Research Exam Semester 3 – 2018-2019

Resit, 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
Q5: Cancer etiology and prognosis – prof. dr. B. Kiemeney
(20 points)

Dietary patterns and colorectal cancer risk in a Korean population - A case-control study

Introduction: Colorectal cancer (CRC) has been recognized as one of the major malignancies in Korea. Analyses of dietary patterns can provide insight into the complex interactions of foods, nutrients, and biologically active components within a diet, which vary among populations. We aimed to investigate the associations between dietary patterns and colorectal cancer risk in Koreans.

Methods: In a study of 923 cases and 1846 controls, dietary patterns were identified based on 33 predefined food groups using a 106-item semiquantitative food frequency questionnaire (SQFFQ). The intake levels of each pattern were categorized into tertiles (low/moderate/high) based on the distribution of the control groups. The associations between dietary patterns and CRC risk were assessed using odds ratios (ORs) and 95% confidence intervals (CIs) after controlling for confounding factors.

Results: Three dietary patterns (traditional, Westernized, and prudent (Note: prudent = 'verstandig') were derived. The traditional and prudent patterns were inversely associated with CRC risk, whereas the Westernized pattern showed a positive association.

a. Which method was used to calculate the adjusted odds ratios (2pt)?

Logistic regression

b. Take a look at table 1.1 (see next page), and calculate the odds ratio for "High Traditional dietary pattern" versus "Low Traditional dietary pattern". (3 pts).

(168 * 615) / (373 * 615) = 0.45 3 pts

(168 / 373) / (615 / 615) = 0.45 3 pts

c. Is your estimate of the p-value for the odds ratio of “High Traditional dietary pattern” versus “Low Traditional dietary pattern” p>0.05 or p<0.05? Please provide an explanation for your estimate (3 pts).

P < 0.05 (1pt), because the odds ratio is similar to the Prudent diet, and there they found significance (2 pts)

Table 1.1: Odds ratios for getting colorectal cancer stratified by Dietary patterns

Dietary patterns	No. of cases	No. of controls	Crude OR (95% CI)
Pattern 1: Traditional			
Low	373	615	
Moderate	382	616	
High	168	615	
Pattern 2: Westernized			
Low			1.0
Moderate			2.24 (1.80 - 2.78)
High			2.57 (2.07 - 3.18)
Pattern 3: Prudent			
Low			1.0
Moderate			0.72 (0.60 - 0.86)
High			0.44 (0.36 - 0.54)

d. Take a look at table 1.1 and explain in words the odds ratio of 2.57 (2.07 - 3.18) for the “High Westernized dietary pattern” (4pts).

- There is a 2.57 times increased risk (0.5 pt) of getting colorectal cancer (0.5 pt) ….
- … for having a high westernized dietary pattern versus a low one (1 pt).
- This effect is statistically significant ….(1 pt)
- … because 1 is not in the 95% CI. (1 pt)

e. Name a potential confounding factor for the relationship between dietary pattern and colorectal cancer (1pt), and explain why this factor may be a confounder (3pt).

1pt for one of the following factors:

- Body mass index
- Smoking status
- Alcohol consumption
- Physical Activity
- First-degree family history of CRC
- Occupation
- Total energy intake

1 pt for mentioning the relationship between confounder and exposure
1 pt for mentioning the relationship between confounder and outcome

f. Among the cases, there were much more people with only an elementary school education and among the controls much more with a university degree. Would you consider "educational level" a confounder and adjust for it? (1 pt). Explain why or why not (2pt), and describe the potential disadvantage of your choice (2 pt).

No you should not correct for education (1 pt)

It is not a confounder because it is not an independent risk factor for RCR (2pt)

- If you would not include education; you might miss education as a variable that indicates the quality of information obtained from cases and controls and thus miss this correction in your relationship under study (2pts).

If a student answers yes,

- Yes + no valid reason = 0 pts
- Yes + If you would include education; you might overcorrect and the effect of the real risk factor (dietary pattern in this case) might (partly) disappear. (2pts)
- Yes + It could act as a proxy for many variables that you have not measured. (2pts) ← *checked with Rogier Donders. There will be no problems with collinearity (only happens when corr. Coef > 0.8 between education level and dietary pattern, which is unlikely). There will be no overcorrection.*

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Question 2
Q5, Q6: Modelling physiological systems– dr. T. Oostendorp (15 points)

Eye rotation

In linear motion Newton's law reads

$$m\frac{d^2}{dt^2}x(t) = F(t)$$

For rotation, Newton's law is

$$I\frac{d^2}{dt^2}\varphi(t) = T(t)$$

where I is the *moment of inertia* of an object (the rotation analogue of mass), $\varphi(t)$ is the orientation, and $T(t)$ is the sum of all moments of force acting on the object.

