monitor the HIV epidemic.

Cheikh Diack is a PhD in Nonparametric Statistics from University of Toulouse III. He has joined Roche since 2011 as a clinical pharmacometrician.

Who responds to treatment? Integration of M&S and ML to advance precision medicine

Patients are not equally benefiting from existing treatments and are responding with high heterogeneity to these therapies. The current trend of designing small proof-of-concept studies with shorter durations makes it even more challenging to show that an investigational drug can surpass standard of care (SOC) or be effective as a 2nd line therapy. To design a trial that instils confidence in resulting decisions, we face questions such as: who are the patients who do not respond optimally to SOC? When is the right time to switch a patient to a new therapy? What is an optimal personal treatment interval?

In this talk, as a case study, we use clinical trial data from ranibizumab -the SOC in neovascular age-related macular degeneration- to show how a coupling of M&S approach and Machine Learning techniques could address aforementioned questions and get us out from this era of Imprecision Medicine.