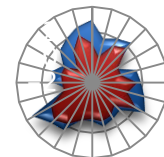


Statistical Aspects of Allometric Scaling in Pharmaceutical R&D

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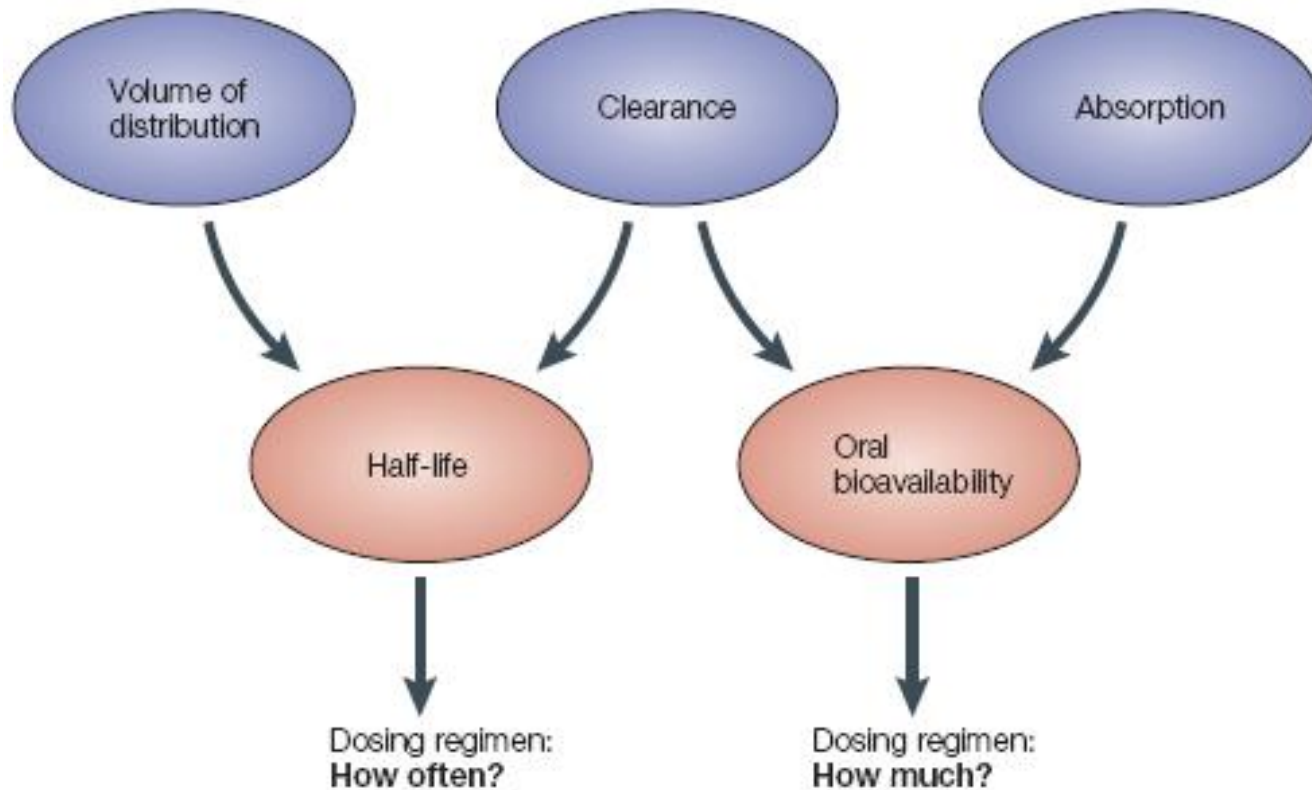


Outline

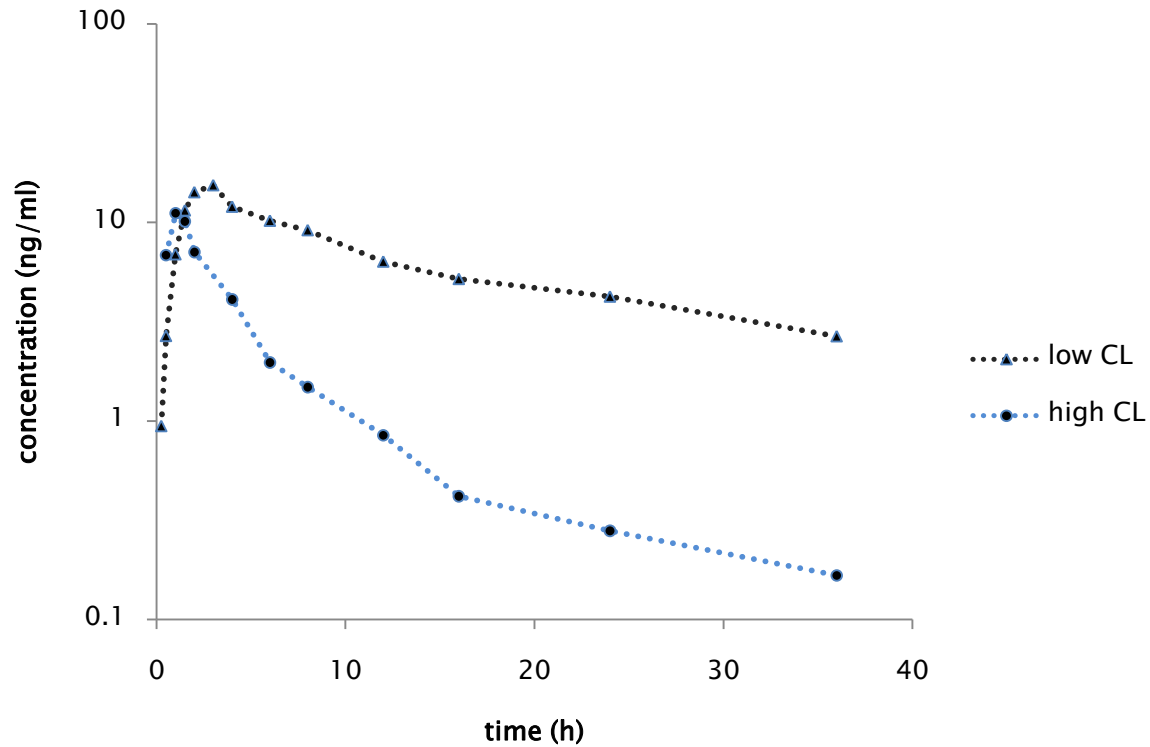
- ▶ Introduction
- ▶ Current allometric scaling practices
- ▶ Data on 24 compounds and 6 species
- ▶ Statistical integration using meta-analysis methods
- ▶ Conclusions
- ▶ Future research

Role of Clearance

Van de Waterbeemd & Gifford 2003



Low Versus High Clearance



Introduction

- ▶ Allometric scaling aims to predict the clearance and volume of distribution in humans via :
 - The plasma concentration time profile in animals (AUC, C_{\max})
 - Compound specific extrapolation of animal data
- ▶ Clearance is the major determinant for the starting dose of the “first-in-human” experiment
- ▶ Current models have deterministic and stochastic components
- ▶ Assumption : the biological processes behind *clearance* are comparable in mammal species

Goals of the Research Project

- ▶ Investigate statistical aspects of current methods
- ▶ Determine the sources of variability
- ▶ Provide alternatives based on
 - Use of statistical model building
 - Likelihood ratio tests
 - Mixed effect models

Experimental Data

- ▶ Experimental data coming from 24 compounds in 6 different species
- ▶ Data set : Mice , rats, rabbits, monkeys, dogs and human

