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Aims

- Translate the statistical **interaction term** to a non-linear mixed effects modeling framework.
- Evaluate the interaction term as a covariate for **clearance of vancomycin** in neonates.

Introduction

- Covariates can partly explain inter-individual variability.
- In linear statistics, an **interaction term** describes how the value of one variable (i.e. covariate) determines the **influence** of the other variable on the **outcome** (i.e. parameter).
- For example, weight is a common covariate on clearance, but for small for gestational age (SGA) neonates that relationship is influenced by gestational age. [PAGE 2024 Poster IV-059]¹

Interaction in linear statistics

- For covariates x_1 and x_2 , the interaction is their **product** x_1x_2
- In a linear model with outcome y and intercept θ_0 :

$$y = \theta_0 + \theta_1x_1 + \theta_2x_2 + \theta_{1,2}x_1x_2$$

Covariate interaction term

The interaction term is defined as $(x_1^{\log(x_2)})^{\theta_4}$ because

$$CL = \theta_1 \cdot x_1^{\theta_2} \cdot x_2^{\theta_3}$$

$$\log(CL) = \log(\theta_1) + \theta_2\log(x_1) + \theta_3\log(x_2)$$

$$\log(CL) = \log(\theta_1) + \theta_2\log(x_1) + \theta_3\log(x_2) + \theta_4 \cdot \log(x_1) \cdot \log(x_2)$$

$$CL = \theta_1 \cdot x_1^{\theta_2} \cdot x_2^{\theta_3} \cdot (x_1^{\log(x_2)})^{\theta_4}$$

log
add
interaction
exponentiate

Case example: vancomycin

Data

- 437 neonates with vancomycin PK measurements.^{2,3}
- Covariates: birth bodyweight (BW) and gestational age (GA).

Methods

- Model comparison of three models:

Base model

$$CL = \theta_1 \cdot BW^{\theta_2} \cdot GA^{\theta_3}$$

Dichotomous interaction model (SGA)

$$CL = \theta_1 \cdot BW^{\theta_2} \cdot GA^{\theta_3} \cdot \theta_4^{SGA}, \text{ where } SGA: SGA = 1, \text{ no } SGA = 0$$

Continuous interaction model

$$CL = \theta_1 \cdot BW^{\theta_2} \cdot GA^{\theta_3} \cdot (BW^{\log(GA)})^{\theta_4}$$

- All analysis were done using **NONMEM**

```
$BASE
TVCL = THETA(1)*((BW/1310)**THETA(2))*((GA/30)**THETA(3))
$SGA
FF = 1
IF (SGA.EQ.1) FF = THETA(4)
TVCL = THETA(1)*((BW/1310)**THETA(2))*((GA/30)**THETA(3))*FF
$INTERACTION
TVCL = THETA(1)*((BW/1310)**THETA(2))*((GA/30)**THETA(3))*
      (((BW/1310)**LOG(GA/30))**THETA(4))
```

Results

- All models were fitted and used to predict clearance based on BW and GA (Figure 1).
- The continuous model showed a lower influence of body weight on clearance with higher GA (Figure 1c).
- The continuous interaction model significantly increased model fit (dOFV=-4.91), while the SGA (Figure 1b) did not (dOFV=-1.14).
- The SGA model shows a dichotomous split in clearance, while the interaction model is smooth (Figure 2).

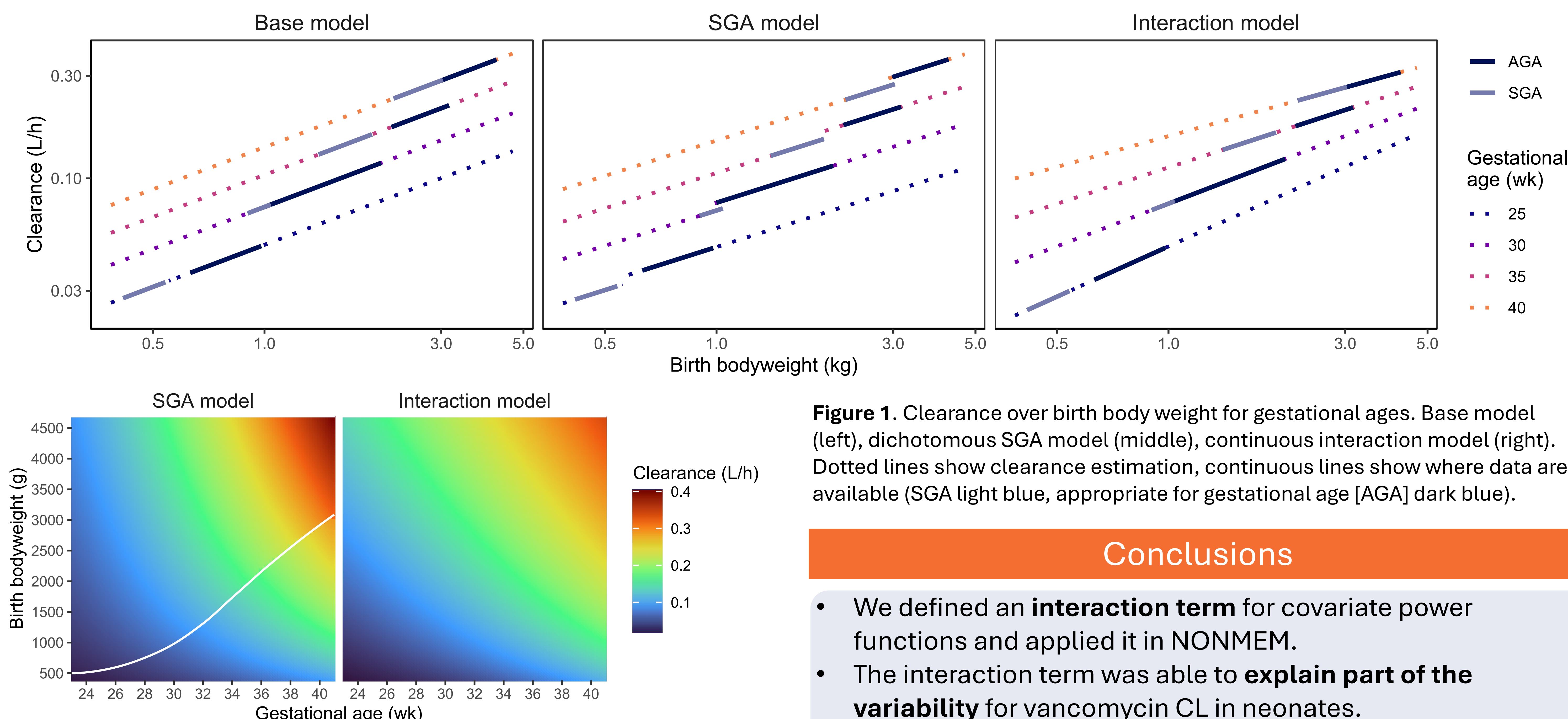


Figure 2. Estimated clearance based on birth body weight and gestational age for the dichotomous SGA model (left) and the continuous interaction model (right)

Conclusions

- We defined an **interaction term** for covariate power functions and applied it in NONMEM.
- The interaction term was able to **explain part of the variability** for vancomycin CL in neonates.
- This term is **not limited** to the pediatric field but can also be used for other **pharmacometric models**.