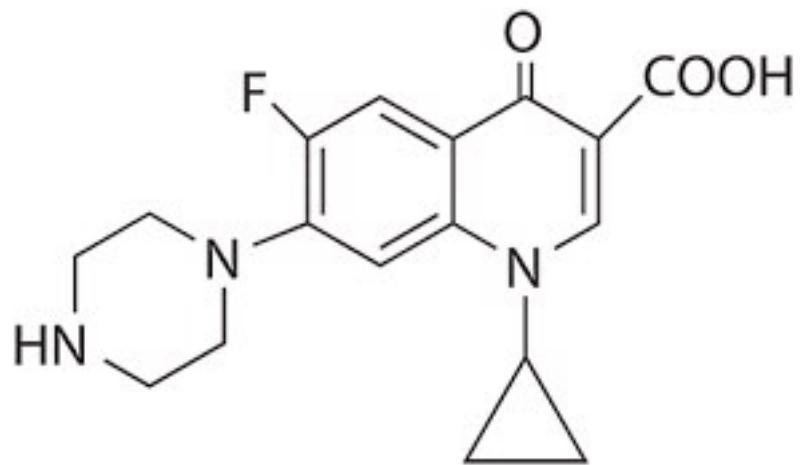


Pharm609 Homework3

Ciprofloxacin pharmacokinetics in paediatric patients



Yaowen Mei (20470193)

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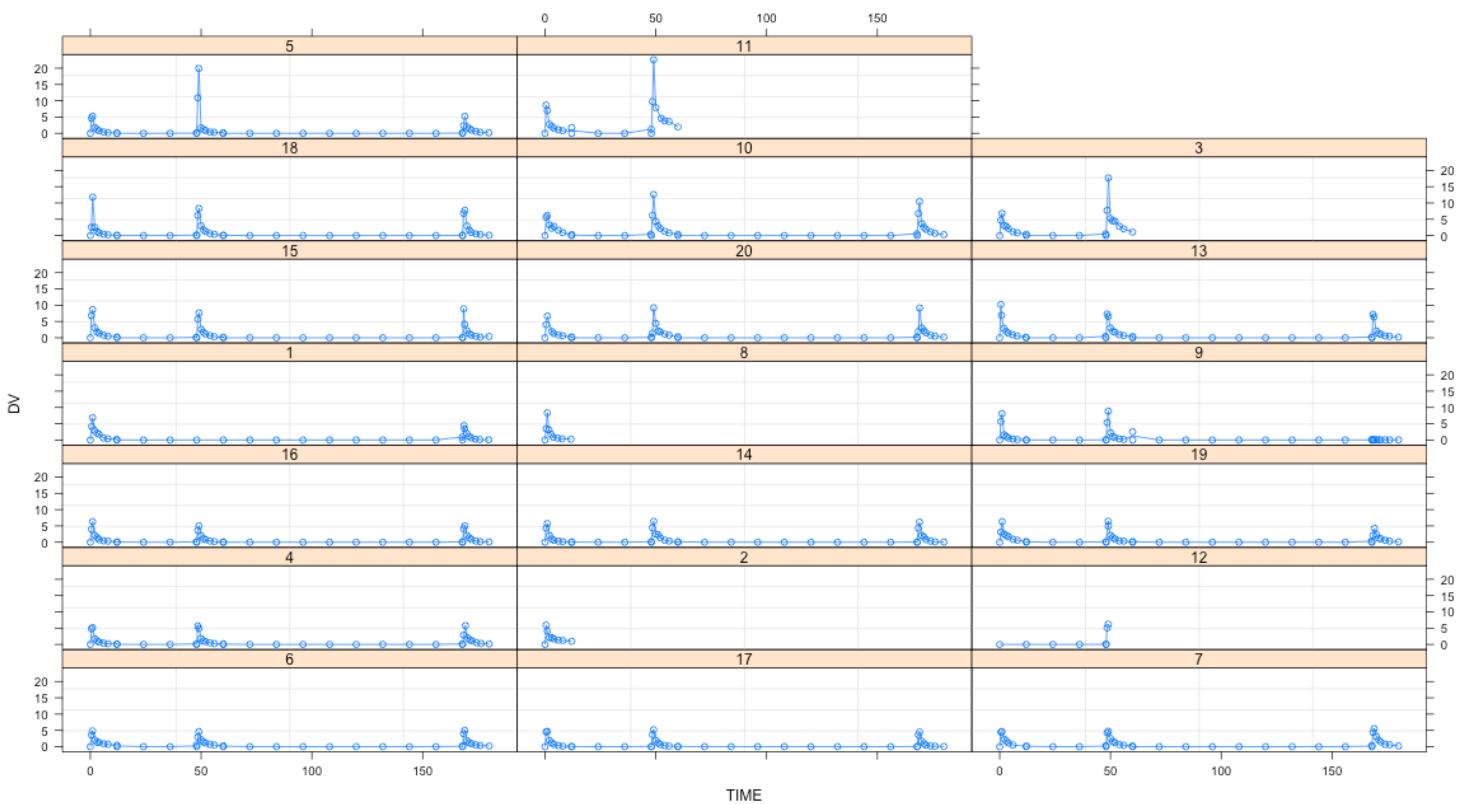
Ciprofloxacin pharmacokinetics in paediatric patients

1. Description of the sample

This data contains 20 paediatric patients' dose amount and concentration profiles with up to 41 time points, where 6 of them are male and 14 of them are female.

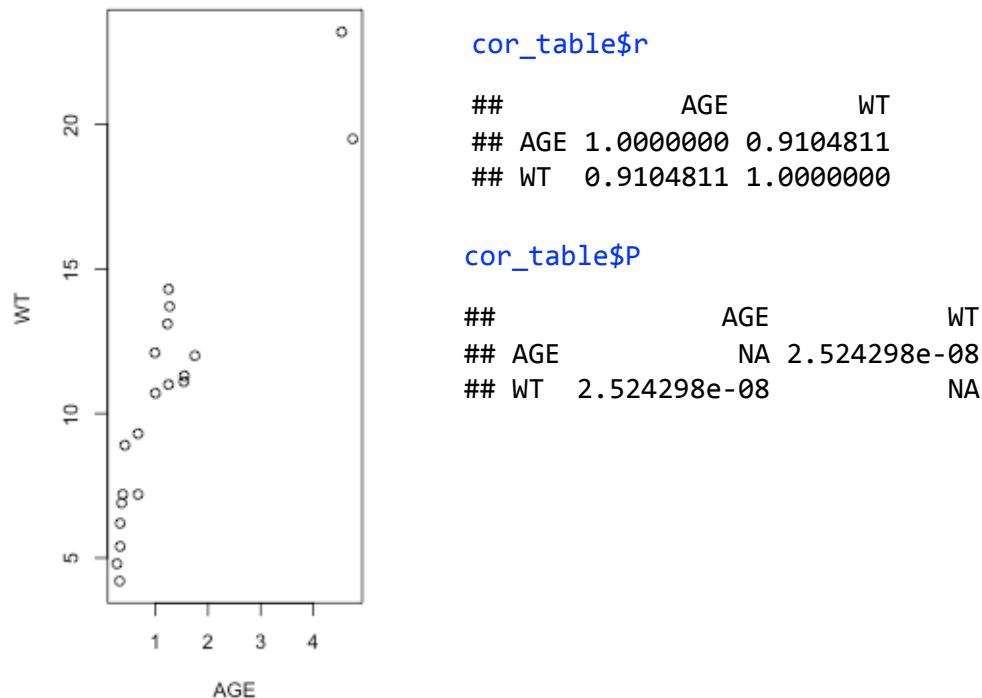
Concentration profiles

The variable DV - Concentration in the unit of mg/L is the response variable, and its profile are presented below in the plot. It is showing that for patient number 3, 5 and 11, the concentration at time 50 hrs are significantly higher than other patines, which means these are the potential outliers. What's more, patines number 2, 8, 3, 11, 12, do not have as many data points collected as the others, and these may contribute to the variability and uncertainty of the final conclusion that we could make from this dataset.



```
sort(table(data$ID))
## 12   2   8  11   3   1   7  20   6  17   4  16  14  19   9  15  13  18  10   5
##  8   9   9  21  22  32  40  40  41  41  41  41  41  41  41  41  41  41  41
```