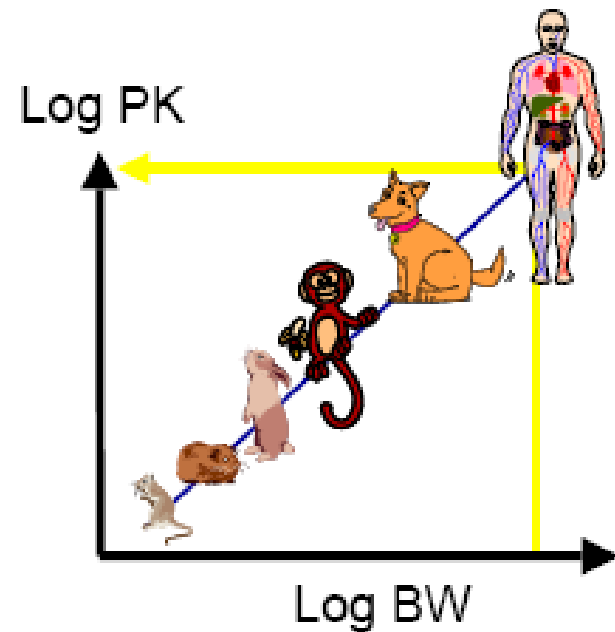
Species	Frequency	Cumulative Frequency
Dog	98	98
Human	791	889
Monkey	45	934
Mouse	27	961
Rabbit	11	972
Rat	83	1055

Current Practice of Allometric Scaling

(Mahmood 2005)

1. Simple allometry
2. Maximum Lifespan corrected
3. Brain weight corrected

Reviews in Mahmood (2005)
Sinha et al (2008)



Simple Allometry (SA)

- ▶ Regression of Clearance versus body weight
- ▶ Model

$$Cl = a * (\text{BodyWeight})^b$$

$$\log (CL) = \log (a) + b \log(\text{BodyWeight})$$

- ▶ Rule of Exponent (Mahmood 2005)
 - Use “b” of body weight as criterion for further decisions
 - Class 1 : If $b < 0.7$ then SA is the final model
 - Class 2 : If $0.7 \leq b \leq 1.0$ then use Maximum Lifespan Potential for correction
 - Class 3 : If $b > 1.0$ then correct for brain weight

Maximum Lifespan Potential

The maximum lifespan is a known function of body weight and brain weight and is used in allometric scaling (Sacher 1959)

$$\text{MLP (years)} = 185.4 * (\text{BrainWeight})^{0.0636} * (\text{BodyWeight})^{-0.225}$$

- ▶ Final model if $0.7 \leq b \leq 0.1$

$$\text{CL} * \text{MLP} = a * (\text{BodyWeight})^b$$

$$\log (\text{CL} * \text{MLP}) = \log (a) + b \log (\text{BodyWeight})$$

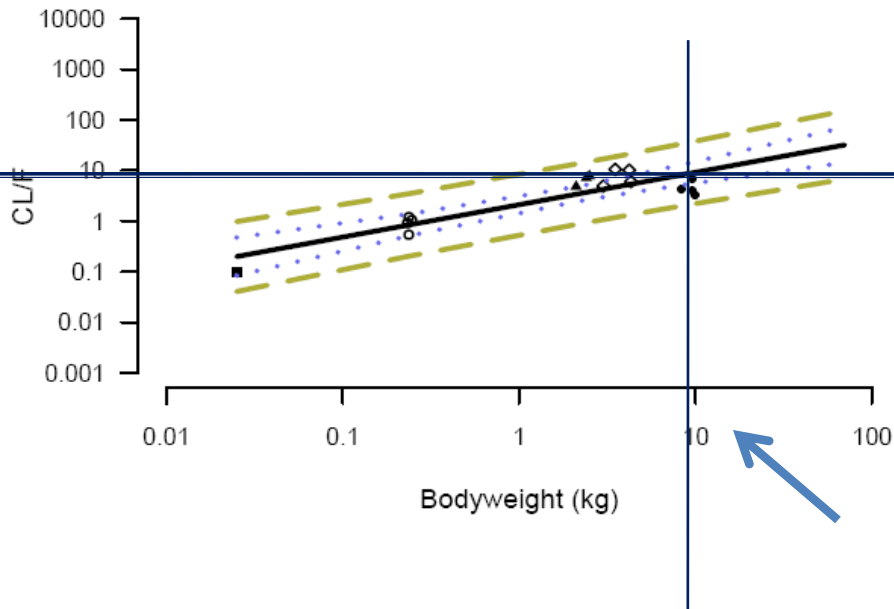
Correction for Brain Weight

- ▶ Including the brain weight
- ▶ Final model if for SA : $b > 1.0$

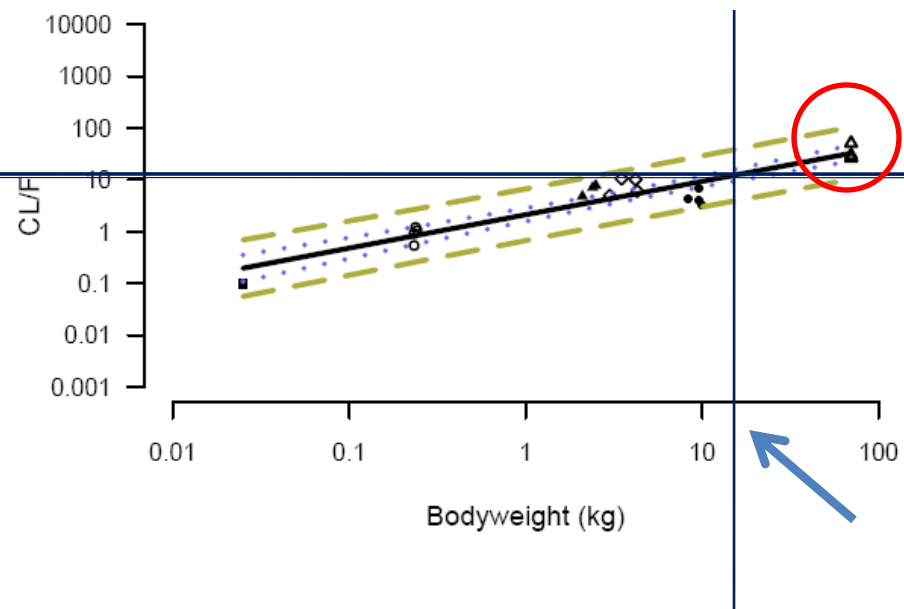
$$CL * BrainWeight = a * (BodyWeight)^b$$

$$\log(CL * BrainWeight) = \log(a) + b \log(BodyWeight)$$

Data Exploration



Extrapolation
without human data



Post hoc analysis
including human data

- Dog
- △ Man
- ◇ Monkey cy
- Mouse
- ▲ Rabbit
- Rat

Mixed Effect Modelling Approach

- ▶ At the end of the pre-clinical R&D before FIH
- ▶ Predict human clearance for new compound
- ▶ Mimic Mahmood method using mixed effects models (Verbeke and Molenberghs 2000)
- ▶ Ignore Allometry via a two-way Random Effects ANOVA
- ▶ Use of all data at hand for prediction
 - All non-human data of new compound
 - All available historical human data

Mahmood Mixed Effect Model (MAMIX)

