Research Re-Exam Semester 1 – 2018-2019

May 1, 2019

During the exam, you have access on a computer to these books:

- Baynes & Dominiczak: Medical Biochemistry
- Campbell: Statistics at square one
- Donders: Literature Measurement errors
- Fletcher: Clinical Epidemiology
- van Oosterom en Oostendorp: Medische Fysica
- Petrie and Sabin: Medical Statistics at a Glance
- Turnpenny: Emery's Elements of Medical Genetics
- Form with statistical formula's

You are allowed to use a calculator of the type Casio FX-82MS.

The questions must be answered in English. If you cannot remember a specific English term, you may use the Dutch term.

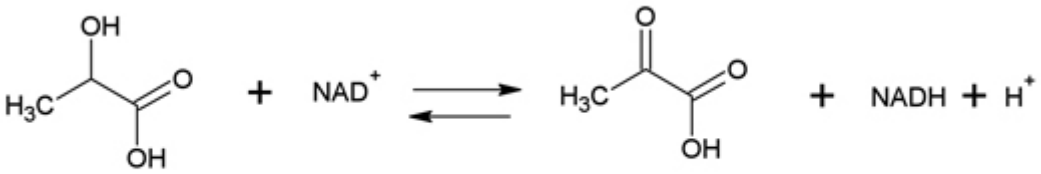
Write your name and student number on the first page of each question

Name:

Student Number:

Question 1

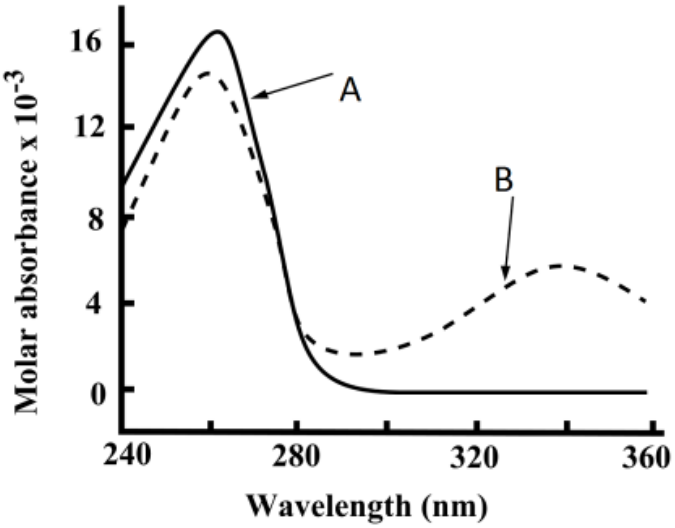
Wet lab research: Dr. G. Bosman
(10 points)