Potential collinearity



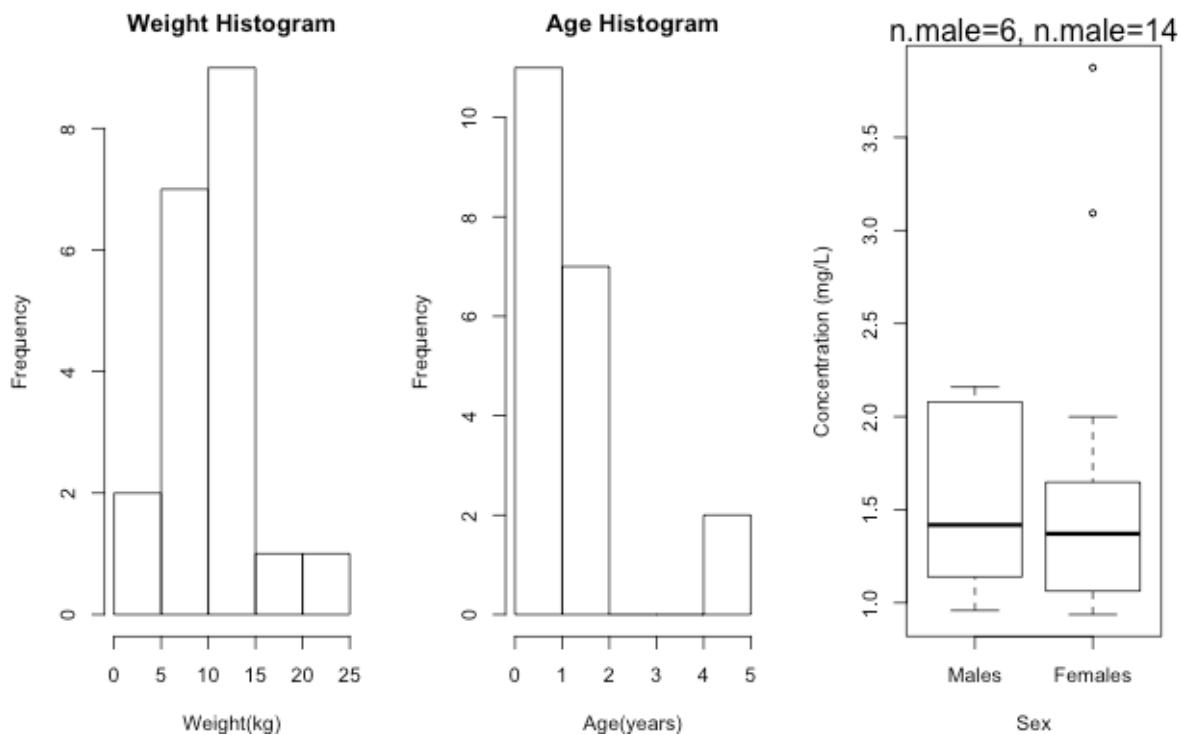
As it is shown in the collinearity plot and in the collinearity table, Age and Weight are significantly correlated ($\text{cor} = 0.91$, and $P_{\text{val}} < 2E-8$, also the collinearity plot between Age and Weight shows a linear trend), and this pair of variables may bring collinearity issues in the modelling. It is also well-known that for paediatric patients, age and weight are physically strongly related with each other, but which variable that should be used in the modelling is depend on the researcher's preference and may vary between different datasets.

Demographic characteristics in the sample

The WT, AGE, and GEND, represent weight, age, and gender, respectively, are the covariates. For weight and age, 1) range of the distribution (min and max values), 2) the measures of the central tendency (median and mean), and also 3) the measures of the location (1st Qu, median, 3rd Qu) are listed in the table below. The histograms indicated the symmetry distribution of weight and asymmetry distribution of Age. Most of the patients are between 0.3 year old to 2 years old, but there are two patients that are about 5 years old.

WT AGE

Min. 4.200 0.270
1st Qu. 7.125 0.375
Median 10.850 0.995
Mean 10.600 1.244
3rd Qu. 12.350 1.338
Max. 23.200 4.750



For the factor of gender, there are totally 6 male patients and 14 females patients in the dataset, the median of the concentration between different genders are almost the same even though the male patients show a much greater IQRs than the females. Additionally, there are two outliers for the females' concentration.

```
sort(table(data.sub$GEND))
## male      Female
##     6        14
```

Information on the outliers and whether they were discarded from the analysis

There are several potential outliers that can be detected from the plots above:

From the concentration profile, patient 5, and 11 could be the potential outliers as they have a unusual high second dose, and patients 2, 3, 8, 12 could be the potential outliers as they do not have enough data points collected as the other patients do.

From the age's histogram, patients 11, and 15 are the potential outliers as their age are significantly greater than the other patines.

From the box plot of Concentration vs. Sex, patients 3, and 11 are the potential outliers as they stand out of $1.5 \times \text{IQR}$ above Q3 (By comparing the concentration profiles, one can see the reason for this is the concentration data points were missed right after their second dose).

However, all these potential outliers are not significantly affect our modelling. As the structural model already includes the time variable, the lack of time points for patients 2, 3, 8, 12 will not affects our result much. Due to the same reason, patients 3 and 11, the potential outlier detected from the box plot of concentration vs. sex, will also not affect our final result. Due to the fact that age and weight are highly correlated, the potential outliers detected from age's histogram will not affects the modelling result much as we will include weight in our covariate model. Also considering the fact that there are only 20 patines' information in this dataset, it is actually not a rich dataset; therefore, I think there is no need to discarded the potential outliers from the analysis.

2. Model selection

2.1.selection of the base model

Mathematical expression of the base model and distributional assumptions

In this study, one compartment IV structural model with exponential random effects and infusion was used, and three residual variance models (Additive, Exponential (Log-additive) and Proportional (Multiplicative)) were explored. The mathematical expression along with the assumption of the distribution involved were list below:

Variance model	Mathematica expression	Variance
Additive (unweighted)	$c_{ij} = \sum_{d_{id} < t_{id}} \frac{D_{id}}{CL_i \times t_{id}} \left[1 - \exp\left(-\frac{CL_i}{V_i} t_{id}\right) \right] \exp\left\{-\frac{CL_i}{V_i} (t_{ij} - t_{id})\right\} + \varepsilon_{ij}$	$Var(c) = \sigma^2$
Exponential (Log-additive)	$c_{ij} = \sum_{d_{id} < t_{id}} \frac{D_{id}}{CL_i \times t_{id}} \left[1 - \exp\left(-\frac{CL_i}{V_i} t_{id}\right) \right] \exp\left\{-\frac{CL_i}{V_i} (t_{ij} - t_{id})\right\} \exp(\varepsilon_{ij})$	$Var(\log(c)) = \sigma^2$
Proportional (Multiplicative, constant CV)	$c_{ij} = \sum_{d_{id} < t_{id}} \frac{D_{id}}{CL_i \times t_{id}} \left[1 - \exp\left(-\frac{CL_i}{V_i} t_{id}\right) \right] \exp\left\{-\frac{CL_i}{V_i} (t_{ij} - t_{id})\right\} (1 + \varepsilon_{ij})$	$Var(c) = \sigma^2 \left[\sum_{d_{id} < t_{id}} \frac{D_{id}}{CL_i \times t_{id}} \left[1 - \exp\left(-\frac{CL_i}{V_i} t_{id}\right) \right] \exp\left\{-\frac{CL_i}{V_i} (t_{ij} - t_{id})\right\} \right]^2$

Where,

$$CL_i = \theta_1 e^{\eta_{CL_i}}$$

$$V_i = \theta_2 e^{\eta_{V_i}}$$

$$\boldsymbol{\eta}_i = \begin{pmatrix} \eta_{CL_i} \\ \eta_{V_i} \end{pmatrix} \sim N(0, \boldsymbol{\Psi}) \quad \varepsilon_{ij} \sim N(0, \sigma^2) \quad \boldsymbol{\Psi} = \begin{pmatrix} \psi_{CL}^2 & \psi_{CL,V} \\ \psi_{CL,V} & \psi_V^2 \end{pmatrix}$$

We assume that all the population PK parameters, both CL and V, vary between subjects. The random effects, so-called *the between subject variability*, η 's are distributed normally with zero mean and variance-covariance matrix $\boldsymbol{\Psi}$. For structural model, $\psi_{CL,V} = 0$, while, for unstructured model, $\psi_{CL,V} \neq 0$.

The within-subjects' errors, ε 's, are assumed to be independent with each other and they have zero mean and constant variance σ^2 .

