Seminar 2: The Gut-Brain Axis

Start Assignment

- Due 7 Oct by 23:59
- Points 0
- Submitting a file upload
- File types pdf, r, and rmd

General Instructions

Written solutions to all the tasks must be submitted before the **deadline: Tuesday October 7 23:59** (as pdf files in Canvas, preferably including the most important parts of your code).

You are also expected to prepare an oral presentation of your solution for each of the tasks. The presentation should aim at taking 15 minutes, to leave room for questions and discussion. At the seminar, a member of your group (randomly chosen by the teacher) will be asked to present the solution.

We expect each of you to spend around 15h on these tasks; please plan your time and meetings keeping this in mind.

Please note that the course book (and the lectures) are not your only sources of information. There are lots of information available in the research/educational literature and on the Internet about statistics as well as R and its possibilities. You are very much encouraged to try and find methods not mentioned in the book or the lectures.

Background: The Gut-Brain Axis

The bidirectional signalling between gastrointestinal (GI) tract and the brain has gained much interest in the recent decades. It is now believed that GI hormones (and interplaying microbiota) play a vital role in regulating digestion, appetite, metabolism and the immune system, neurological function, and much more (See Figure 1). The research has led to novel therapies for treating Type II Diabetes Melittus (T2DM) and obesity. Several other compounds for other indications are being investigated.

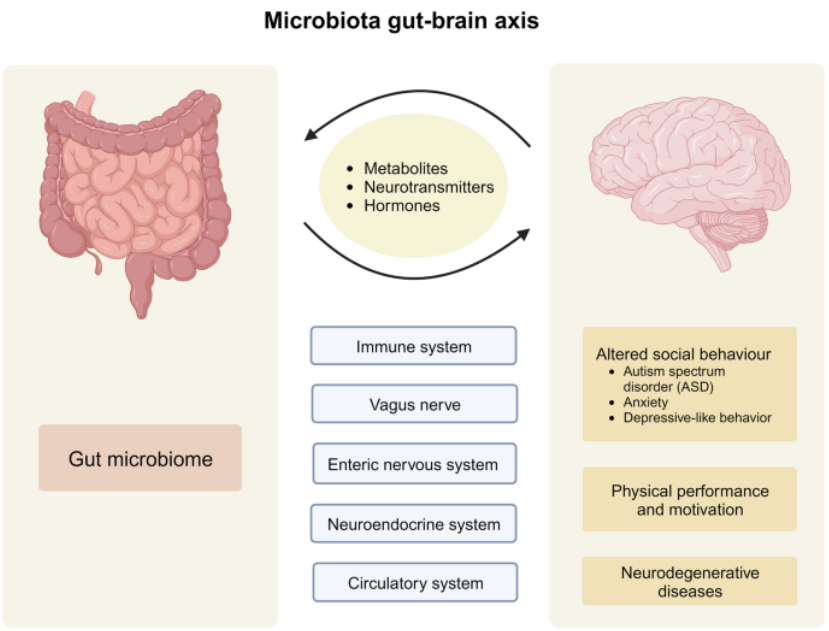

Figure 1. The Microbiota Gut-Brain Axis (source: Log *et al*. 2024; url: https://www.nature.com/articles/s41392-024-01743-1 (https://www.nature.com/articles/s41392-024-01743-1))

In this assignment you are tasked with leading the statistical analysis and data modelling at a research institution, investigating the impact of GI hormone levels and their impact on gastric motility and weight management. The research institution is ultimately aiming to find novel candidate compounds for weight maintenance as a treatment for T2DM.

Task 1: DiGeHormone - Investigating Factors Influencing Gastric Emptying in Type II Diabetes Mellitus

A large cross-sectional study, named DiGeHormone, has been carried out in a population of individuals suffering from Type II Diabetes Mellitus (T2DM). The aim of the study is to investigate the association between a set of endogenous gastrointestinal (GI) hormones, T2DM disease factors and gastric emptying (GE).

The dataset (Data_T1.csv (https://canvas.kth.se/courses/55919/files/9585454?wrap=1) (https://canvas.kth.se/courses/55919/files/9585454/download?download_frd=1)) includes basic demographic information, T2DM related factors, and GI biomarkers in 450 individuals with a T2DM diagnosis. A full description of the variables follow in Table 1 below.

- Explore the dataset through summary statistics and visualisations.
- Model the data to assess the impact of biomarkers on GE half-life (t1/2).
- Examine the output of the model(s), diagnose and assess model performance.