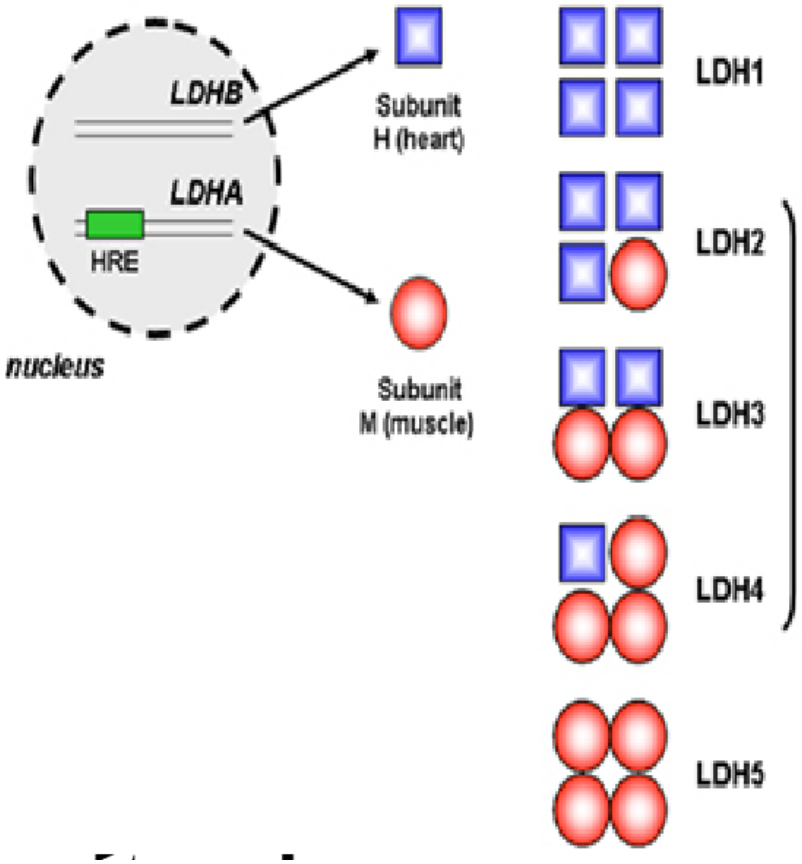
Lactic Acid Pyruvic Acid

The enzyme lactate dehydrogenase (LDH) catalyzes the conversion of lactic acid into pyruvic acid and vice versa.

a. The ΔG of this reaction is +25.1 kJ/mol. Which component will, in equilibrium conditions, be present in the highest concentration? Explain your answer. (2 pt)



b. The reaction as shown below Question 1a can be used to measure the characteristics of LDH.This graph shows the absorbance spectra of two components involved in such a measurement. Which component is indicated by the letter B? Explain your answer. (2 pts)



c. LDH is a multimeric enzyme. As depicted above, multiple isoforms of LDH occur, depending on the combination of the two subunits. LDH5 has a higher Km and a higher Vmax for pyruvate reduction than LDH1. Sketch the Michaelis-Menten graphs of these two isoforms. (6 pt)

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Question 2
Q1 Modelling – dr. T. Oostendorp
(15 points)

Chlorothiazide is a drug that is used in the treatment of hypertension. The pharmacokinetics of chlorothiazide after intravenous injection is well described by a single compartment model. For a single compartment model with linear kinetics the differential equation that describes the relation between the concentration $c(t)$ and the dose velocity $D(t)$ is

$$V\frac{d}{dt}c(t) = D(t) - k\,c(t)$$

where V is the volume of the compartment.

Figure 2.1 shows the measured plasma concentration of chlorothiazide after intravenous injection of 500 mg chlorothiazide.