Evidence of the choice on diagonal or unstructured variance-covariance matrix of the random effects:

	Name	Description	Scenario	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI
1	Ad_diag_power			tvV θ_2	7.60002		0.82996385	10.920548	5.9686824	9.2313576
2	Ad_diag_power			tvCl θ_1	6.62972		0.83721562	12.62822	4.9841287	8.2753113
3	Ad_diag_power			stdev0	1.41719		0.21929888	15.474205	0.98614652	1.8482335
4	Ad_unstr_power			tvV	8.35339		0.84901708	10.163743	6.6846023	10.022178
5	Ad_unstr_power			tvCl	7.13528		0.78058952	10.939858	5.6009903	8.6695697
6	Ad_unstr_power			stdev0	1.40338		0.21802293	15.535559	0.97484446	1.8319155
7	Log_diag_power			tvV	19.5198		2.6790483	13.724774	14.25399	24.78561
8	Log_diag_power			tvCl	5.64322		0.80343637	14.237197	4.0640236	7.2224164
9	Log_diag_power			stdev0	0.658439		0.11649464	17.692548	0.42946267	0.88741533
10	Log_unstr_power			tvV	18.5932		2.2822138	12.274454	14.107389	23.079011
11	Log_unstr_power			tvCl	5.63518		0.76754804	13.620648	4.126524	7.143836
12	Log_unstr_power			stdev0	0.658102		0.11560277	17.566087	0.43087868	0.88532532
13	Multi_diag_power			tvV	15.9923		1.8042727	11.282134	12.445907	19.538693
14	Multi_diag_power			tvCl	4.69264		0.53743837	11.452793	3.6362766	5.7490034
15	Multi_diag_power			stdev0	0.616577		0.05898983	9.5673095	0.50062939	0.73252461
16	Multi_unstr_power			tvV	15.8269		1.786393	11.287068	12.315651	19.338149
17	Multi_unstr_power			tvCl	4.69353		0.5345746	11.389606	3.6427955	5.7442645
18	Multi_unstr_power			stdev0	0.615025		0.05984647	9.7307378	0.49739362	0.73265638

Figure 4. Fixed effects estimates for Residual Variance Model: Additive, Log-additive, Multiplicative (Diagonal & Unstructured)

	Name	Description	Scenario	Label	nV	nCI
1	Ad_diag_power			Omega		
2	Ad_diag_power			nV	$\psi_{CL}^2 0.22007576$	
3	Ad_diag_power			nCI	$\psi_{CL,V}$	0 $\psi_V^2 0.24935141$
4	Ad_diag_power			Correlation		
5	Ad_diag_power			nV	1	
6	Ad_diag_power			nCI	0	1
7	Ad_diag_power			Shrinkage	0.1226296	0.10450484
8	Ad_unstr_power			Omega		
9	Ad_unstr_power			nV	0.18289957	
10	Ad_unstr_power			nCI	0.18530651	0.2067233
11	Ad_unstr_power			Correlation		
12	Ad_unstr_power			nV	1	
13	Ad_unstr_power			nCI	0.9529928	1
14	Ad_unstr_power			Shrinkage	0.041517044	0.041462929

Figure 5. Variance-Covariance Estimates for Additive Residual Variance Model (Diagonal & Unstructured)

	Name	Description	Scenario	Label	nV	nCl
15	Log_diag_power			Omega		
16	Log_diag_power			nV	$\psi_{CL}^2 0.22876145$	
17	Log_diag_power			nCl	$\psi_{CL,V} 0$	$\psi_V^2 0.30485402$
18	Log_diag_power			Correlation		
19	Log_diag_power			nV		1
20	Log_diag_power			nCl		0 1
21	Log_diag_power			Shrinkage	0.095734384	0.044155303
22	Log_unstr_power			Omega		
23	Log_unstr_power			nV		0.28011405
24	Log_unstr_power			nCl		0.30390724 0.35173934
25	Log_unstr_power			Correlation		
26	Log_unstr_power			nV		1
27	Log_unstr_power			nCl		0.96819565 1
28	Log_unstr_power			Shrinkage	0.062499868	0.034563309

Figure 6. Variance-Covariance Estimates for Log-Additive Residual Variance Model (Diagonal & Unstructured)

	Name	Description	Scenario	Label	nV	nCl
29	Multi_diag_power			Omega		
30	Multi_diag_power			nV	$\psi_{CL}^2 0.17714211$	
31	Multi_diag_power			nCl	$\psi_{CL,V} 0$	$\psi_V^2 0.22616536$
32	Multi_diag_power			Correlation		
33	Multi_diag_power			nV		1
34	Multi_diag_power			nCl		0 1
35	Multi_diag_power			Shrinkage	0.11228515	0.048217004
36	Multi_unstr_power			Omega		
37	Multi_unstr_power			nV		0.18976913
38	Multi_unstr_power			nCl		0.17972873 0.24571403
39	Multi_unstr_power			Correlation		
40	Multi_unstr_power			nV		1
41	Multi_unstr_power			nCl		0.83231888 1
42	Multi_unstr_power			Shrinkage	0.10112979	0.042713525

Figure 7. Variance-Covariance Estimates for Multiplicative Residual Variance Model (Diagonal & Unstructured)

	Hide	Name	Method	Lineage	-2(LL)	AIC	-2(LL)Delta	AIC Delta	#Subj	pvalue
1	False	Ad_diag_power	FO		1621.6882	1631.6882	NC	NC	20	NC
2	False	Ad_unstr_power	FOCE ELS	Ad_diag_power	1580.954	1592.954	40.73418	38.73418	20	1.7441E-10
3	False	Log_diag_power	FOCE ELS		973.90834	983.90834	NC	NC	20	NC
4	False	Log_unstr_power	FOCE ELS	Log_diag_power	936.46108	948.46108	37.44726	35.44726	20	9.39185E-10
5	False	Multi_diag_power	FOCE ELS		1111.8107	1121.8107	NC	NC	20	NC
6	False	Multi_unstr_power	FOCE ELS	Multi_diag_power	1091.4318	1103.4318	20.3789	18.3789	20	6.35264E-06

Figure 8. Comparison between unstructured models and diagonal models for all three residual variance models: 1) Additive, 2) Log-additive and 3) Multiplicative without covariates.

In this study, three residual variance model (with diagonal or unstructured variance-covariance matrix) was explored, they are namely to be 1) additive, 2) log-additive and 3) multiplicative. The calculated results from *phoenix* were presented in Figure 4 to Figure 7.

In Figure 4, all the fixed effects (the θ 's) were presented with their standard deviation and 95% Confidence Interval, 95%CI, and also the Coefficients of Variation, %CV. The variance-covariance estimates for different models are presented in Figure 5, 6, and 7. Based on this information, one can calculate the BSVs in Volume and Clearance by the equation:

$BSV = \sqrt{\eta} \times 100\%$. The calculation result are presented in Table 1-1. It is clearly that all the

Table 1-1 The calculation of BSVs for different models

AD_DIAG_POWER	Omega		BSV in V (%)	BSV in CL(%)
AD_DIAG_POWER	nV	0.22007576	46.9122329	
AD_DIAG_POWER	nCl	0	0.24935141	49.9350988
AD_DIAG_POWER	Shrinkage	0.1226296	0.10450484	
AD_UNSTR_POWER	Omega			
AD_UNSTR_POWER	nV	0.18289957	42.7667592	
AD_UNSTR_POWER	nCl	0.18530651	0.2067233	45.4668340
AD_UNSTR_POWER	Shrinkage	0.04151704	0.04146292	
LOG_DIAG_POWER	Omega			
LOG_DIAG_POWER	nV	0.22876145	47.8290131	
LOG_DIAG_POWER	nCl	0	0.30485402	55.2135871
LOG_DIAG_POWER	Shrinkage	0.09573438	0.04415530	
LOG_UNSTR_POWER	Omega			
LOG_UNSTR_POWER	nV	0.28011405	52.9258018	
LOG_UNSTR_POWER	nCl	0.30390724	0.35173934	59.3076167
LOG_UNSTR_POWER	Shrinkage	0.06249986	0.03456330	
MULTI_DIAG_POWER	Omega			
MULTI_DIAG_POWER	nV	0.17714211	42.0882537	
MULTI_DIAG_POWER	nCl	0	0.22616536	47.5568459
MULTI_DIAG_POWER	Shrinkage	0.11228515	0.04821700	
MULTI_UNSTR_POWER	Omega			
MULTI_UNSTR_POWER	nV	0.18976913	43.5624987	
MULTI_UNSTR_POWER	nCl	0.17972873	0.24571403	49.5695501
MULTI_UNSTR_POWER	Shrinkage	0.10112979	0.04271352	

between subject variabilities (BSVs) are relatively large (around 50%). It is also worth to note that Shrinkage indicates in what extend that the EBEs shrinks towards the population mean. Additive_Unstructured Model, Log-additive_Unstructured Model have the smallest shrinkage value, which shows that these two models are better than the others when considering the EBEs.