We will use Newton's law for rotation to study eye rotation.

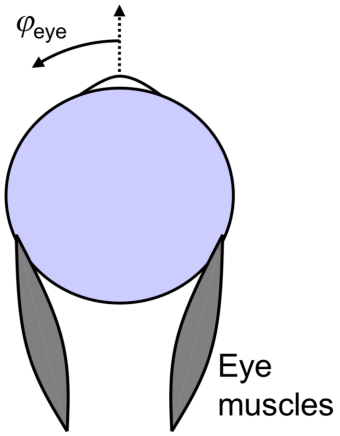


Figure 2.1 Eye ball geometry

Figure 2.1 shows the geometry of the eye ball. Three moments of force are involved:

1. $T_{\text{spring}} = -k\,\varphi$: the spring moment of force that forces to eye to the central direction,
2. T_{friction}: the friction moment of force, which is proportional to the velocity,
3. T_{muscle}: the moment of force exerted by the eye muscles.

a. Explain that the differential equation for the eye direction is: (3 pt)

$$I\frac{d^2}{dt^2}\varphi(t) = -k\,\varphi(t) - \beta\frac{d}{dt}\varphi(t) + T_{\text{muscle}}(t)$$

$I\frac{d^2}{dt^2}\varphi(t) = T_{\text{spring}} + T_{\text{friction}} + T_{\text{muscle}}$

T_{spring} is given above

T_{friction} is proportional to the velocity = $\frac{d}{dt}\varphi(t)$

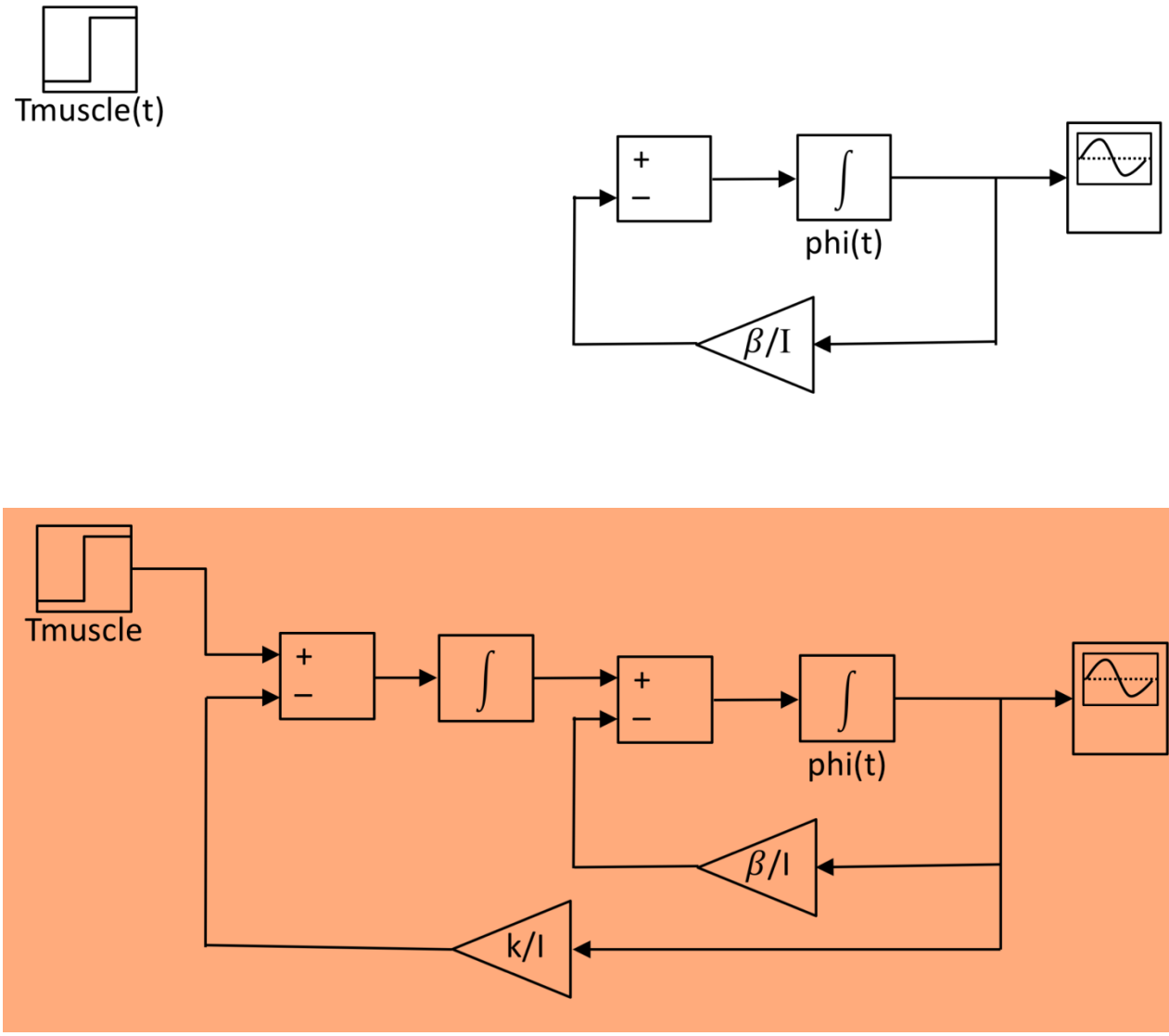
b. Determine the moment T_1 of the muscle force that is needed to keep the eye stationary at an angle φ_1. (3 pts)