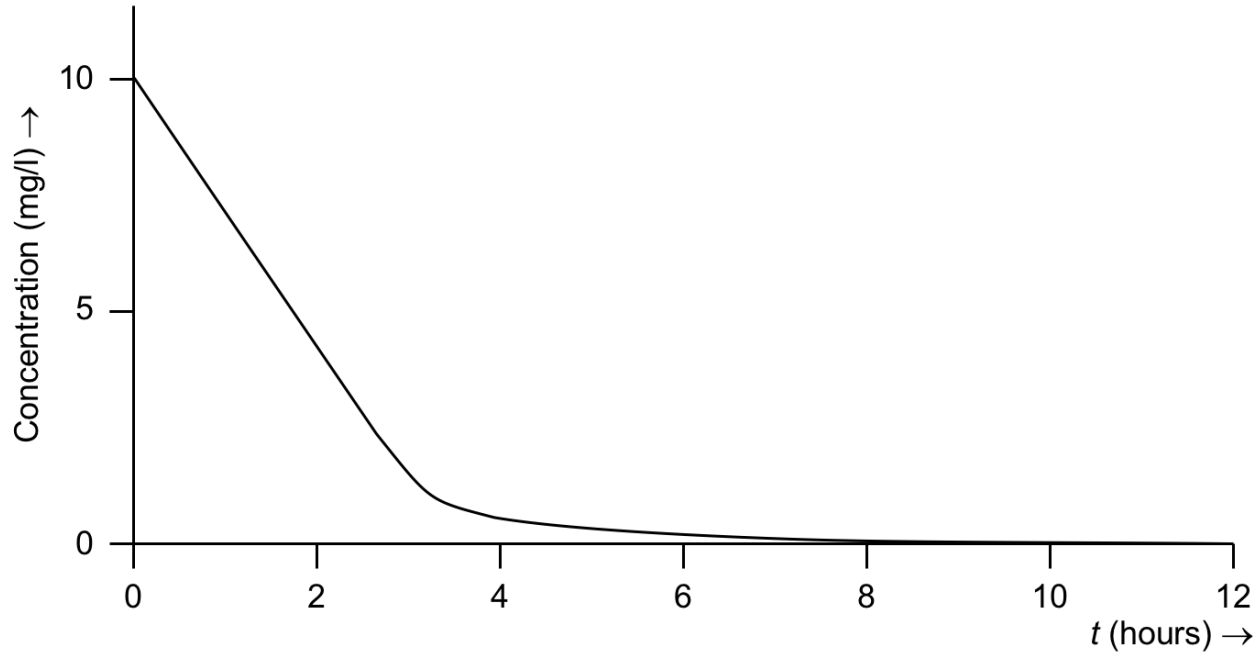

Figure 2.1 Plasma concentration after intravenous injection of 500 mg chlorothiazide.

a. Explain how you can deduct from the plot in figure 2.1 that the elimination of chlorothiazide does not follow linear kinetics. Refer in you answer to the differential equation in the introduction of this question. (4 pts)

b. Use figure 2.1 to calculate the value of V in the single compartment model for chlorothiazide. (2 pt)

The elimination of chlorothiazide is better described by Michaelis Menten (MM) kinetics. in MM-kinetics, the elimination velocity $v(t)$ is given by

$$v(t) = \frac{V_{\max}}{K_{\mathrm{m}} + c(t)}\ c(t)$$

c. Give the differential equation for a single compartment model for chlorothiazide with MM-kinetics elimination. Explain how you arrive at that equation. (4 pt)

For patients with a healthy liver, the value of $V_{\max}$ for chlorothiazide is 150 mg/hr. For patients with reduced liver functionality, the value is 100 mg/hr.

d. Explain why a dose of 1000 mg every 8 hours, will result in equilibrium in patients with a healthy liver, whereas in patients with reduced liver functionality no equilibrium is reached. (5 pt)

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Question 3
Signals: Electromyography – dr. T. Oostendorp
(10 points)

Figure 3.1 shows the electric activity of a muscle recorded at the body surface (the EMG).