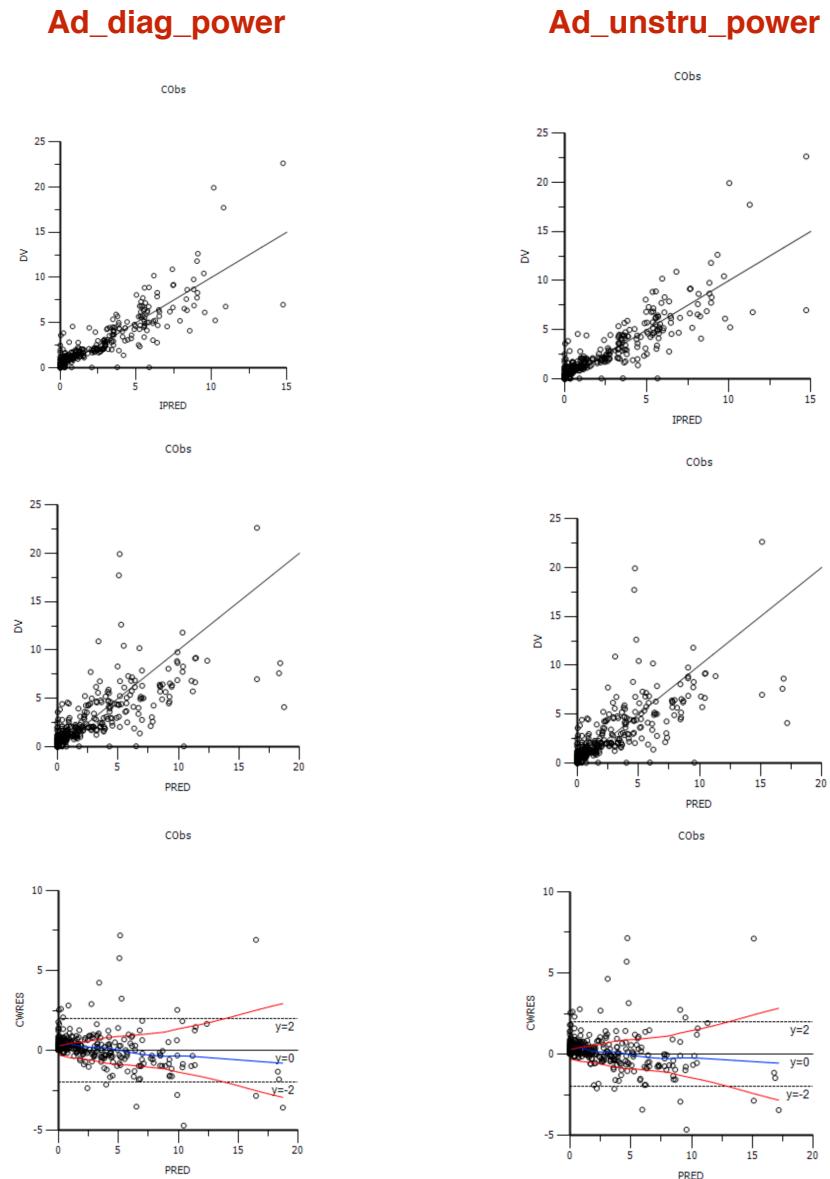
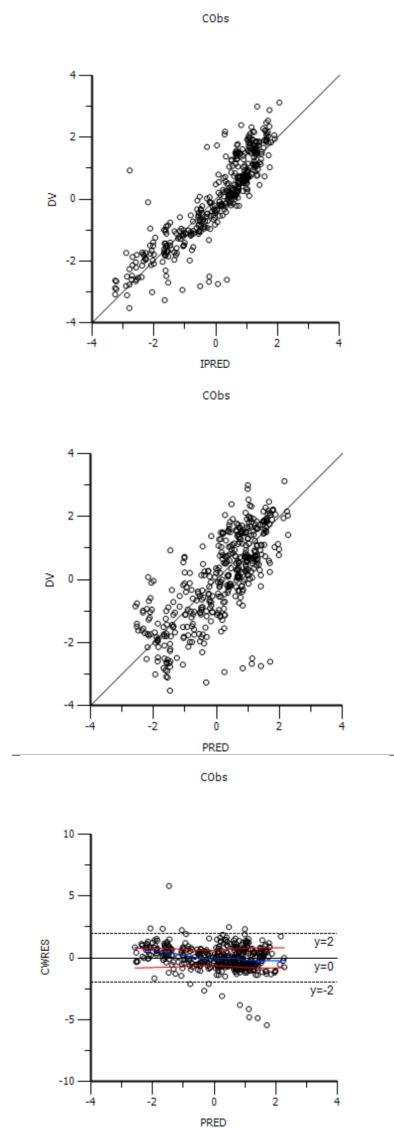


Figure 9. Predicted values and residual plots for additive model

Log-add_diag_power



Log-add_unstru_power

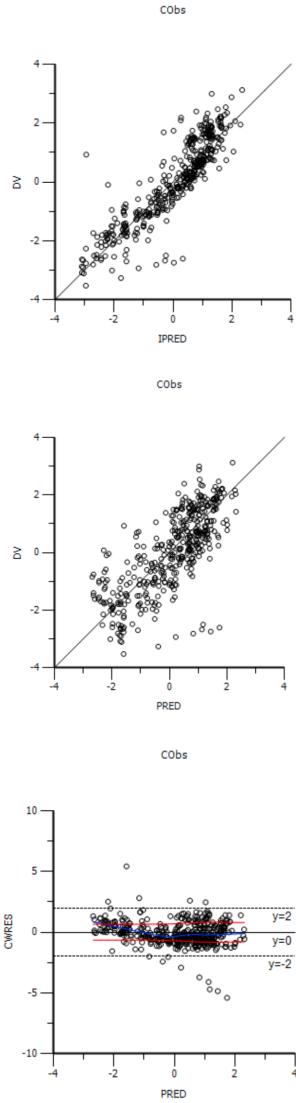
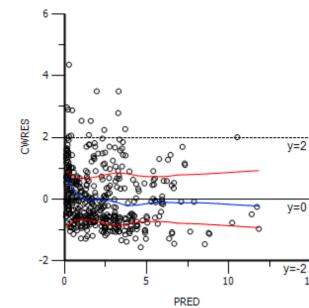
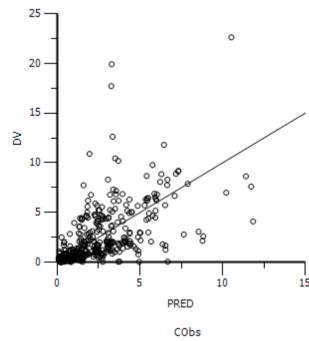
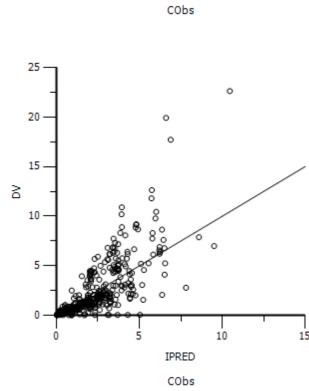


Figure 10. Predicted values and residual plots for Log-additive model

Multi_diag_power



Multi_unstru_power

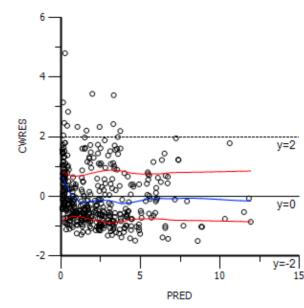
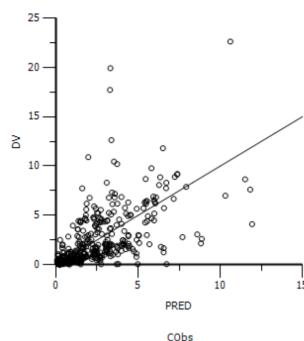
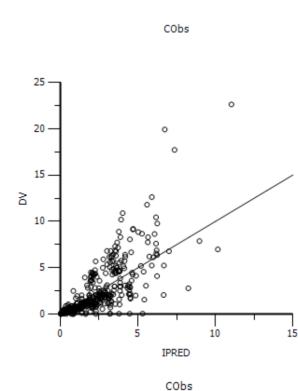


Figure 11. Predicted values and residual plots for Multiplicative model

Then, the graphic model assessment was conducted, the predicted values and residuals plots for different models are listed above from Figure 9 to 11. Ideally, the individual prediction should fall very close to the unity line. When comparing these different models, one can see that only Log-additive models (either diagonal and unstructured one) shows this trend. The DV vs. PRED plots shows a little bit divergency from the unity line. The reason for this is that for the population predictions, as they are typically not as accurate as the individual predictions do, a larger deviations around the unity line should be expected. Then the residual plots were compared: all the residual plots shows a distribution around zero, which is good, but only the Log-additive plots shows a constant variance, and it has the least outliers

than the other ones. The residual plots for Additive models show a increasing variance, which is against to the constant variance assumption.

