**PHARM 609: ADVANCED PHARMACOKINETICS**

**Winter, 2016.**

**Assignment #2: Simple and Multiple Linear Regression**

Instructor: Dasha Hajducek.

Due date: March 14, 2016.

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Instructions:

- Please submit the solutions in PDF form via email to cdmariac@uwaterloo.ca.
- Graphs must be labeled clearly.
- Careful interpretation of statistical measures and plots must be provided.

**Background (Bonate, 2011):**

Carboplatin is a platinum-containing drug used in the treatment of solid tumors. Clinical studies have shown that patients with high AUC have a greater chance of responding than patients with low AUC. For example, in 78 patients with testicular teratoma, five of eight patients who had an AUC of less than 4 mg/mL min relapsed, whereas none of the patient's whose AUC was greater than 4 mg/mL min relapsed (Horwich et al. 1991).

An equation that can be used to dose a patient to achieve a target AUC: Dose = AUC x CL.

All that is needed now is an equation to predict carboplatin clearance. The major determinant of carboplatin clearance is via the kidney at a rate equal to the glomerular filtration rate (GFR). Newell et al. (1993) studied the pharmacokinetics of carboplatin in 22 children with solid tumors. While administering the patient's carboplatin dose, most of them received a single bolus dose of 51Cr-EDTA. The clearance of 51Cr-EDTA is equal to the patient's GFR. Also demographic information was collected on each patient, including sex, weight, body surface area (BSA), and age.

**References:**


- Newell,D.R. et al. (1993) Carboplatin pharmacokinetics in children: the development of a pediatric dosing formula. The United Kingdom Children's Cancer Study Group. *Journal of Clinical Oncology,* 11(12):2314-2323.
- Horwitch, A., Gumbrell L.A., Harland S.J. (1991) Carboplatin dose in combination chemotherapy for testicular cancer. *European Journal of Cancer*, 27(6):691-5.
- Bonate, P.L. (2011) Pharmacokinetic-Phamacodynamic Modeling and Simulation, Springer, Second Edition, New York.

**Data: Carboplatin Clearance**
**Available on LEARN named "Carboplatin.csv".**

**Variables:**
Patient: subject identifier
Age: age in months
Sex: F/M
Weight: weight (kg)
BSA: body surface area ($m^2$)
GFR: kidney glomerular filtration rate equivalent to Cr-EDTA CLearance (mL/min)
CL.Carbo: Carboplatin Clearance (mL min)
AUC.Carbo: Carboplatin AUC (mg/mL min)
Dose: (mg/m2)

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Carry out a statistical analysis with the objective of characterizing Carboplatin Clearance with respect to Sex, Age, Weight, BSA and GFR as potential predictors.

Comments:
You are welcome to check Bonate's discussion about this case study; however, make sure to provide arguments based on your own critical thinking to support your decisions and interpretation. The final model and implementation of the modeling stage are not unique.

1. Perform an exploratory analysis of Carboplatin Clearance as the response variable and potential predictors Sex, Age, Weight, BSA and GFR.

   a. Describe and summarize the distribution of the variables involved in the study.
   b. Provide a preliminary assessment of the linear relationships between covariates and response.
   c. Assess whether the response variable may require a logarithmic transformation.
   d. Assess whether any categorical variables may have an effect in the response.

2.

   (a) Perform a pre-modeling collinearity assessment via a correlation table for the continuous variables.

   (b) Identify the set of variables in (a) that may contribute to collinearity (if any).

3.

(a) Perform individual simple linear fits for each covariate vs. Carboplatin Clearance.

(b) Give the interpretation of the estimated slope when using the models with sex and age variables in (a).

(c) Produce scatter plots for each variable in (a) adding the fitted line, the value of the coefficient of determination $R^2$ and report any evidence of a relationship other than linear (e.g. curvilinear, no slope). Provide an interpretation of $R^2$.
Hint: use the `mtext()` function to add text to the plots.

(d) Fit a linear model for Carboplatin Clearance vs. Age, Weight and BSA. Does the conclusion regarding the significance of these variables agree with the corresponding individual simple linear fits performed in (a)? Support your answer.
Hint: look at the correlations between Age, Weight and BSA calculated in (2).

4. Find a regression equation that best fits Carboplatin Clearance by implementing the two stepwise selection methods given in class. Establish a level of significance to use throughout the process.

Whenever deemed applicable, please present tables with relevant statistical summaries to back up your decisions.

5.

(a) If the models that resulted from stepwise selection methods in 3 are not the same, please select the most appropriate and explain why.

(b) Write the equation of the model selected in 5(a) with all of its components, including the underlying statistical assumptions.

(c) Write the matrix representation of the model and give the dimensions of the matrices and vectors.

6. For the model selected in 5(a):

(a) Perform a post-modeling collinearity assessment through the Variance Inflation Factor and the Condition Number. Comment on the results.

(b) Perform a residual analysis and state the model assumptions that are to be checked in each plot, as well as whether the assumptions are being met.

(c) Identify outliers through the analysis on the residuals in (b) and assess their influence. Are there any influential outliers? Are there any influential observations that are not outliers? If so, please give the patient's number.

Notes: Recall that studentized residuals are accessed through the "MASS" package.
Download the R package "car" to implement the `vif()` function.

7.

(a) Fit a model for the logarithm of Carboplatin Clearance with Weight and BSA as covariates.

(b) Provide the interpretation of the estimated coefficients for Weight and BSA on the response under this model.

(c) Construct a Normal Quantile plot (add the straight line as visual aid) and histogram for the transformed and untransformed variables. Compare the plots for the two and comment on the effect of transforming the data.

Do you think the transformation works for these data?

8.

(a) Fit a model for the Carboplatin Clearance with Weight centered to its mean and BSA as covariates.

(b) Interpret the value of the estimated slope.

9.

(a) Explain in your own words the Maximum Likelihood Estimation method.

(b) Estimate the coefficients $\beta_0$, $\beta_1$ and $\sigma^2$ of the linear model of Carboplatin Clearance vs. Weight and BSA using the Maximum Likelihood method through the `mle()` function (`library(stats4)`). Provide 2 sets of starting values. Please comment.