In a stationary situation, al derivatives are zero. This yields:

$0 = -k\ \varphi_1 - 0 + T_1$

$T_1 = k\ \varphi_1$

c. The figure below is the uncomplete Simulink diagram for this model, where the eye moves from one direction to another one. Complete the diagram. (6 pts)



Because the moment of inertia of the eye is relatively small, it can be discarded (set to zero) in the model.

d. What is the order of the differential equation if the mass is the eye is discarded? Explain your answer. (3 pts)

If I is set to zero, the differential equation reduces to

$$0 = -k\,\varphi(t) - \beta\frac{d}{dt}\varphi(t) + T_{\text{muscle}}(t)$$

The highest order derivative in this equation is 1, so it is a first order equation.

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Question 3
Q5: Molecular Cancer Research – dr. P. Groenen
(15 points)

I. Western blot: procedures and interpretation.

Small cell lung cancer (SCLC), the most aggressive type of lung cancer, accounts for approximately 15% of lung cancer cases and is responsible for 25% of lung cancer-related deaths. Here, investigators studied AZD3965, a MCT1 specific inhibitor. They also investigated the effects of hypoxia. Two cell lines were studied (DMS114 and DMS79), tubulin was used as reference protein.

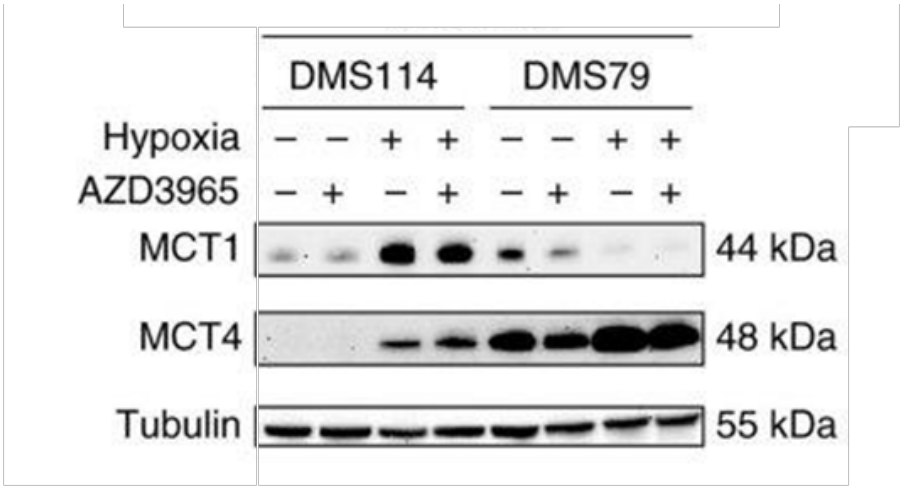

Figure 3.1. Protein expression analysis of MCT1, MCT4 and tubulin in the DMS114 and DMS79 cell lines treated with the MCT1 inhibitor AZD3965 in either a normoxic or a hypoxic environment.