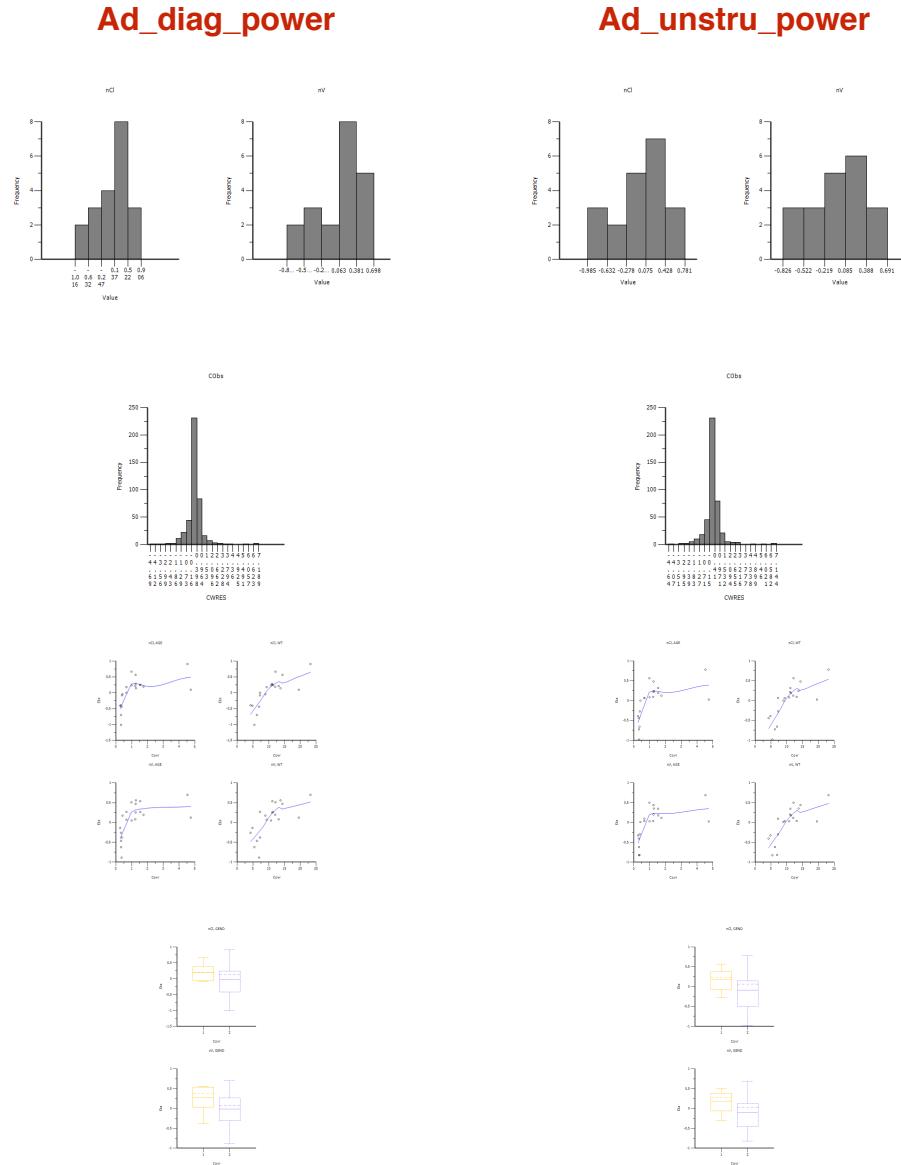
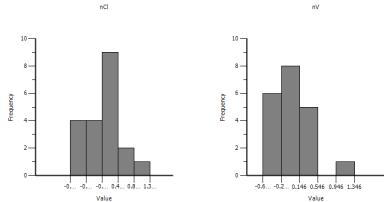


Figure 12. Predicated Eta's, Residuals Plots, and Predicted Eta's vs. Covariates Plots for Additive Model

Log-add_diag_power



Log-add_unstru_power

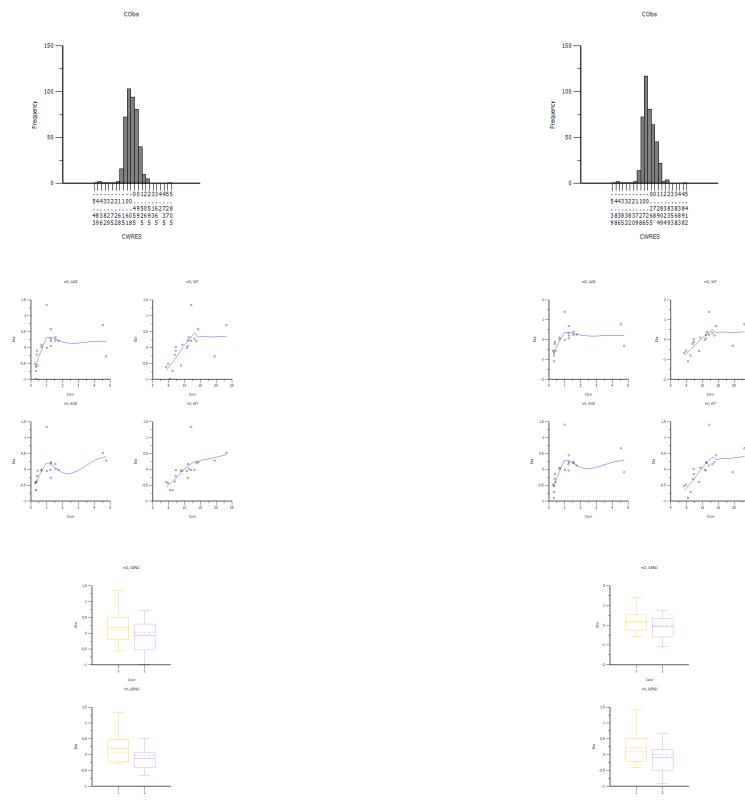
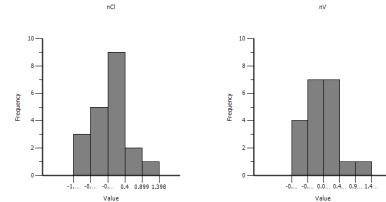
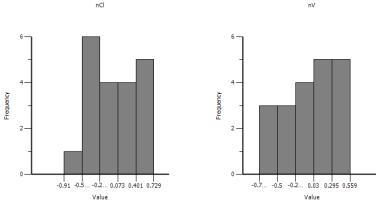
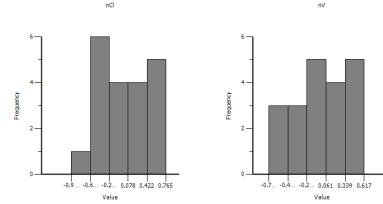


Figure 13. Predicated Eta's, Residuals Plots, and Predicted Eta's vs. Covariates Plots for Log-Additive Model

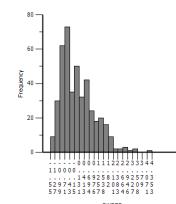
Multi_diag_power



Multi_unstru_power



CORe



CORe

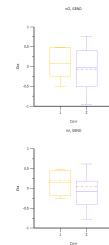
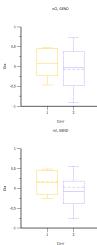
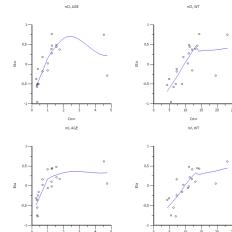
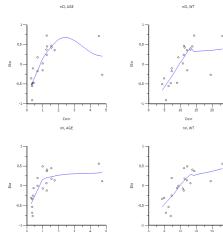
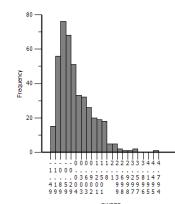


Figure 14. Predicated Eta's, Residuals Plots, and Predicted Eta's vs. Covariates Plots for Multiplicative Model

Then, we look at Figure 12 to Figure 14, from the first two rows of these plots (the predicated Eta's Plots, and residual plots), we can see that the Log-Additive ones shows more symmetry in the predicated Eta's plots, and also the residual plots for the Log-Additive ones look more normally distributed (the residual plots for the Additive models look too narrow, and the residual plots for the Multiplicative models shifted to the left). At this point, from the graphic model assessment, one can draw a conclusion that **Log-Additive models are better than the**

others. But whether the diagonal one is better or the unstructured one is better still need to be discussed.