$$\log(y) = (\beta_1 + b_{1i}) + \beta_2 \log(Bw) + \varepsilon$$

Where

$y = CL, CL*MLP$ or $CI*Brw$

CL is clearance

Bw is body weight

b_{1i} = compound specific intercept $\sim N(0, \sigma_1)$

β_1 = overall intercept

β_2 = overall slope of body weight

$\varepsilon \sim N(0, \sigma)$

Random Effect ANOVA

$$\log(y) = (\beta_1 + b_{1i}) + \beta_2 \text{ Species} + \varepsilon$$

Where

y = CL, CL*MLP or CI*Brw

CL is clearance

Species = factor indicator of species

b_{1i} = compound specific intercept $\sim N(0, \sigma_1)$

β_1 = overall intercept

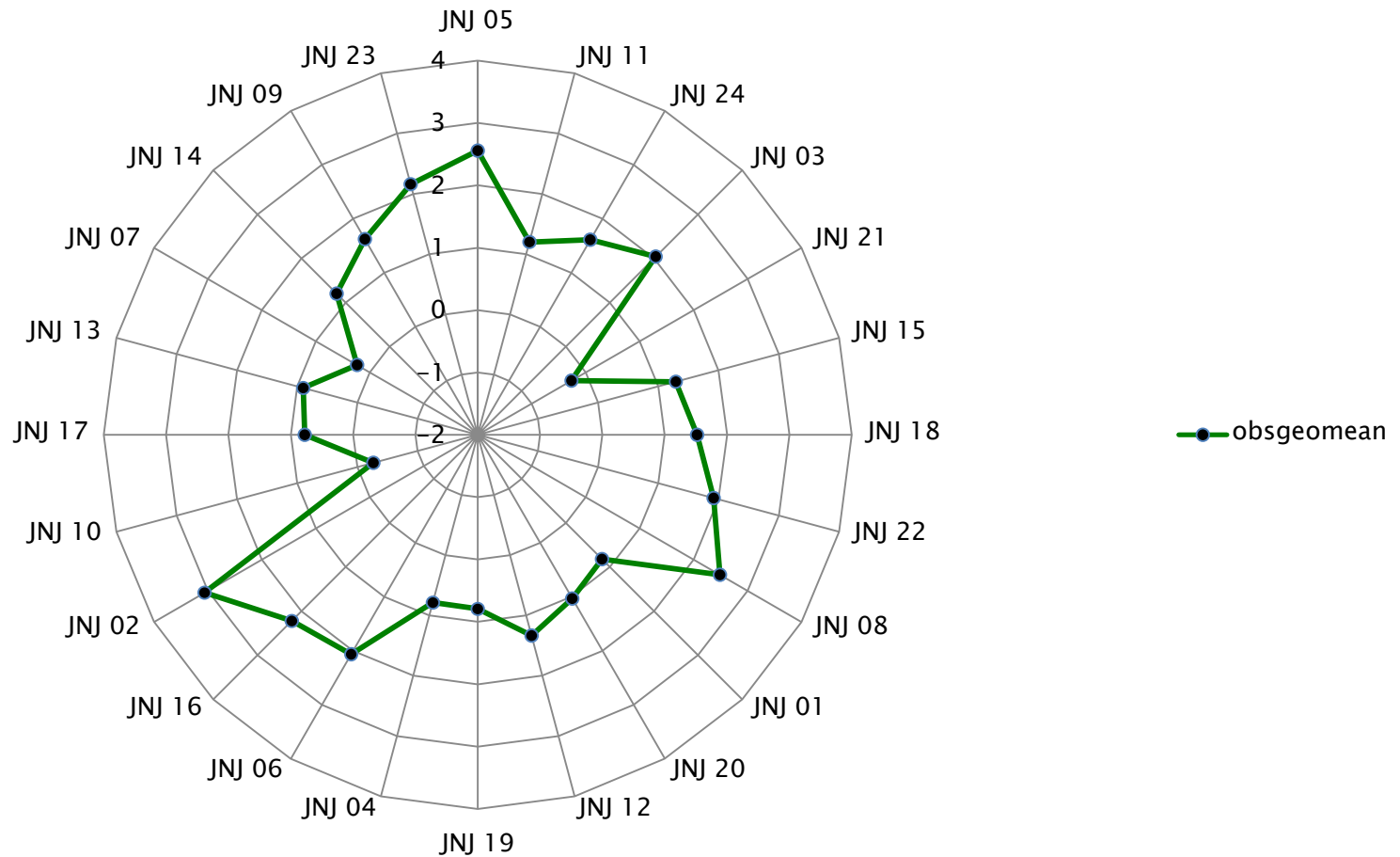
β_2 = average effect of species

$\varepsilon \sim N(0, \sigma)$

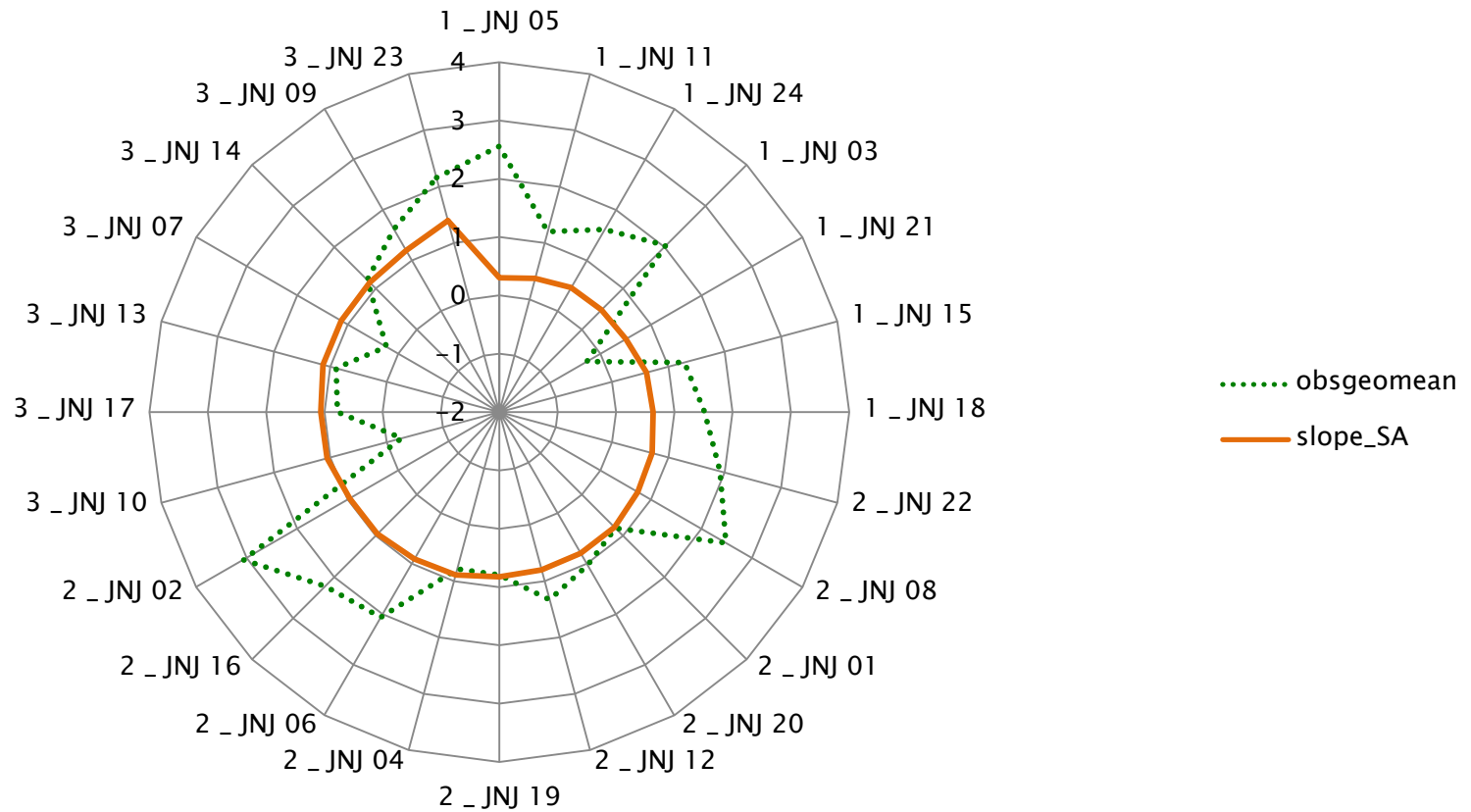
Results

- ▶ Based on cross validation (leave out human data for new compound)
- ▶ Compare predictions for all 24 compounds
 1. Method of Mahmood
 2. Mixed effect version of Mahmoods' method (MAMIX)
 3. RE - ANOVA (Species)

