PHARM 609: ADVANCED PHARMACOKINETICS

Winter, 2016.

Assignment #1: Preliminaries

Instructor: Dasha Hajducek.

Due date: January 27, 2016.

Instructions:

Please submit the assignment in digital form (Word, pdf) via email to cdmariac@uwaterloo.ca.

Calculations must be done in R, please attach your R Code and output to your answers in each problem.

Topics: Normal, LogNormal, CI's

Download the data set 5FuCL.csv from the LEARN site.
These data consist of measurements obtained from 26 patients with advanced carcinomas under a variety of doses and treatment schedules of 5-Fluorouracil (5-FU). (Ref. Bonate, 2011).

1.

a. Make a histogram and Normal Q-Q plot of the CL variable (CL=Clearance).

b. Calculate the natural logarithm of CL and label it "logCL".
Make a histogram and Normal Q-Q plot of the logCL variable.
Hint: the R function log() calculates the natural logarithm by default.

c. Comment on the effect of transforming the data.

2. Assume CL comes from a logNormal distribution.

Table. LogNormal quantities in terms of μ, σ^2 from the Normal Distribution.

LogNormal
Mean = $\exp(\mu+\sigma^2/2)$
SD = $\exp(\mu+\sigma^2/2)* \sqrt{(\exp(\sigma^2)-1)}$
CV = $\sqrt{(\exp(\sigma^2)-1)}$ ~ (approx) σ
Median = $\exp(\mu)$

How to calculate u (expectation value), is it the same as sample's mean value ?

a. Based on the table above (note the one given in class has mistakes), calculate the corresponding mean, SD, CV and Median for the logNormally distributed variable CL.

b. Calculate the approximate CV of CL. Compare its value with the exact CV.
The approximate is to be used with caution as it may vary with the sample size. It is a good tool for looking at the data at a first glance, though.
When reporting the CV it is advised to use the exact formula CV=$\sqrt{(\exp(\sigma^2)-1)}$.

3.

a. The Sex variable in this data set is coded as 0=males, and 1=females. Change the labels from numeric to strings.

b. Write the formulae for the 90% CI for the mean logCL and calculate it for women and for men.

c. Back transform the 90% CI for the mean of logCL in (b) to its original scale, that is, for CL.

Note that the back transformed interval in (c) does not correspond to the 90% interval for the mean of CL, but to its median (recall Median = $\exp(\mu)$). You can verify that the median of CL lies in the middle of the interval for CL.

It is also advised to report the median instead of the mean when dealing with skewed distributions, as the mean is sensitive to extreme values and therefore not representative of the central tendency of the data.

Topics: Hypothesis tests, CI's

Download the data set BodyTemps.txt from the LEARN site (since this is a txt file please use the read.table() function). This data set is based on an article that examined whether the true mean body temperature is 98.6 degrees Fahrenheit.

"A Critical Appraisal of 98.6 Degrees F, the Upper Limit of the Normal Body Temperature, and Other Legacies of Carl Reinhold August Wunderlich," _Journal of the American Medical Association_, 268, 1578-1580.

Variable descriptions:
temp = body temperature (Fahrenheit)
sex = gender (1=male, 2=female)
hr = Heart rate (beats per minute)

4.

a. Change the labels of the Sex variable from numeric to string, from 1 to "male" and from 2 to "female".
b. Construct a box plot of the temperature for each gender.
c. Briefly describe the main features of the box plots and compare between genders.

5. Suppose that researchers are interested in assessing whether the temperature between genders is different. Denote the population mean temperatures by μ_{fem} and μ_{male}, for females and males, respectively.

a. State the null and alternative hypotheses in words as well as mathematically.
b. State the test statistic under H_0 and its sampling distribution, assuming that:
   (i) these data are approximately normally distributed (i.e. Student's t) and that
   (ii) both the female and male populations have the same variance.
c. Explain briefly what the concept of "sampling distribution" of the T statistic means.

6. Perform a hypothesis test to compare the mean temperatures between genders, by using the R function t.test(), the assumptions (i)&(ii) above, and your response in 5.

a. In general, how is the p-value interpreted?
b. What do you conclude from its value, in the context of the data? Use a 0.05 significance level.
c. Does the conclusion drawn from the p-value agree with the 95% CI provided in the output? Why?

7. Note the title of the paper cited above.

For each gender, perform a separate hypothesis test to assess whether the mean temperature for women and men agrees with the postulated value of 98.6 degrees Fahrenheit. That is, for each gender:

a. State the hypotheses in words and also by using μ_{fem} and $\mu_{male.}$

b. Perform the test using t.test() R function.
   Hint: t.test(variable, mu=postulated), please see the R help.

c. In order to reproduce the R output from the t.test() function in (b), calculate for males and females, the value of
   i. the observed test statistics
   ii. p-values and
   iii. 95% CI's.

d. Briefly explain what a 95% CI means in the context of the data.

e. Compare the results found for each gender. Do you think that the population mean temperature is truly 98.6 degrees Fahrenheit?