Variable	Unit

GE: gastric emptying half-life ($t_{1/2}$)	minutes
Sex	0: female, 1: male
Age	years
BW: body weight	kg
BMI: body mass index	kg/m^2
Glucose, fasting	mmol/L
Insulin, fasting	mU/L
HbA1c: haemoglobin A1c	%
Matsuda Index	n/a
HOMA-B: homeostasis model assessment of Beta-cell function	n/a
Diabetes complications	0: none reported, 1: yes, reported.
Metformin	0: no metformin, 1: metformin prescription.
Gastrin	pg/mL
CCK: cholecystokinin	pmol/L
Total Ghrelin	pg/mL
Amylin, fasting	pmol/L
Glucagon	pmol/L
GLP-1: glucagon-like peptide 1	pmol/L
PYY: peptide YY	ng/L

% end %

Task 2: The Time Dynamics of Fasted vs. Fed Gastric Emptying in Rat

Biomedical engineers have carried out a study of gastric retention over time in rats with the aim of better understand the findings in DiGeHormone study and and coming research studies that are being planned. The time dynamics of gastric emptying were studied using scintigraphy.

Scintigraphy is a nuclear medicine imaging technique considered the gold-standard method for measuring gastric emptying.

Two experiments were carried out:
(i) fasted state: scintigraphy of the stomach following administration of radio-labelled water;
(ii) fed state: scintigraphy of the stomach following administration of a radio-labelled high-calorie, high-fat meal.

The data-file (**Data_T2.csv (https://canvas.kth.se/courses/55919/files/9585494?wrap=1)** ↓ **(https://canvas.kth.se/courses/55919/files/9585494/download?download_frd=1)**) contains three variables, time [minutes], and volume of gastric content over time for the fasted state (GE_fasted) and fed state (GE_fed).

- Model fasted gastric emptying (GE_fasted) to determine the rate and half-life of gastric emptying.
- Model the fed state gastric emptying profile.
- In larger studies we normally depend on secondary parameters (such as half-life) rather than the time-dynamic profiles.
  For the fed state gastric emptying profile, how informative is half-life for describing the time-dynamics?
  Can you propose alternative secondary parameters?

Task 3: Dose-Response Curve in Rats

The organic chemists at the institute have developed a series of analogous GLP-1 agonists. Following initial screening, the compound DiGeMon-123 appears to be the most promising candidate in terms of delaying gastric emptying. The hypothesis is that gastric retention will lead to higher satiety and therefore promote weight loss or maintenance of body weight.

Preclinical pharmacologists have carried out a study in Zucker rats (an animal model of obesity), examining the effect of DiGeMon-123 on gastric retention at 30 minutes, following a low, medium and high dose (5, 10 and 20 mg). The data is available here: **Data_T3.csv (https://canvas.kth.se/courses/55919/files/9585573?wrap=1)** ↓ **(https://canvas.kth.se/courses/55919/files/9585573/download?download_frd=1)** (each row represents GE-data from one rat).

- Given the dose-response data, predict the required dose to produce a retention of 50% of gastric content at 30 minutes.
- Predict the dose that produces 80% gastric retention at 30 minutes.

Only continue from here **After** you have carried out and documented your model predictions:
Remember - the aim of the course is not to provide perfect fits, rather it's the learning journey :-)

- Novel study data is available for the following dose levels: 50, 100 and 150 mg. Compare your predictions to the data.
  If needed, suggest ways of refining your model and update it. Data is available here: **Data_T3B.csv (https://canvas.kth.se/courses/55919/files/9585625?wrap=1) (https://canvas.kth.se/courses/55919/files/9585625/download?download_frd=1)**
- If we were to only consider the pharmacological effect (gastric retention at 30 minutes) while wanting to limit exposure (the lowest possible dose), what dose level would you suggest for a follow-up experiment?

Task 3: The Follow-up Study of DiGeMon-123 in Rats

The biomedical researchers have carried out a follow-up parallel study in obese Zucker rats. The rats have repeatedly been administered DiGeMon-123 according to your recommendations. Then, the researchers have documented their Lee index (a measure of obesity in rats).

The data-file: **Data_T4.csv (https://canvas.kth.se/courses/55919/files/9585687?wrap=1) (https://canvas.kth.se/courses/55919/files/9585687/download?download_frd=1)** , contains information on treatment (TRT - 0: control, 1: treated with DiGeMon-123), Time (treatment time in weeks), and LeeIdx (Lee Index).

- Model the data to investigate if the GLP-1 agonist has any effect on Lee index.
- Present and discuss your findings.