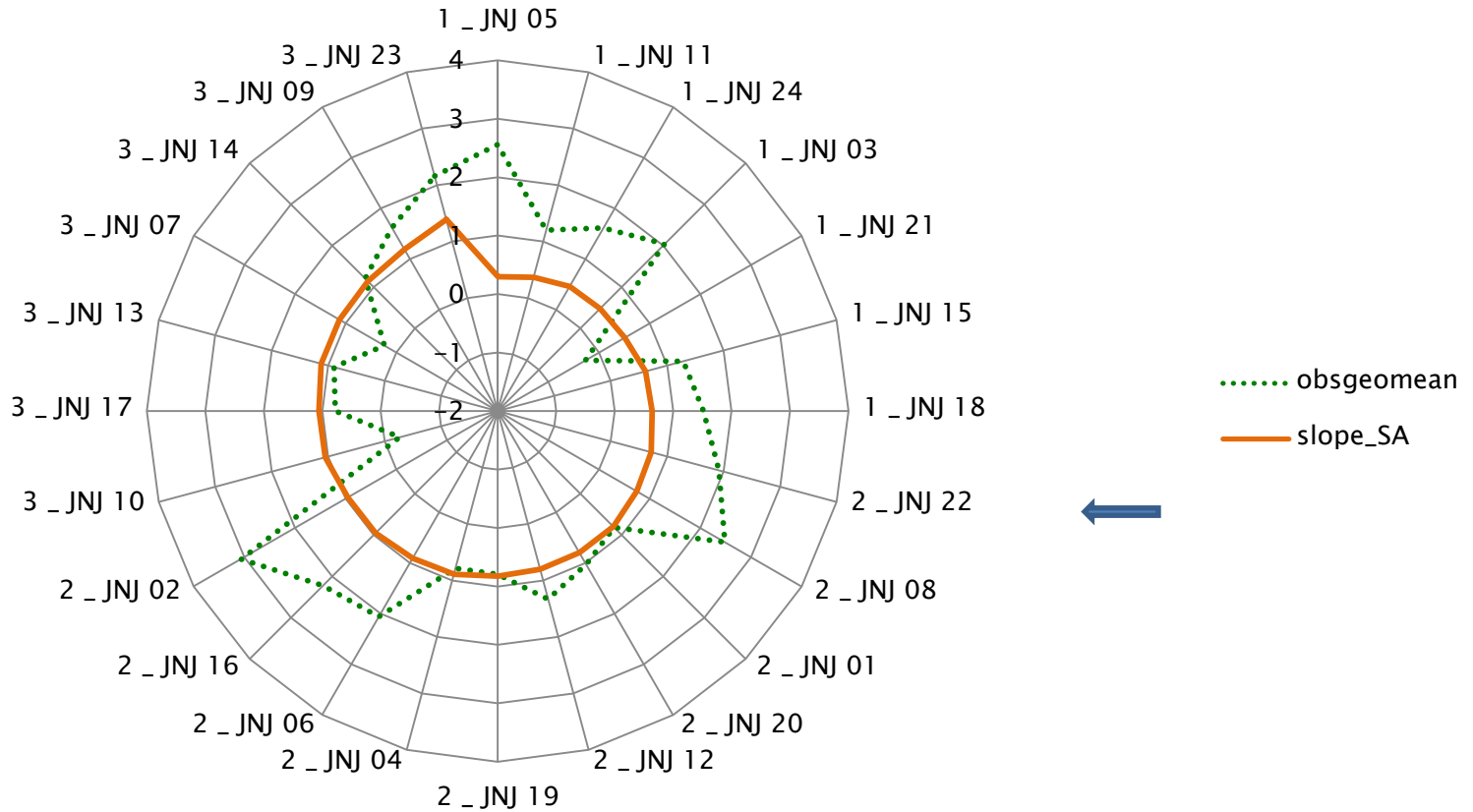
Observed Human Clearance (Log10)



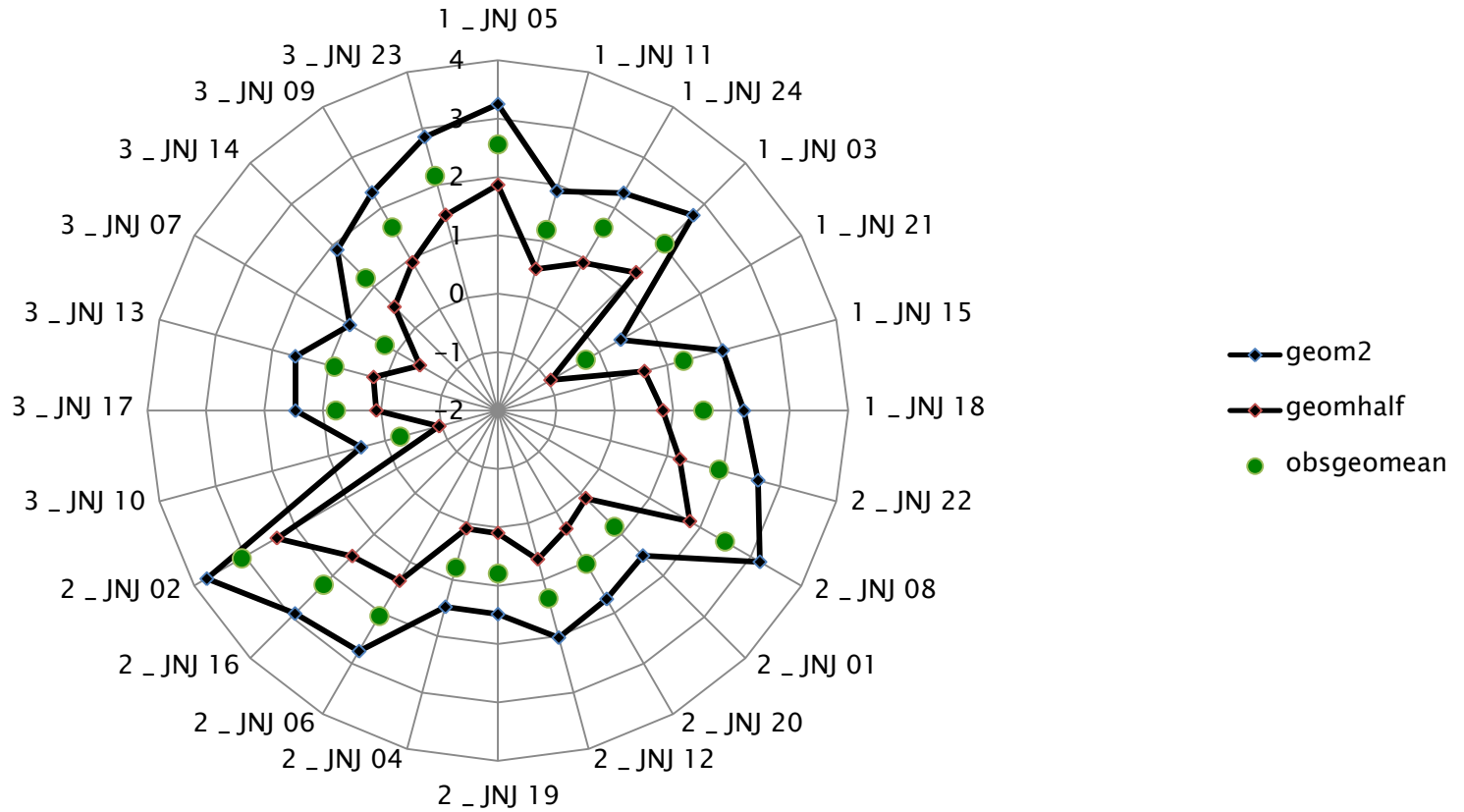
Slopes Simple Allometry (Mahmood 2005)