a. Explain the effects of hypoxia on the AZD3965 inhibitor sensitivity for the two cell lines. (4 pts)

DMS114 shows upregulation of MCT1 under hypoxia, and these cells are resistant to the inhibitor under normoxic and hypoxic conditions. DMS79 shows downregulation of MCT1 under hypoxia and some inhibition of MCT1 by AZD3965 under normoxic conditions.

b. MCT1 and MCT4 are both enzymes that mediate efflux of lactate from tumor cells that depend on glycolysis for their ATP production. Provide a mechanism explaining why the hypoxia response differs between both cell lines (compare lanes 3 and 7 in figure 3.1). (3pts)

Under hypoxic conditions MCT4 levels in DMS79 increase dramatically. In DMS114 both MCT1 and MCT4 can be observed. The combined MCT1 plus MCT4 lactate efflux level is needed for the cells to survive. It is likely that the lactate efflux levels in DMS79 by the observed MCT4 levels are sufficient for the cells to survive. As a result MCT1 levels decrease.

c. MCT1 and MCT4 are highly homologous proteins. Would you use monoclonal or polyclonal antibodies for separate detection of these proteins? Please explain your answer and also argue why the other possible answer is not correct.
(4 pts)

monoclonal antibodies; the two antibodies raised in different animals (2 points). With polyclonal antibodies cross-reactivity would occur and distinction between MCT1 and MCT4 would become impossible; differences in MCT1 and MCT4 level cannot be measured adequately (2 points).

II. Tumor heterogeneity

Targeted therapies have been developed to counteract processes of tumor proliferation by inhibition of intracellular signaling through phosphorylated kinases (see Figure 3.2). In order to determine the diagnosis and treatment options for a patient with colon cancer, tumor cells are obtained by collecting a tumor biopsy. By genetic analysis, two mutations are identified in this biopsy: an activating mutation in the *GNAQ/11* oncogene and an activating mutation in the *BRAF* oncogene.

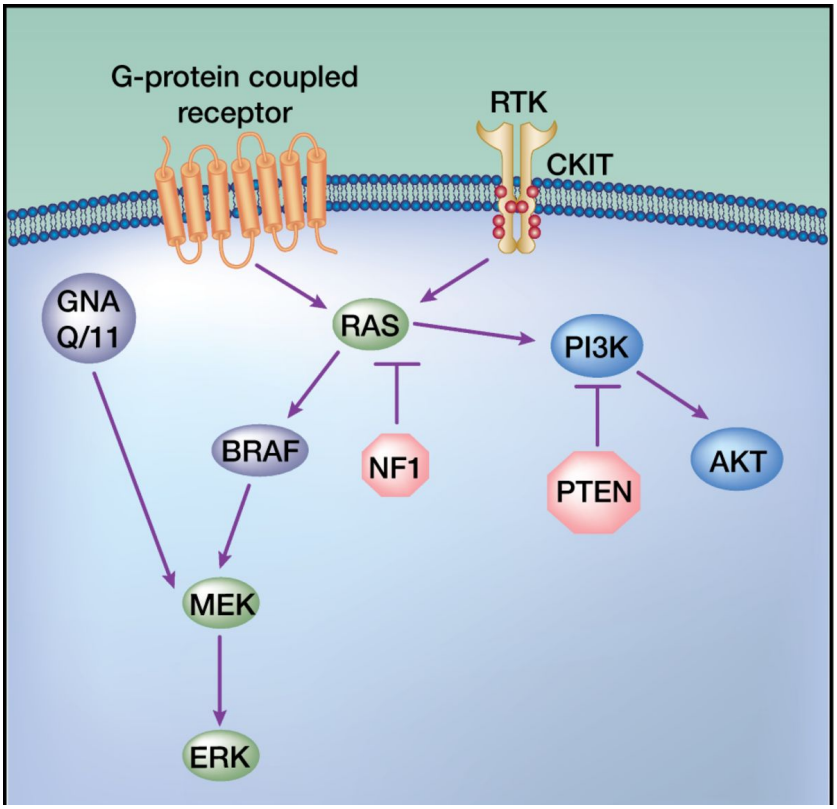

Figure 3.2 Schematic overview of oncogenic intracellular pathways.

d. Based on the presence of these mutations and on the pathway scheme (Figure 3.2), choose the most optimal targeted therapy for treatment of this patient from the options listed below. Explain why this is the best treatment option. (4pts)