Now, let's look back to Figure 8, from the p-value provided by the model comparator, one can see that unstructured model are statistically significantly better ($p_val << 0.05$) than the diagonal model for both of the Additive, lLog-additive and Multiplicative residual variance models. Also, by finding the model with the lowest AIC values, one can confirm the conclusion that was previously drawn from the graphic model assessment: Log-additive is better than the others (AIC= 948.46).

Preliminary assessment of the effect of the covariates on the response:

Eventually, we find that Log-Additive-unstructured model is the best model to be used as our base model. It is the time to conduct the preliminary assessment of the effects of the covariates on the response. The predicted Eta's vs. covariates plots was presented in the third and forth row in Figure 12, 13, 14. One can see that Weight and Age have some effects on all these six models (a linear trend was shown in the plots of predicated Eta's vs. Weight/Age instead of all the Eta's distributed uniformly regardless of the Weight/Age values, and for weight, this trend is up to 15kg, and for age, this trend is up to 1.5 years). It is also can be seen that Etas are more sensitive to weight because the slopes of Eta vs. Weight are greater than that of Eta vs. Age. Which indicates that when adding covariates, weight should be added first, instead of age. Last but not the least, in all the box plots of Eta vs. Gender, it shown that gender is a less effective covariate as the median of Eta for both male and female are almost the same. This gives us a clue that maybe later, we do not need to include gender in our covariate model.

2.2.selection of the covariate model

From the reference (Jian wang, 2015), two different scaling approaches of weight variable should be compared: 1) power function model (the median body weight in dataset is used); and 2) allometric scaling model (the standard adult weight of 70kg is used)

$$F_{size} = \left(\frac{Weight}{Weight_{median}} \right)^{PWR}$$

$$F_{size} = \left(\frac{Weight}{Weight_{std}} \right)^{0.75}$$

Let's start with adding weight to CL and V, We assume that η 's are distributed normally with zero mean and variance-covariance matrix Ψ , where $\psi_{CL,V} \neq 0$.

The within-subjects' errors, ε 's, are assumed to be independent with each other and they have zero mean and constant variance σ^2 . the mathematical expression is listed below:

Log-unstr-power-wt(med) and Log-unstr-power-wt(std):

$$c_{ij} = \sum_{d:t_{id} < t_{ij}} \frac{D_{id}}{\underbrace{\theta_1 Wt_{CL,i}^* e^{\eta_{CL_i}}}_{CL_i} \times t_{id}} \left\{ 1 - \exp \left(- \frac{\theta_1 Wt_{CL,i}^* e^{\eta_{CL_i}}}{\underbrace{\theta_2 Wt_{V,i}^* e^{\eta_{V_i}}}_{V_i}} t_{id} \right) \right\} \exp \left\{ - \frac{\theta_1 Wt_{CL,i}^* e^{\eta_{CL_i}}}{\theta_2 Wt_{V,i}^* e^{\eta_{V_i}}} (t_{ij} - t_{id}) \right\} \exp(\varepsilon_{ij})$$

$$Wt_{CL,i}^* = \left(\frac{Wt_i}{Median(Wt_i)} \right)^{\theta_3} \text{ for the model denoted as wt(med)}$$

$$Wt_{V,i}^* = \left(\frac{Wt_i}{Median(Wt_i)} \right)^{\theta_4} \text{ for the model denoted as wt(med)}$$

$$Wt_i^* = Wt_{V,i}^* = Wt_{CL,i}^* = \left(\frac{Wt_i}{70kg} \right)^{0.75} \text{ for the model denoted as wt(std)}$$

$$\eta_i = \begin{pmatrix} \eta_{CL_i} \\ \eta_{V_i} \end{pmatrix} \sim N(0, \Psi) \quad \varepsilon_{ij} \sim N(0, \sigma^2) \quad \Psi = \begin{pmatrix} \psi_{CL}^2 & \psi_{CL,V} \\ \psi_{CL,V} & \psi_V^2 \end{pmatrix}$$

	Name	Method	Lineage	LogLik	-2(LL)	AIC	-2(LL)Delta	pvalue
1	Log_unstr_power	FOCE ELS		-468.23054	936.46108	948.46108	NC	NC
2	Log_unstr_power_wt(med)	FOCE ELS	Log_unstr_power_wt(std)	-461.68809	923.37618	939.37618	1.54038	0.462925
3	Log_unstr_power_wt(std)	FOCE ELS	Log_unstr_power	-462.45828	924.91656	936.91656	11.54452	NC
	Name	Method	Lineage	LogLik	-2(LL)	AIC	-2(LL)Delta	pvalue
1	Log_unstr_power	FOCE ELS		-468.23054	936.46108	948.46108	NC	NC
2	Log_unstr_power_wt(med)	FOCE ELS	Log_unstr_power	-461.68809	923.37618	939.37618	13.0849	0.00144095
3	Log_unstr_power_wt(std)	FOCE ELS	Log_unstr_power_wt(med)	-462.45828	924.91656	936.91656	-1.54038	1

Figure 15. Testing for Significance of Wt; Variance-Covariance of η 's: Unstructured Residual Variance Models: Log-additive; scaling of Weight: 1) wt(med) 2) wt(std)

If we use model comparator to compare Log-additive-unstructured model with the Log-additive-unstructured model with weight as a covariant (either rescaled by median or standard adult weight), we can find that the model with weight as a covariate is statistically significantly better than the base model ($p_val = 0.0014 << 0.05$), but when comparing the Log-additive-unstructured model with weight rescaled by median with the Log-additive-unstructured model with weight rescaled by its standard value, there is no statistically significance to say one is better than the other as the p_val is relatively large ($p_val >> 0.005$)

Therefore, we draw a conclusion that we indeed need add weight as a covariate, but how to scale weight can not be decided yet. Then, we add age as the second covariate.

For the Log-additive unstructured model with Weight rescaled by its median and Age rescaled by its median (**Log-unstr-power-wt(med)-Age(1plus)**):

$$c_{ij} = \sum_{d t_{id} < t_{ij}} \frac{D_{id}}{CL_i \times t_{id}} \left\{ 1 - \exp \left(-\frac{CL_i}{V_i} t_{id} \right) \right\} \exp \left\{ -\frac{CL_i}{V_i} (t_{ij} - t_{id}) \right\} \exp(\varepsilon_{ij})$$

$$CL_i = \theta_1 Wt_{CL,i}^* e^{\eta_{CL_i}} \left[1 + (Age_i - Median(Age_i))^{\theta_5} \right]$$

$$V_i = \theta_2 Wt_{V,i}^* e^{\eta_{V_i}} \left[1 + (Age_i - Median(Age_i))^{\theta_6} \right]$$

$$Wt_{CL,i}^* = \left(\frac{Wt_i}{Median(Wt_i)} \right)^{\theta_3}$$

$$Wt_{V,i}^* = \left(\frac{Wt_i}{Median(Wt_i)} \right)^{\theta_4}$$

$$\eta_i = \begin{pmatrix} \eta_{CL_i} \\ \eta_{V_i} \end{pmatrix} \sim N(0, \Psi) \quad \varepsilon_{ij} \sim N(0, \sigma^2) \quad \text{For the} \quad \Psi = \begin{pmatrix} \psi_{CL}^2 & \psi_{CL,V} \\ \psi_{CL,V} & \psi_V^2 \end{pmatrix}$$

Log-additive unstructured model with Weight rescaled by its standard value and Age rescaled by its median (**Log-unstr-power-wt(std)-Age(1plus)**):

$$c_{ij} = \sum_{d t_{id} < t_{ij}} \frac{D_{id}}{CL_i \times t_{id}} \left\{ 1 - \exp \left(-\frac{CL_i}{V_i} t_{id} \right) \right\} \exp \left\{ -\frac{CL_i}{V_i} (t_{ij} - t_{id}) \right\} \exp(\varepsilon_{ij})$$

$$CL_i = \theta_1 Wt_{CL,i}^* e^{\eta_{CL_i}} \left[1 + (Age_i - Median(Age_i))^{\theta_5} \right]$$

$$V_i = \theta_2 Wt_{V,i}^* e^{\eta_V} \left[1 + (Age_i - Median(Age_i))^{\theta_6} \right]$$

$$Wt_i^* = Wt_{V,i}^* = Wt_{CL,i}^* = \left(\frac{Wt_i}{70kg} \right)^{0.75}$$

$$\boldsymbol{\eta}_i = \begin{pmatrix} \eta_{CL_i} \\ \eta_{V_i} \end{pmatrix} \sim N(0, \boldsymbol{\Psi}) \quad \varepsilon_{ij} \sim N(0, \sigma^2) \quad \boldsymbol{\Psi} = \begin{pmatrix} \psi^2_{CL} & \psi_{CL,V} \\ \psi_{CL,V} & \psi^2_V \end{pmatrix}$$