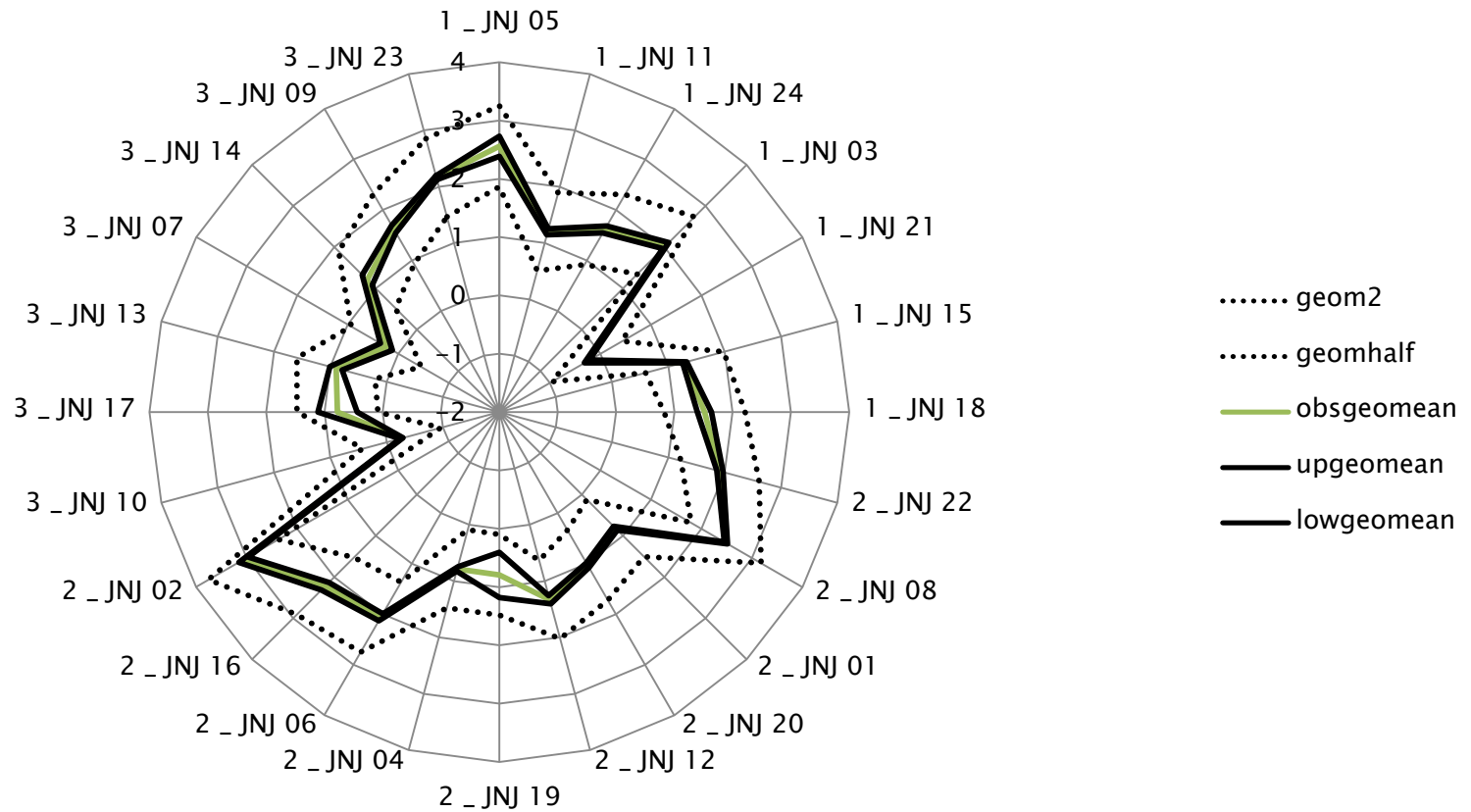
Slopes Simple Allometry (Mahmood 2005)



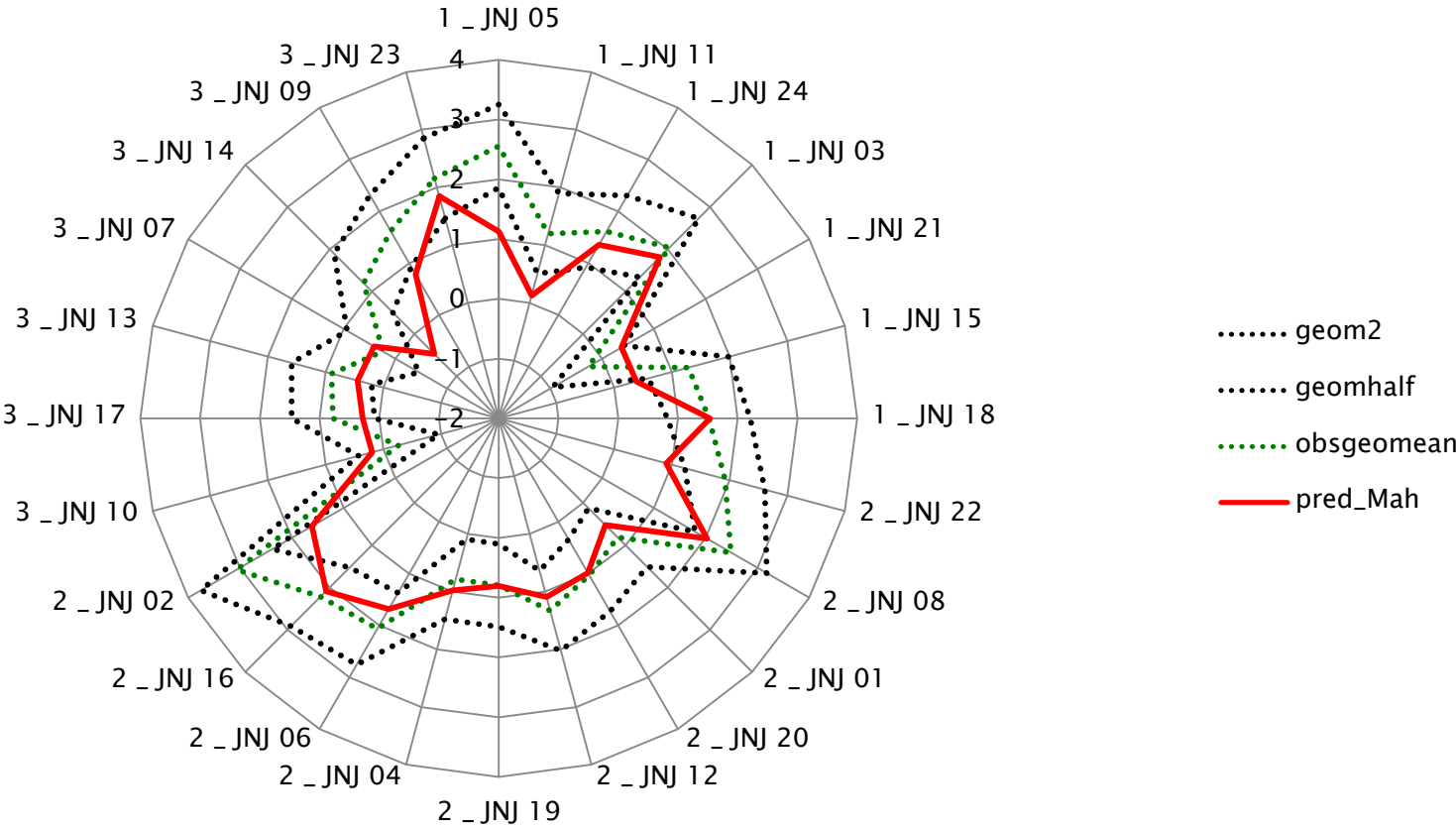
Specification Limits



Observed Human Data (95% CI)