- a CKIT receptor tyrosine kinase (RTK) inhibitor
- a MEK kinase inhibitor
- a PI3K kinase inhibitor
- a BRAF kinase inhibitor

The MEK inhibitor is the best option, since the MEK pathway isactivated because of an activating mutation in both *BRAF* and GNAQ/11 (2 points). Both these signaling molecules converge at MEK (1 point)). There are no activating mutations found in the tyrosine kinase receptor-RAS-PI3K-AKT pathway. (1 point)

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Question 4
Q6: Statistics – dr. J. in ’t Hout
(15 points)

Based on the following article: Leucht, S., et al. "Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors." *American journal of psychiatry* 174.10 (2017): 927-942.

Background Antipsychotic drug efficacy may have decreased over recent decades. The authors present a meta-analysis of all placebo-controlled trials in patients with acute exacerbations of schizophrenia, and they investigate which trial characteristics have changed over the years and which are moderators of drug-placebo efficacy differences.

The primary outcome was overall efficacy. Potential moderators of efficacy were analyzed by meta-regression.

a. The researchers used a random-effects model.
   - Explain the major assumption in a random-effects model with regard to the treatment effects. (1.5p)
   - Explain the difference under the assumption of a fixed-effect model (1.5p)
   - Indicate a valid reason why the authors have chosen for a random-effects model (2p). (5p total)

The RE model assumes that the underlying true effects in the studies have been sampled from a distribution of true effects (not one common true effect). (1.5p)

In a fixed-effect model it is assumed that there is one common true effect underlying to all studies. (1.5p)

The authors may have chosen for a RE model because the studies show quite some diversity over the inclusion period of 60 years. (2p)

b. Depending of the study, efficacy of the treatment per patient was scored with the Positive and Negative Syndrome Scale (PANSS, with an SD of 18) or the Brief Psychiatric Rating Scale (BPRS, with an SD of 15). The standardized mean difference (SMD) for overall efficacy of all studies combined was 0.47.
   - Explain how the this SMD must be interpreted for the PANSS (3p), including the difference on the PANSS scale and
   - explain why the authors used the SMD (2p). (5p total)

For the PANSS an SMD of 0.47 corresponds to a difference of 8.46 (0.47 x 18) points (2p) between the antipsychotics and the placebo treatment (1p)

The authors used it in order to be able to combine different scales: the PANSS with the BPRS (2p).

c. The SMD was 0.47 but after accounting for small-trial effects and publication bias the SMD was 0.38. Explain what these effects are (1 point each), and why (1p) it could be expected that the SMD decreased after these two adjustments. (3p total)

Small-trial effects refers to the phenomenon that the effects in small-trials are often more extreme than in larger trials. In this case, small-trials may have larger SMDs than bigger trials. (1p)

Publication bias refers to the phenomenon of selective publication of positive results, so that the published results are more extreme (positive) than the unpublished results (1p)

Correcting for these two phenomena will decrease the SMD (1p).