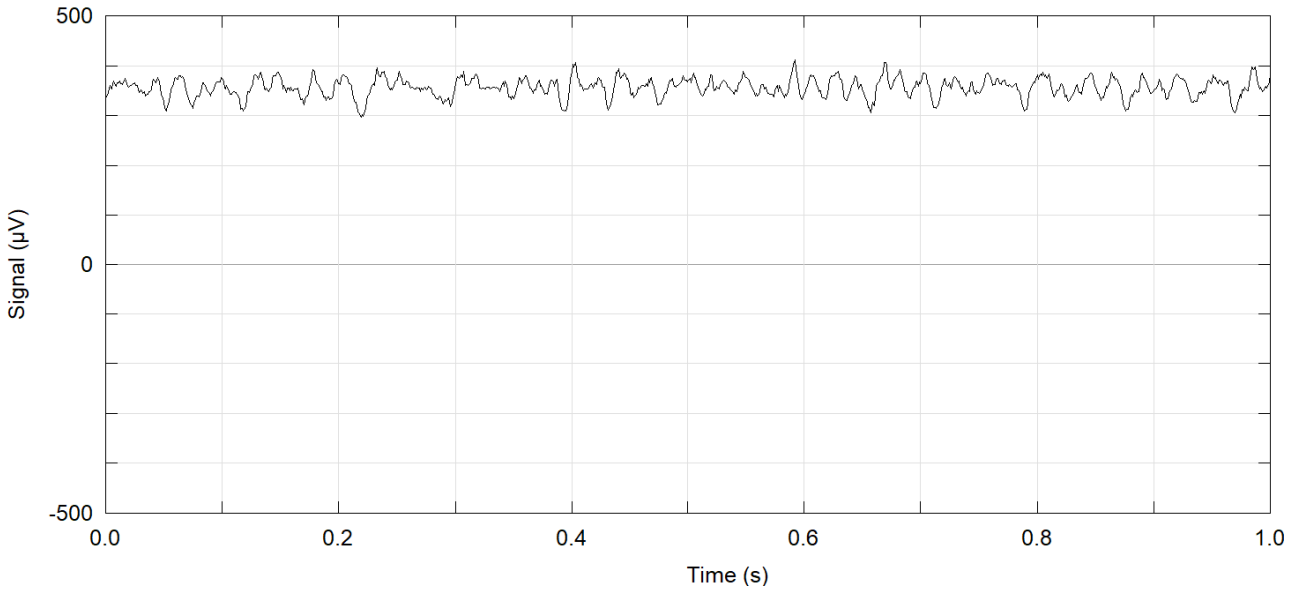

Figure 3.1 Recorded EMG signal.

a. Explain why 20 Hz is not a proper sample rate for this EMG-signal. (3 pt)

Figure 3.2 shows the spectra of three different signals.