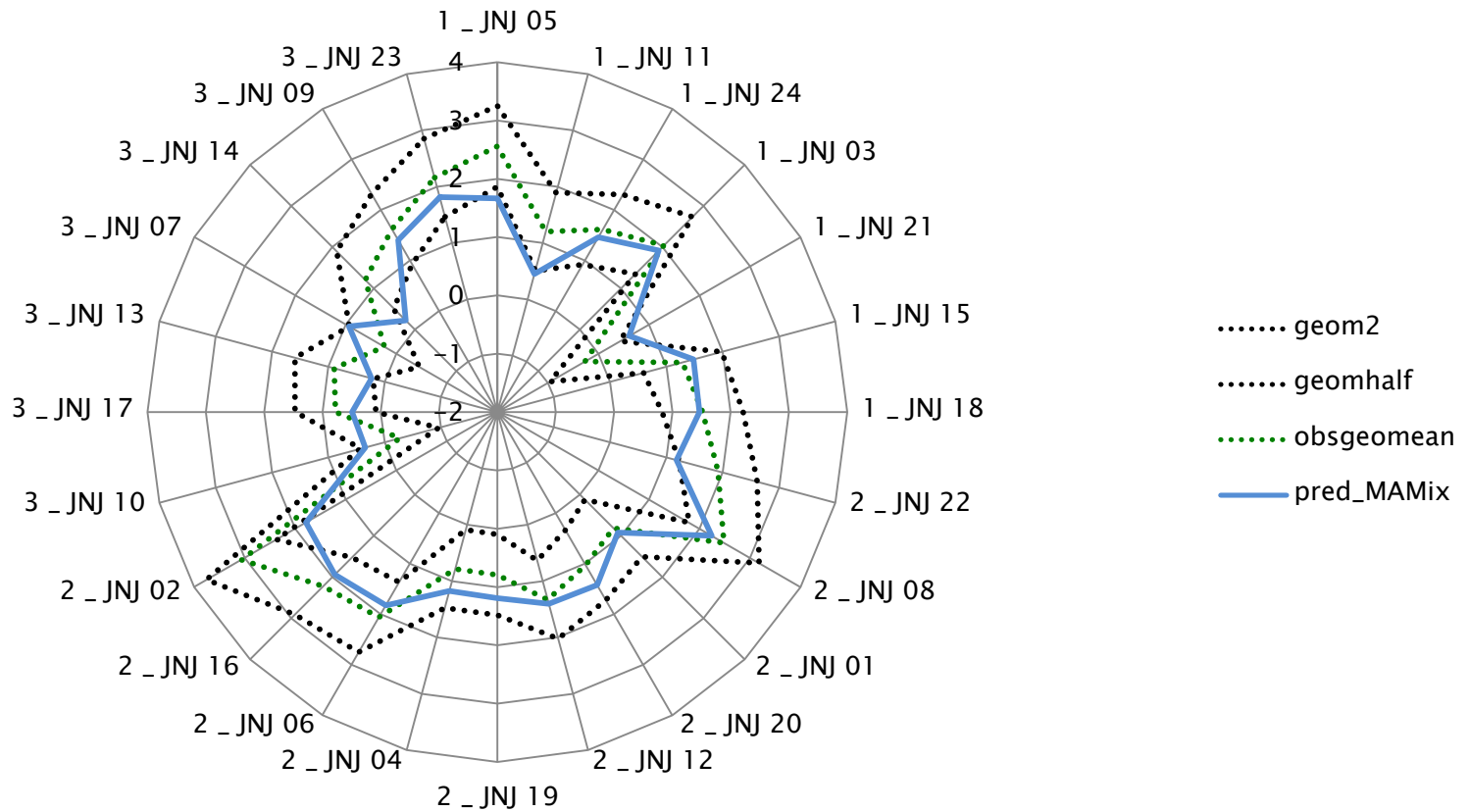


Mahmood (2005)