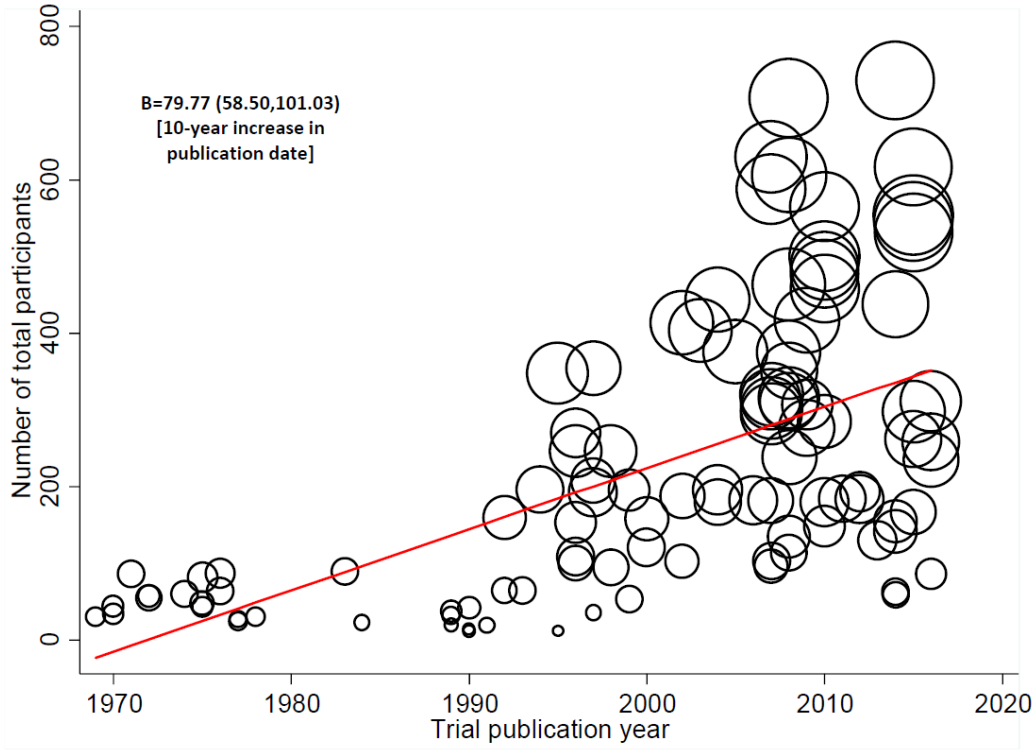


Figure 4.1. Association between publication year and sample size. Studies are indicated by small and large circles.

d. The authors conducted a meta-regression analysis on the association between publication year and sample size, see Figure 4.1. Explain in words how to interpret the result, including estimate and confidence interval. (2p)

A study that is performed ten years later than another study would include *on average* (1p) 79.77 additional participants (CI 58.5-101.0) (1p)

Name:

Student Number:

Question 5
Q6: Measuring and modelling reflexes – dr. E. Tanck & dr. T. Oostendorp
(20 points)

Karate
A young man is practicing his karate kick (as can be seen in Figure 5.1). He's holding his position a couple of seconds. This exercise results in forces in the hip joint.
The mass of the man is 85 kg, a leg weighs 15 kg. The center of mass of the man is located above the small toe (see dotted line; square = centre of mass). Assume g=10 m/s^2.