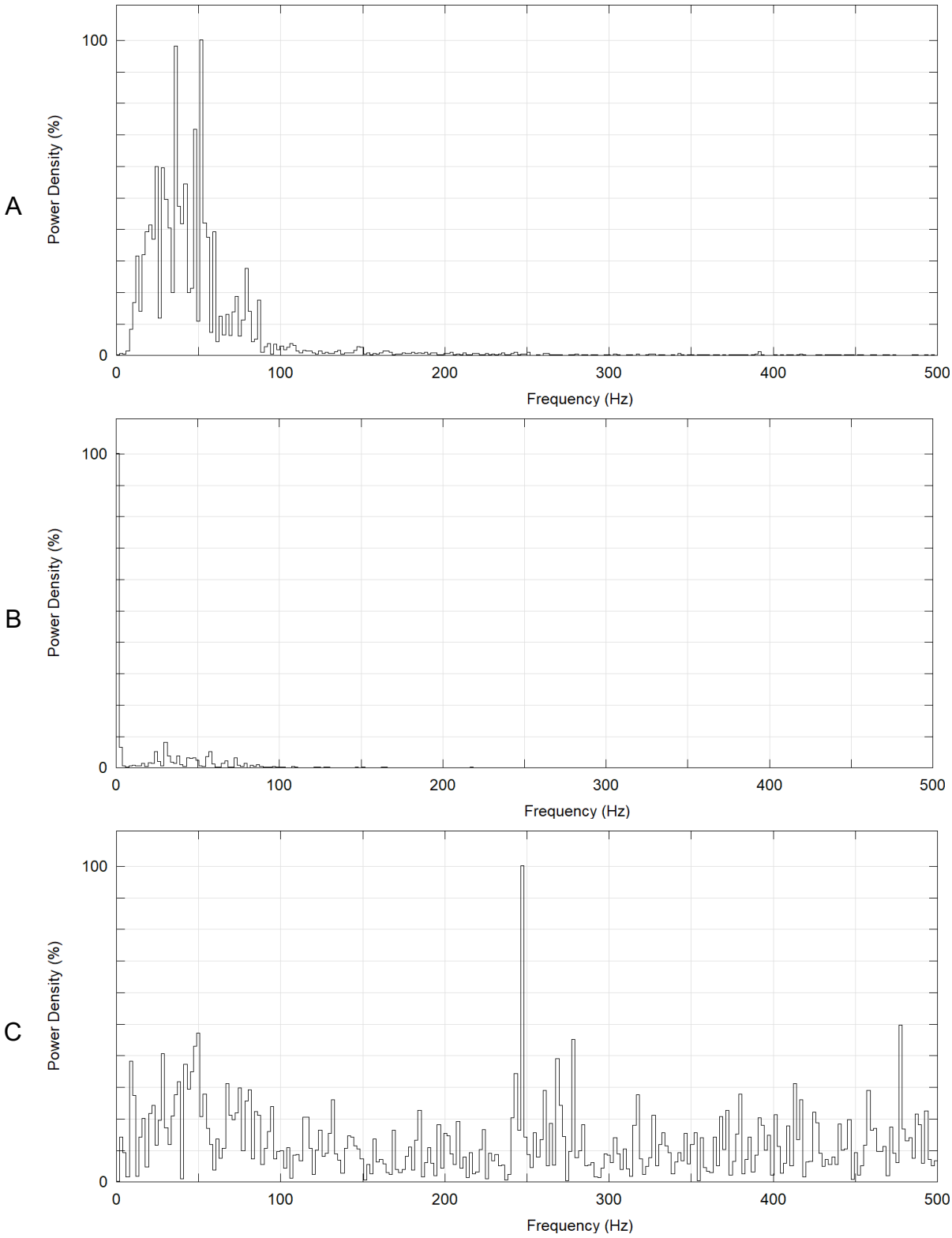

Figure 3.2 Three different spectra.

b. Which of the 3 spectra in figure 3.2 corresponds to the signal of figure 3.1? Explain why the other 2 cannot correspond to that signal. (3 pt)

The researcher who recorded the signal shown in figure 3.1 decides to apply a high-pass filter to the signal.

c. What is indicated along the x- and y-axis of the step response? (2 pt)

d. Sketch the step response of a high pass filter (2 pts)

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Question 4
Methods, measures and study designs in epidemiological studies – dr. F. de Vegt (20 points)

Use '*Reeves et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study'- abstract and table*' for question 4 and 5.

a. In the study of Reeves et al., information concerning physical activity was obtained by using a questionnaire. Give two advantages and two disadvantages for this method for the assessment of physical activity. (4 pnt)

b. Which are the determinant(s), the outcome(s) and the study population in this study? (3 pnt)

c. The study design was a prospective cohort study. Explain why a case-control design is not appropriate to study this research question. (3 pnt)

d. See Table 1, third row. Give an interpretation for the result 27.0 (25.9-28.2) (3 pnt).

e. See Table 1, the results concerning follow-up. Calculate the cumulative incidence (CI) of all cancers in the study population (2 pnt).

f. See Table 1, the results concerning follow-up. Calculate the incidence density (ID) of all cancers in the study population (2 pnt)

g. In which situations is it better to calculate an ID instead of an CI? Explain (3 pnt)

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Question 5
Statistics – dr. R. Donders
(15 points)

Use '*Reeves et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study'- abstract and table*' for question 4 and 5.

In the paper of Reeves et al the results of a very large cohort study are presented. In total 1,222,630 women participated in this study. In Table 1 of the paper data about the alcohol intake of the women are presented.

a. Is alcohol intake approximately normally distributed? Give a proper motivation based on the data in Table 1 of the paper.(3 pts)

b. Assume that the population standard deviation is equal to the sample estimate: 6.1 g/day. What is the standard error of the sample mean? (3 pts)

c. The alcohol intake needs to be derived from information provided by the participants. Often they are asked to fill in a diary in which they record which alcoholic beverages they consumed and how many. As with any measurement, this measurement will contain random measurement error. Suppose that the measurement of alcohol intake would have been done without any measurement error, the standard deviation of this variable would become smaller. Explain why this is? (3 pts)

d. The standard errors for all variables are relatively small due to the very large sample size. So even with random measurement error, a large sample suffices to make very accurate estimates. Can the problem of a systematic measurement error be overcome by a large sample size? Provide a proper motivation. (3 pts)

e. Suppose that all women in this sample have been observed for at least one year and every woman would be cancer free at the start of the study. Then these data can be used to estimate the probability of obtaining a certain cancer within the first year of observation. One could also use these data to estimate the probability of dying of this cancer within the first year. For which of these probabilities (proportions) will the standard error be the smaller? Provide a proper motivation. (3 pts)