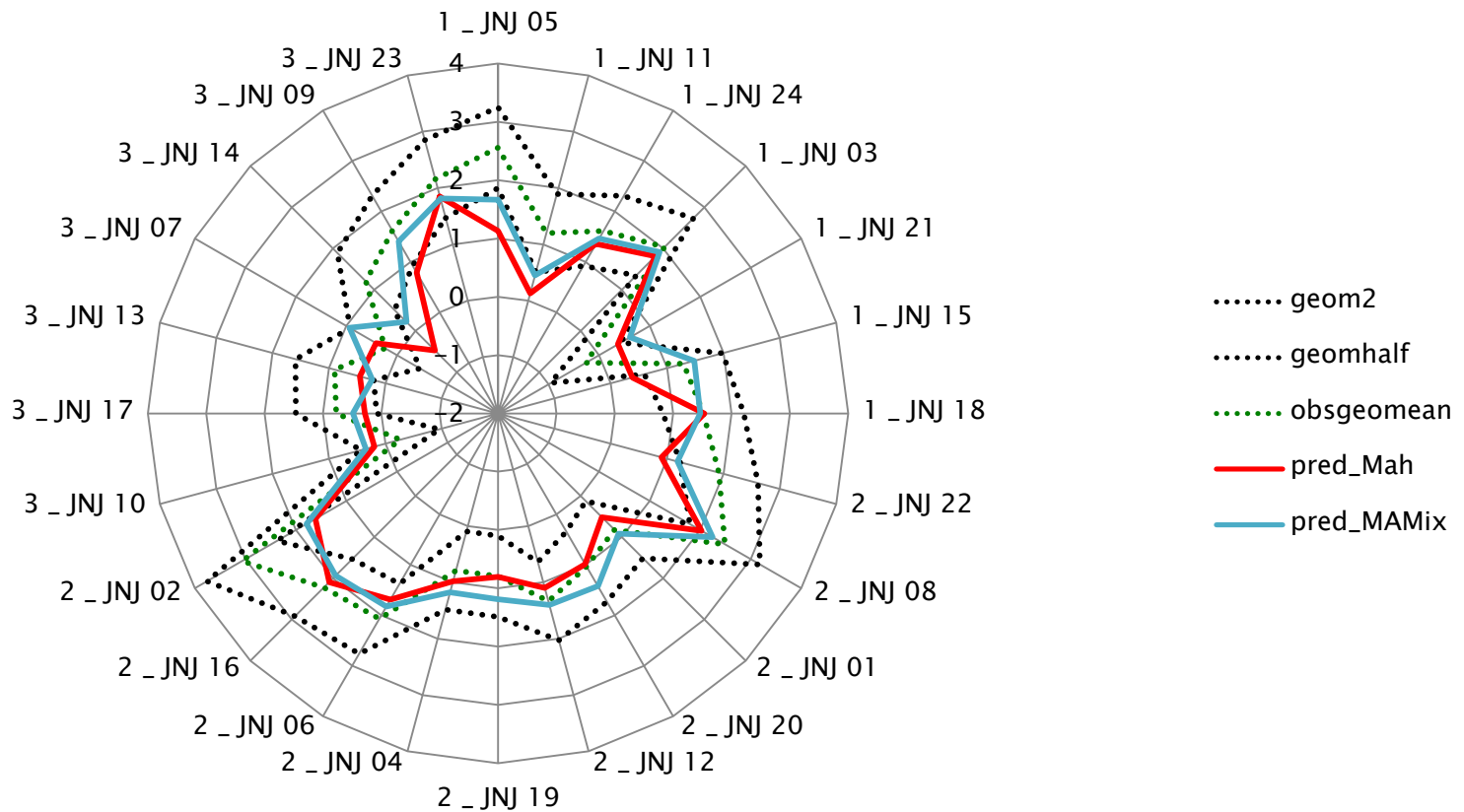


Mixed Model Approach

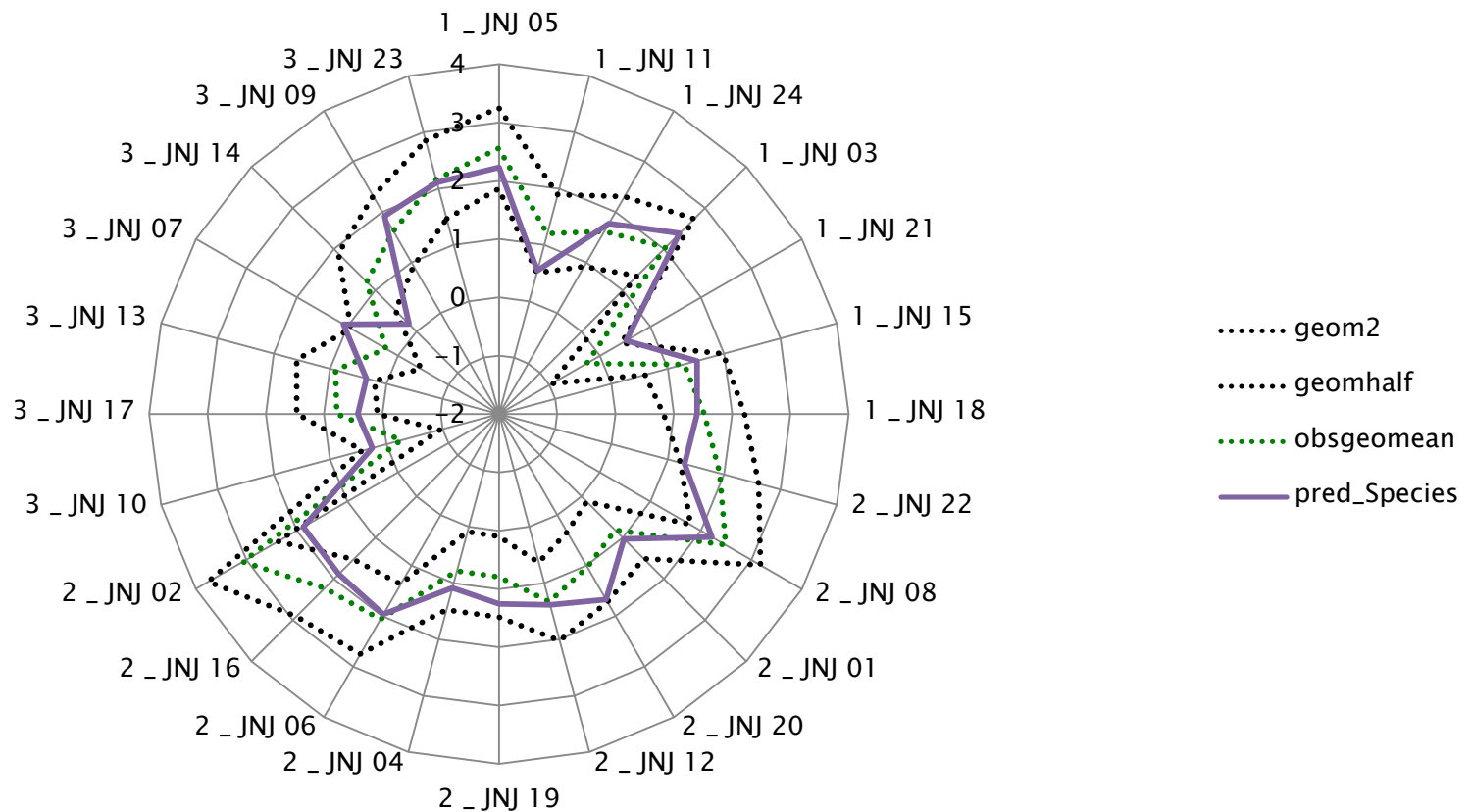
3 classes according to Mahmood



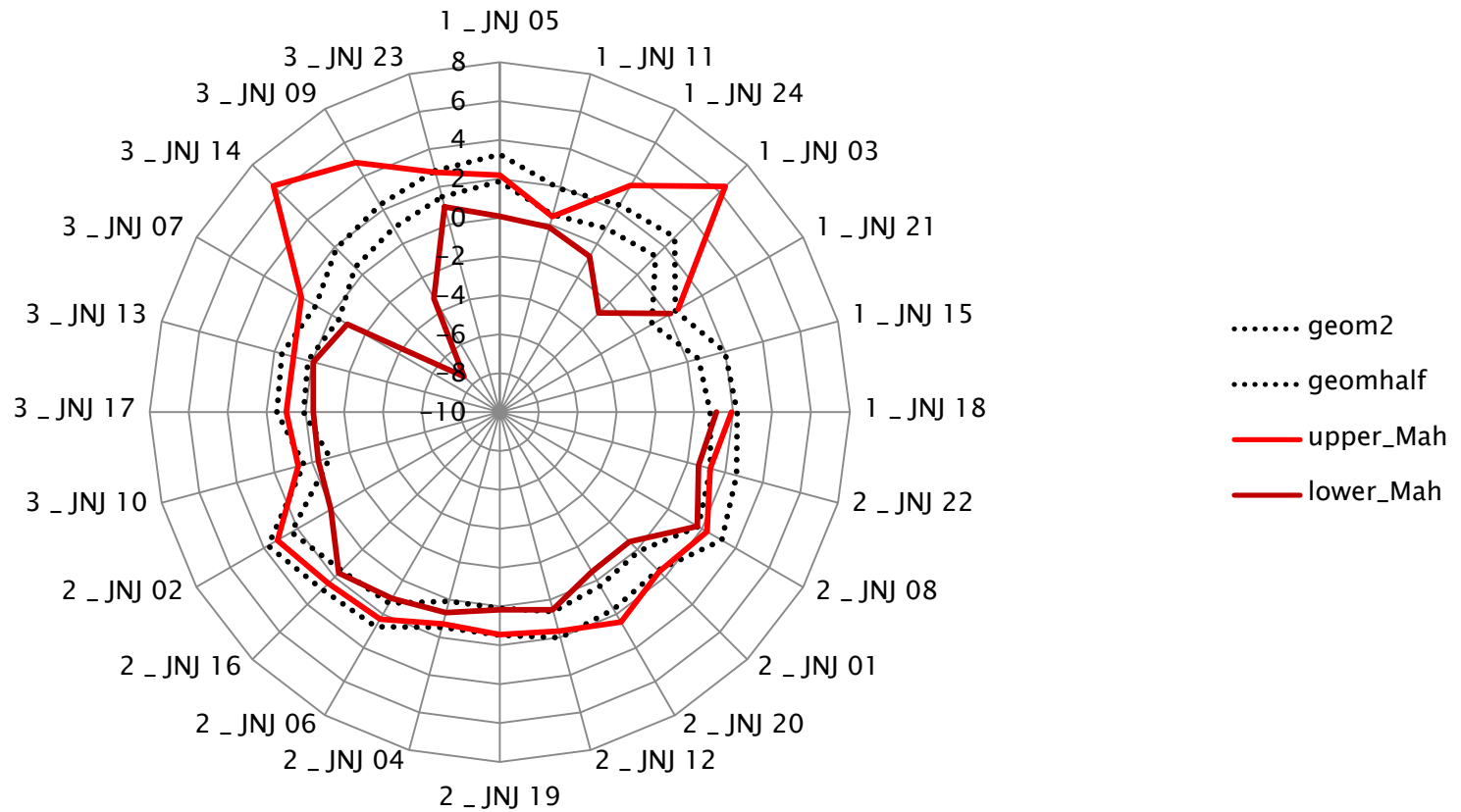
Predictions according to Mahmood and the Mixed Model