	Compare	Name	Lineage	AIC	-2(LL)Delta	#Obs	#Subj	pvalue
1	True	Log_unstr_power_wt(med)	Log_unstr_power	939.37618	13.0849	431	20	0.00144095
2	True	Log_unstr_power_wt(std)	Log_unstr_power_wt(med)	936.91656	-1.54038	431	20	1
3	True	Log_unstr_power_wt(med)_Age(1plus)	Log_unstr_power_wt(med)	933.252	10.12418	431	20	0.00633231
4	True	Log_unstr_power_wt(std)_Age(1plus)	Log_unstr_power_wt(std)	940.62326	0.2933	431	20	0.863596

Figure 16. Testing for Significance of Age in CL&V; Variance-Covariance of η 's: Unstructured; Residual Variance Models: Log-additive; Scaling of weight: 1) by its' median, and 2) by its' standard value; Scaling of the age: by its' median

After adding age as a covariate, we found out that adding age to the **Log-additive-unstructure-wt(med)** model is statistically significant better than the one without age ($p_{val} = 0.006 << 0.05$). But **Log-additive-unstructure-wt(std)_Age(1plus)** model is not statistically significant better than the **Log-additive-unstructure-wt(std)** model ($p_{val} = 0.86 >> 0.05$). Also considering the fact without adding age as covariate, **Log-additive-unstructure-wt(med)** performed no better than **Log-additive-unstructure-wt(std)**. Also gives us the smallest AIC value (AIC=933.252; therefore, we can draw a conclusion that **Log-additive-unstructure-wt(med)_Age(1plus) > Log-additive-unstructure-wt(std)_Age(1plus) ≈ Log-additive-unstructure-wt(std) ≈ Log-additive-unstructure-wt(med)**.

As we already know from the preliminary assessment that gender does not affect the modelling much, and actually if gender is included in the covariate model, only Retcode 3 can be achieved. Which indicates that we should not include gender in our covariate model. Finally, the **final mode** is chosen to be: **Log-additive-unstructure-wt(med)_Age(1plus)**

$$c_{ij} = \sum_{d t_{id} < t_{ij}} \frac{D_{id}}{CL_i \times t_{id}} \left\{ 1 - \exp \left(-\frac{CL_i}{V_i} t_{id} \right) \right\} \exp \left\{ -\frac{CL_i}{V_i} (t_{ij} - t_{id}) \right\} \exp(\varepsilon_{ij})$$

$$CL_i = \theta_1 Wt_{CL,i}^* e^{\eta_{CL_i}} \left[1 + (Age_i - Median(Age_i))^{\theta_5} \right]$$

$$V_i = \theta_2 Wt_{V,i}^* e^{\eta_{V_i}} \left[1 + (Age_i - Median(Age_i))^{\theta_6} \right]$$

$$Wt_{CL,i}^* = \left(\frac{Wt_i}{Median(Wt_i)} \right)^{\theta_3}$$

$$Wt_{V,i}^* = \left(\frac{Wt_i}{Median(Wt_i)} \right)^{\theta_4}$$

$$\boldsymbol{\eta}_i = \begin{pmatrix} \eta_{CL_i} \\ \eta_{V_i} \end{pmatrix} \sim N(0, \boldsymbol{\Psi}) \quad \varepsilon_{ij} \sim N(0, \sigma^2) \quad \boldsymbol{\Psi} = \begin{pmatrix} \psi_{CL}^2 & \psi_{CL,V} \\ \psi_{CL,V} & \psi_V^2 \end{pmatrix}$$

Scenario	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf
1	tvV	23.0242		3.3596131	14.59166	16.420504	29.627896	
2	tvCl	7.56388		0.96399689	12.744741	5.669036	9.458724	
3	dVdWT	1.26701		0.34678524	27.370363	0.58536472	1.9486553	
4	dCldWT	1.58419		0.30610619	19.322568	0.98250395	2.1858761	
5	dVdAGE	-0.139461		0.058738403	-42.118157	-0.25491792	-0.02400408	
6	dCldAGE	-0.187711		0.039632058	-21.113338	-0.26561226	-0.10980974	
7	stdev0	0.658355		0.11655471	17.70393	0.42925365	0.88745635	

	Scenario	Label	nV	nCI
1		Omega		
2		nV	0.12499951	
3		nCI	0.11908484	0.12481166
4		Correlation		
5		nV	1	
6		nCI	0.95339911	1
7		Shrinkage	0.13058954	0.088565148

Figure 17. Fixed effects and variance - covariance matrix for the final model:
Log-additive-unstructure-wt(med)_Age(1plus)

As we can see from Figure 18, for our final model, the conditionally weighted residuals are distributed normally, and the individual predicated Eta's fitted closely to the unity line. After added Weight and Age as covariates, the plots of Eta vs. covariates shows no linear trend anymore. The DV vs. PRED plots shows no divergency and it can be seen from the plots of Etas vs. Genders that gender has no effects on Eta's.

Log_add_unstrc_power_wt(med) Age(1plus)

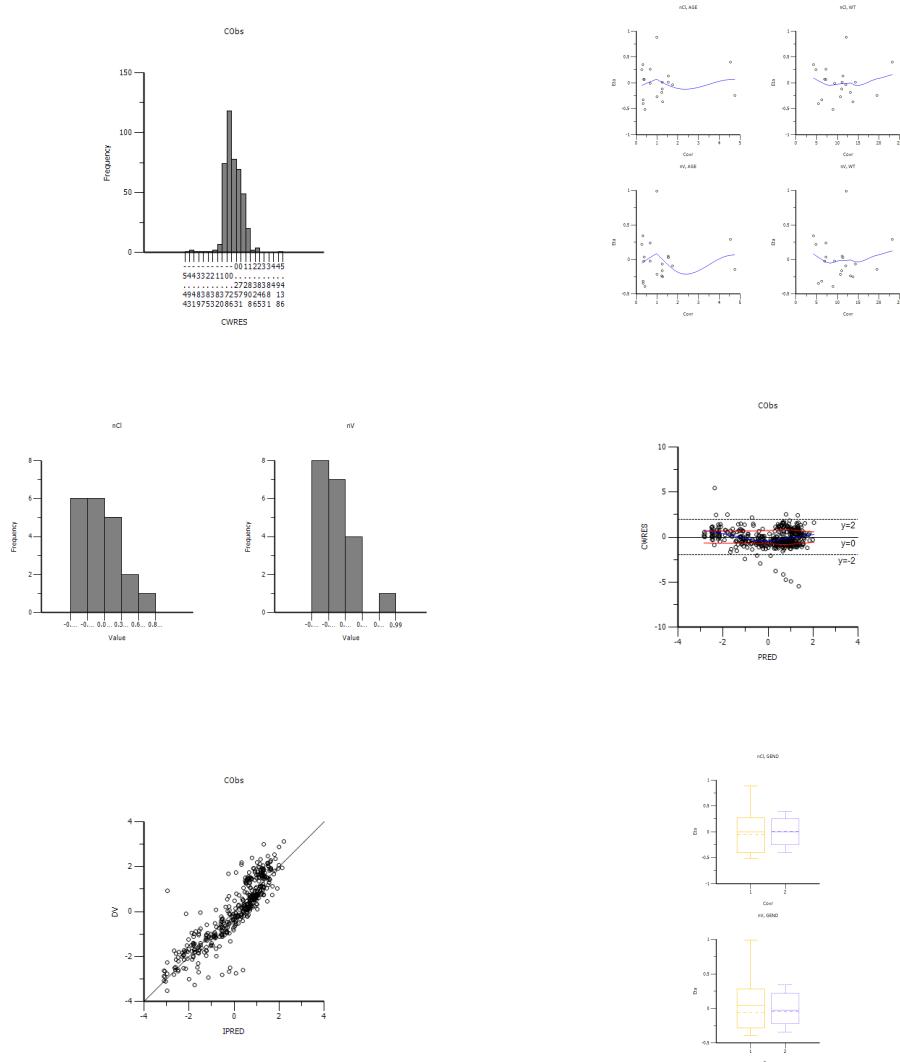


Figure 18 The predicated Eta's, Residuals plots, predicted Eta's vs. covariates plots fo r final model.