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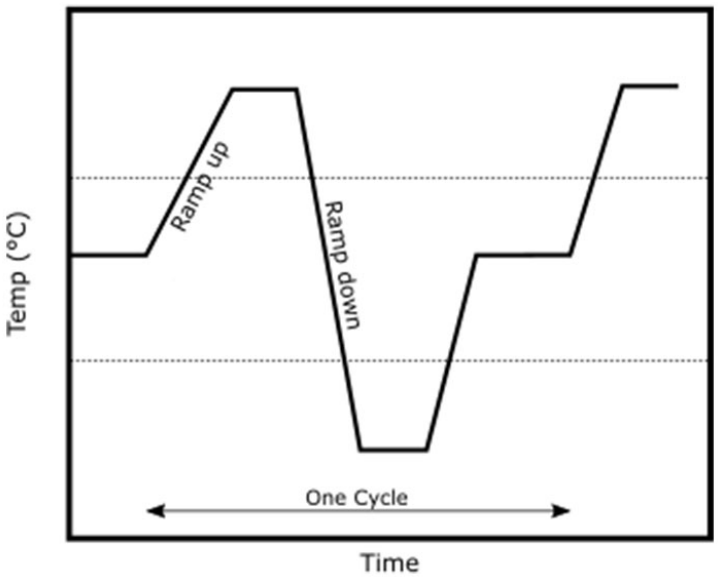
Question 6
Genetic lab practice research: dr. D. de Bruijn
(10 points)

To the right, you can see a typical thermal profile of a PCR reaction. The double headed arrow indicates the duration of one cycle. Each cycle consists of three distinct steps that are executed at different temperatures. This figure will be used for questions a-b.



a. What are the temperatures that fit best with each of these steps? Write them at (or near) each step in the figure. (2 pts)

b. Each step of the PCR reaction serves an important purpose for the amplification of DNA. Give the accurate name for each of these steps and provide a short explanation of what happens during each of these PCR steps. (3 pts)

Below, you see a snapshot from the 1000Genomes browser with genotype information of SNP rs297731. This table contains genotype frequencies and numbers of persons per genotype (between brackets) for four different American populations (i.e. CLM=Colombian in Medellin, MXL=Mexicans in L.A., PEL=Peruvians in Lima, PUR=Puerto Ricans).

1000GENOMES phase_3: CLM	A|A: 0,362 (34)	A|G: 0,521 (49)	G|G: 0,117 (11)
1000GENOMES phase_3: MXL	A|A: 0,484 (31)	A|G: 0,406 (26)	G|G: 0,109 (7)
1000GENOMES phase_3: PEL	A|A: 0,459 (39)	A|G: 0,471 (40)	G|G: 0,071 (6)
1000GENOMES phase_3: PUR	A|A: 0,313 (30)	A|G: 0,635 (61)	G|G: 0,052 (5)

c Use the data in the above table to calculate the *allele frequency* of the A and G alleles in the PUR population (box 1) and calculate the expected *genotype frequencies* (AA, AG and GG) for this population under assumption of Hardy-Weinberg Equilibrium (box 2). Write down your calculations and round your results to 3 decimals. (4 pt)

Box1 (3 decimals)	A	G
Allele frequency PUR		

Box 2 (3 decimals)	AA	AG	GG
Genotype frequency PUR			

d. Use the genotype frequencies from the previous question (c) to calculate the expected number of people, round to whole numbers (use Box 3) and compare this with the actual numbers of people for each genotype in the PUR population as given in the table of the 1000Genomes browser. What is the best evaluation of the differences between these genotype distributions? (1 pt)

Box 3 (whole numbers)	AA	AG	GG
Actual number of people			
Expected number of people			

End of the exam!

Did you write your name and student number on the first page of each question?