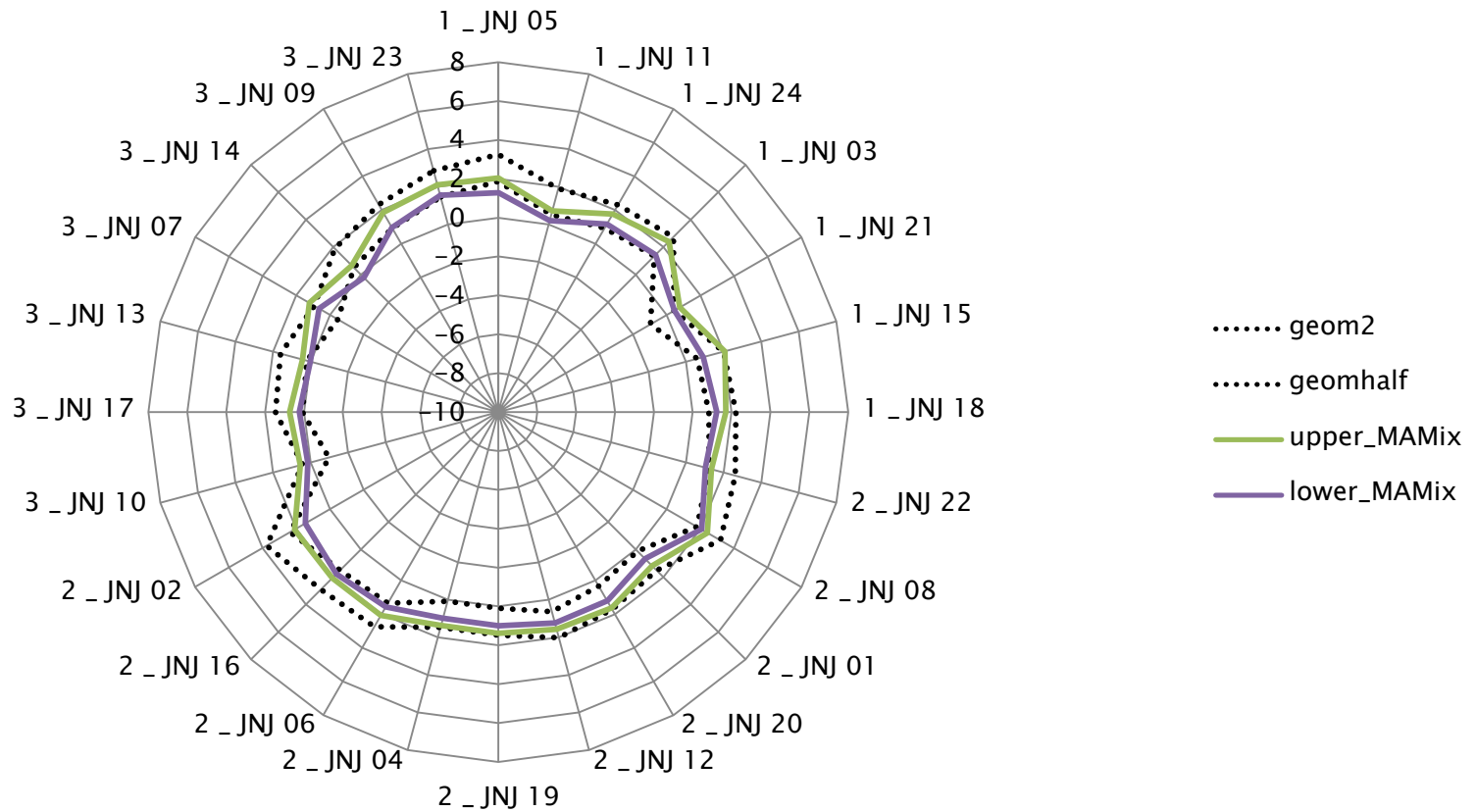
Random Effect ANOVA on Species (Ignoring Classes Mahmood)



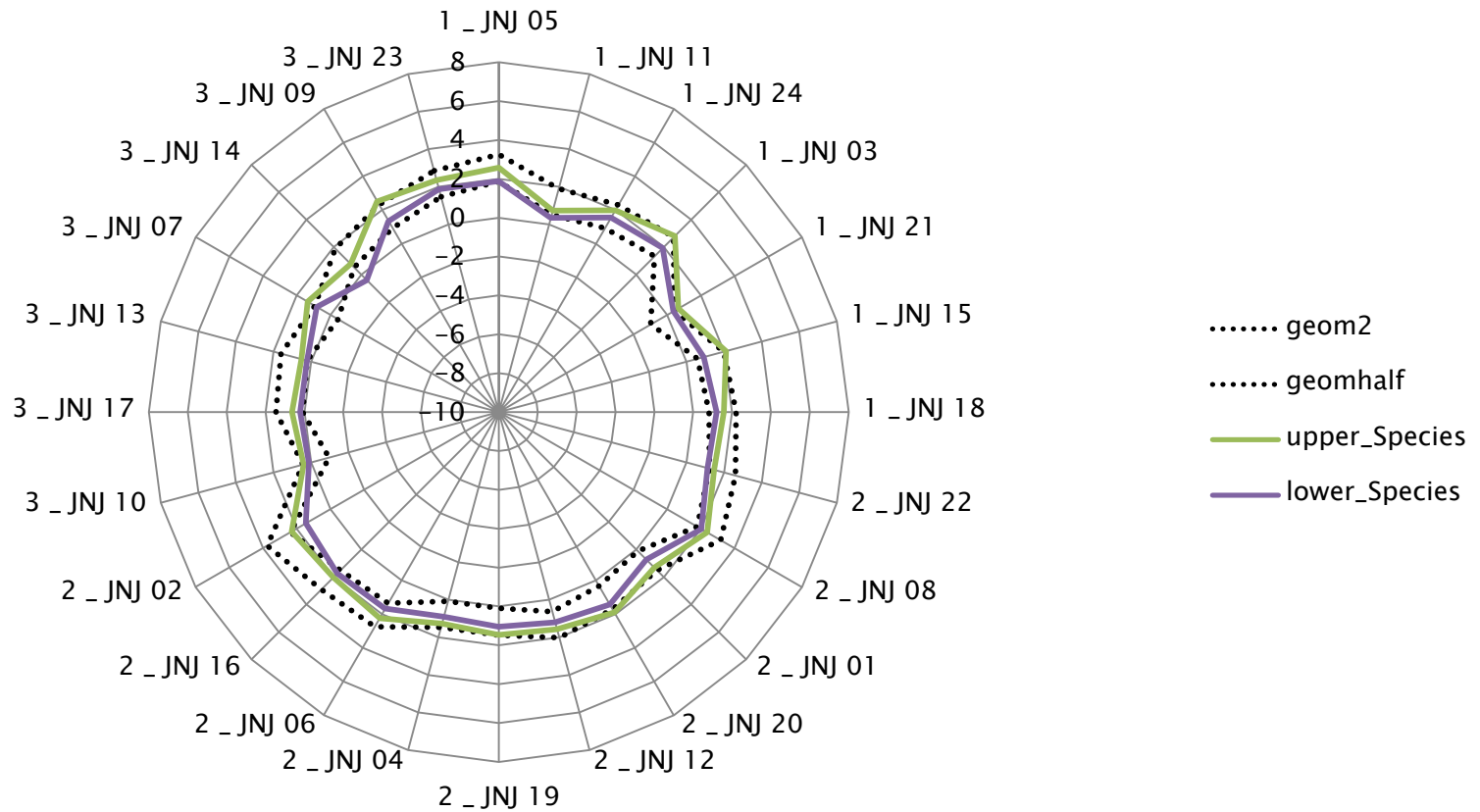
Confidence Intervals Mahmood (Animals Only)



Confidence Intervals Mixed Model with Classes of Mahmood



Confidence intervals Random Effect ANOVA on Species (Ignoring Classes Mahmood)



Percent Error

Variable	N	Mean	Std Dev	Minimum	Maximum
abs_pe_Mah	24	53.33	58.627	1.22	241.83
abs_pe_MAMIX	24	61.64	90.331	3.67	330.24
abs_pe_Species	24	61.04	90.8766	2.21	353.07

$Abs_PE = Abs (100 * (Observed - predicted) / Observed)$

PE smallest for method of Mahmood

PE similar for the 2 Mixed models

Conclusions

- ▶ General rule behind allometric scaling applicable to data at hand
- ▶ Method Mahmood has low precision and is rather conservative
- ▶ Mixed model approach seems to be promising because it produces more precision using historical human data
- ▶ Proposed mixed models have only moderate accuracy in terms of prediction
- ▶ Sample sizes of experiments in animal species is important
- ▶ Further statistical investigation is required because :
 - Body weight at two sides of the equation
 - MLP confounded with brain weight

Further Research

- ▶ Problem of over fitting using advanced models to the data at hand
- ▶ Design of allometric animal PK studies
- ▶ Inclusions of individual weights of animals and humans
- ▶ Using a statistical criterion for goodness of fit e.g. likelihood ratio test to build advanced models
- ▶ Combination of published meta-analysis data if available
- ▶ Using Bayesian model including informative priors from literature
- ▶ Inclusion of physicochemical properties of compounds (e.g. permeability, solubility, BCS drug class etc.)
- ▶ Deterministic feature need to be studied and confirmed

References

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- ▶ Verbeke G. and Molenberghs G. (2000) Linear mixed models in practice a SAS-oriented approach Springer New York