Interpretation of the meaning of the estimated covariate coefficients and variance components:

$$\begin{aligned}
 CL_i &= \theta_1 \left(\frac{Wt_i}{Median(Wt_i)} \right)^{\theta_3} e^{\eta_{CLi}} \left[1 + (Age_i - Median(Age_i))^{\theta_5} \right] \\
 V_i &= \theta_2 \left(\frac{Wt_i}{Median(Wt_i)} \right)^{\theta_4} e^{\eta_{Vi}} \left[1 + (Age_i - Median(Age_i))^{\theta_6} \right] \\
 \ln CL_i &= \ln(\theta_1) + \theta_3 \ln \left(\frac{Wt_i}{Median(Wt_i)} \right) + \ln \left[1 + (Age_i - Median(Age_i))^{\theta_5} \right] + \eta_{CLi} \\
 \ln V_i &= \ln(\theta_2) + \theta_4 \ln \left(\frac{Wt_i}{Median(Wt_i)} \right) + \ln \left[1 + (Age_i - Median(Age_i))^{\theta_6} \right] + \eta_{Vi}
 \end{aligned}$$

θ1: mean CL when Wt = Median of Weight, and Age = Median of Age is 7.56388 L/ (kg*hr)

θ2: mean V when Wt = Median of Weight, and Age = Median of Age is 23.0424 L/Kg

θ3: mean change in Log(CL) for unit change in ln(Wt /Median of Weight) is 1.58419 (with Age = Median of Age)

θ4: mean change in Log(V) for unit change in ln(Wt /Median of Weight) is 1.26701
(with Age = Median of Age)

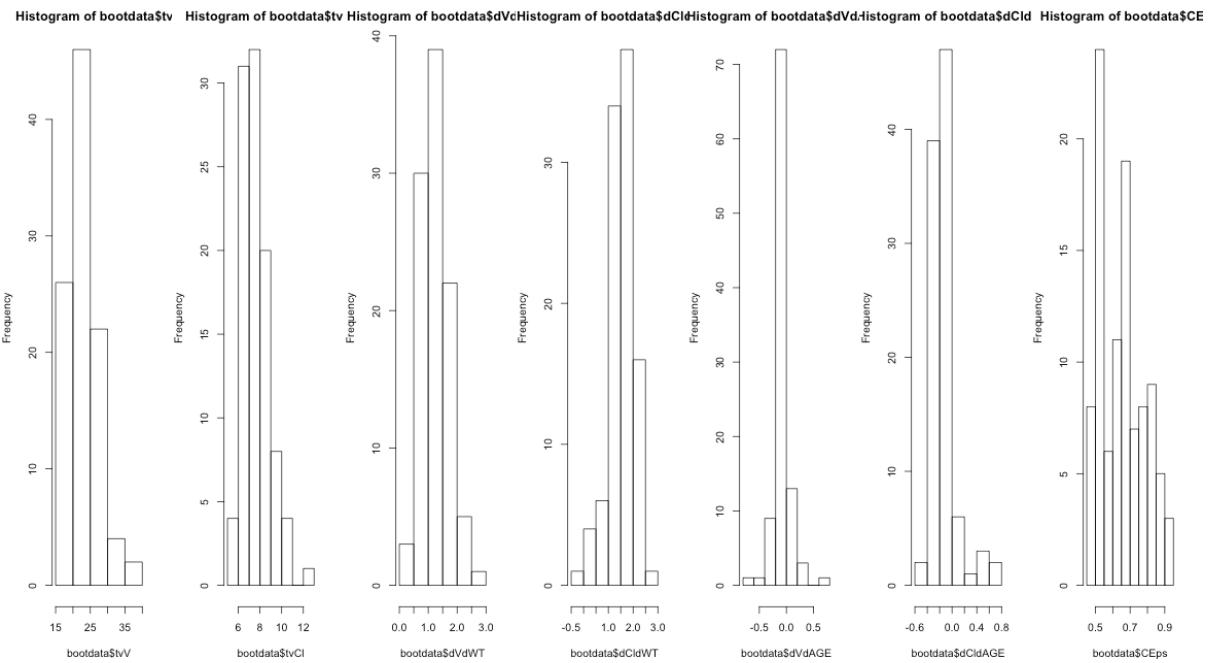
θ5: mean change in Log(CL) for 2 unit change Age is $\ln(1+2^{-0.1877})$ for the typical subject with Weight = Median of Weight

θ6: mean change in Log(V) for 2 unit change Age is $\ln(1+2^{-0.139461})$ for the typical subject with Weight = Median of Weight

$\psi_{CL} = 0.1248116$: the variability associated with CL is 12.48% for the subjects with a weight of median weight and age with median age.

$\psi_V = 0.12499$: the variability associated with Volume is 12.49% for the subjects with a weight of median weight and age with median age.

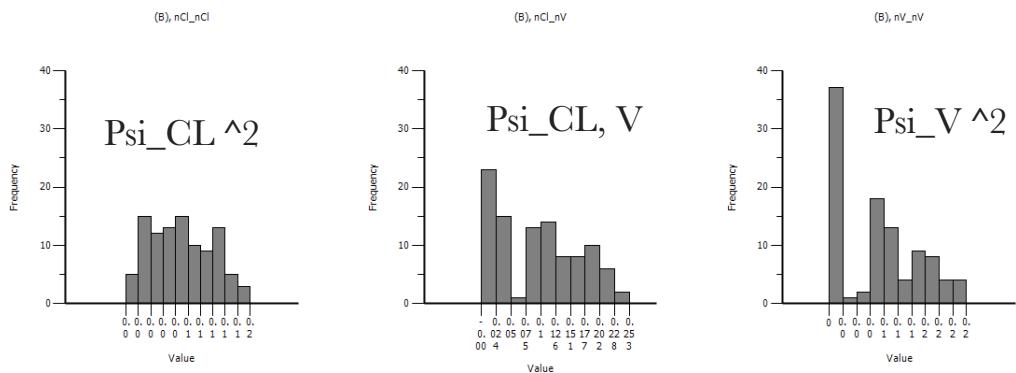
3. Bootstrap Estimation



Boot Theta Histogram for 100 replicates

	Scenario	Parameter	Mean	Stderr	CV%	Median	2.5%	97.5%
1 (B)		tvV	23.384504	4.1364774	17.688968	22.960054	18.280774	32.58673
2 (B)		tvCl	7.626632	1.2439192	16.310202	7.5362363	5.733403	10.315399
3 (B)		dVdWT	1.2461444	0.47360109	38.005313	1.2033384	0.43056691	2.2318124
4 (B)		dCldWT	1.5255377	0.49328821	32.335366	1.5272458	0.41702574	2.2900237
5 (B)		dVdAGE	-0.097630923	0.15086944	-154.53039	-0.13045021	-0.24321124	0.27440896
6 (B)		dCldAGE	-0.12841671	0.1954396	-152.1917	-0.19313201	-0.24179828	0.54519138
7 (B)		stdev0	0.65325498	0.12703196	19.445999	0.65063718	0.474815	0.90099529

Theta and sigma estimates:



Boot Omega Histogram for 100 replicates

	Scenario	Label	nV	nCl
1	(B)	Omega		
2	(B)	nV	0.10430389	
3	(B)	nCl	0.097031182	0.10059292
4	(B)	Correlation		
5	(B)	nV		1
6	(B)	nCl	0.94727782	1

Bootomegas: the BSV got from bootstrap

As we can see from the bootstrap result, all the thetas are most likely normally distributed, even though the θ_2 shows a little bit log normally distributed, and the sigma shows a little bit tendency to have two picks. The boot omega histogram indicated that the Etas for CL are normally distributed, but for Volume, the omega histogram failed to show a normally distribution. The Etas we got from bootstrap are smaller than the ones we got from Maximum Likelihood precision estimates.

The comparison in percent change of Boot strap vs. ML precision estimates are listed below:

The bootstrap does not seem to make the precision of estimates better. The reason for this may be due to the fact that we should do 1000 replicates instead of 100.

4. summary and conclusions

In conclusion, we presented a pharmacokinetic analysis to explore the clearance of ciprofloxacin in paediatric patients. In the dataset, 6 male patients and 14 female patients' concentration profiles were collected up to 41 time points. For the base model, three residual variance models 1) additive, 2) log-additive, and 3) multiplicative both with diagonal and unstructured variance-covariance matrix of the random effects were compared. The base model turn out to be best is the Log-additive_unstrcture_power model. Even though there are some potential outliers can be detected from descriptive analysis, but when considering the fact that the dataset is not a rich dataset, and the potential outliers are not seriously affect our modelling, there is no need to discard them from our dataset. For the covariates, Weight turns out to be the most important one. When we adding age as the second covariates, it turns out that rescaling weight by its median provides better result. Gender has some very limited affects on our estimation, and when gender is included as a covariate, the program does not

converge properly. Therefore, we may choose to not include Gender as a covariate variable. Eventually, the final model is selected to be :

Log-additie_unstructure_power_Wt(med)_Age(1plus). After carefully interpretation of all the coefficients we got from our final model, we examined that bootstrap failed to improve the estimation, the reason for this may because I did not run enough replicates for the bootstrap.