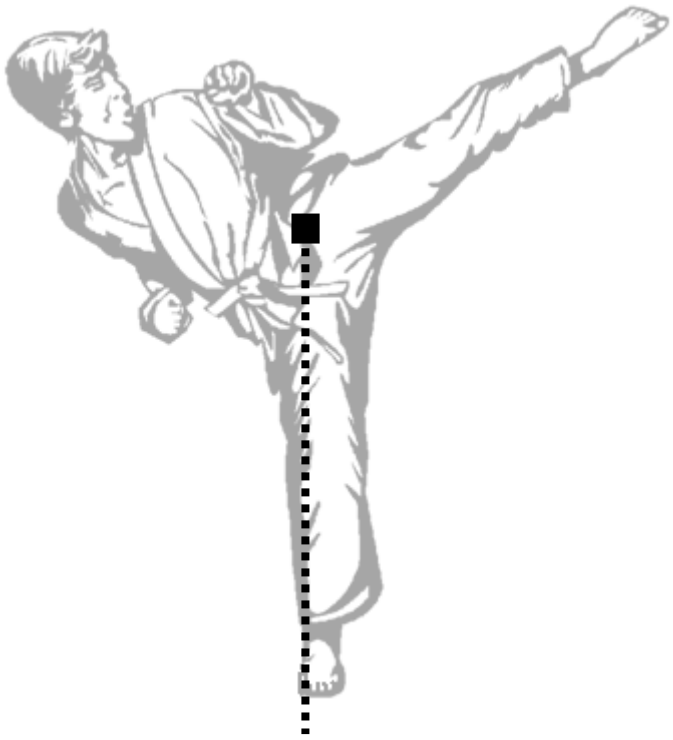
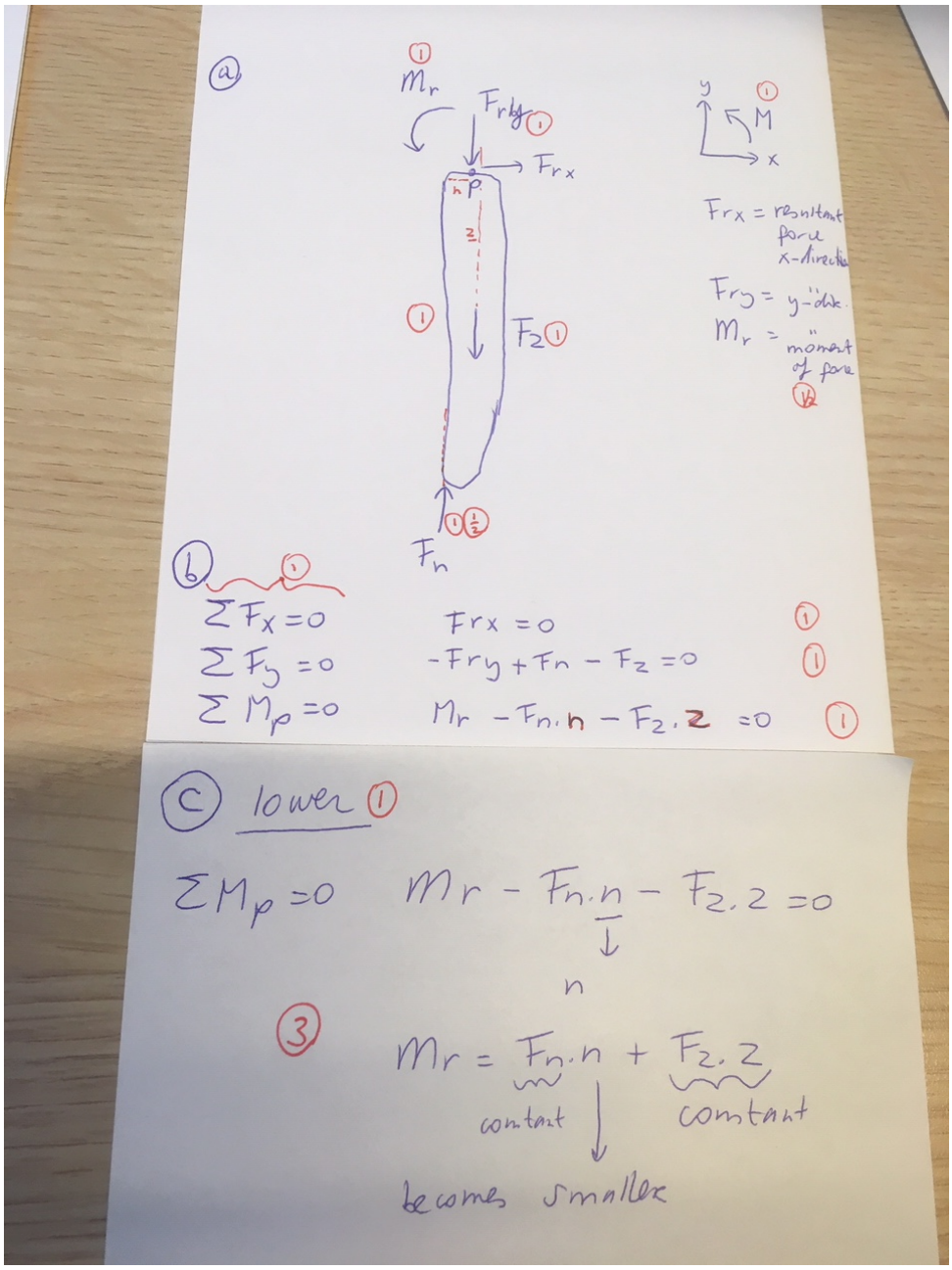


Figure 5.1 Karate kick

a. Create, on the next page, a free body diagram (FBD) to calculate the resultant forces and moment of force in the hip joint. Make your diagram large enough so everything can be labeled clearly. Create a legend to specify all components of the FBD. (7 points)

Full page needed for question a



b. Give the Equilibrium equations that belong to your FBD (4 points). You do not have to calculate the forces.

Halve a page needed for question b

c. What happens to the resultant moment of force when the man changes his position and moves his centre of mass a little to the right, just above the centre of his right foot (he holds this new position for a couple of seconds)? Choose from: higher than, lower than or equal to the original position and explain your answer using an equilibrium equation. (4 points)

Quarter page needed for question c

During this exercise, the Electromyogram (EMG) from the muscles in the thigh are recorded, in order to determine their relative contributions throughout a kick.

d. Explain why the amplitude of the EMG is not a very reliable measure for the voluntary activity of a muscle. (2 points)

The voluntary EMG has a stochastic character (is “noisy”), because the different motor units are not synchronized. Hence the amplitude of the EMG depends on chance.

e. What is a more reliable measure for the voluntary activity of a muscle? Explain your answer (3 points)

The RMS (Root Mean Square) of the EMG is more reliable, as this describes the mean activity over a longer period of time.

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