Problem Set 1
Statistics, Computation and Applications

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Problem 1.1: The Salk Vaccine Field Trial

The first polio epidemic hit the United States in 1916. By the 1950s several vaccines against the disease had been discovered. The one developed by Jonas Salk seemed the most promising in laboratory trials. By 1954, the National Foundation for Infantile Paralysis (NFIP) was ready to try the vaccine in the real world. They ran a controlled experiment to analyze the effectiveness of the vaccine. The data is shown in the table below (grade refers to the educational stage):

Table 1: Table 1: NFIP study results.

	Size	Polio rate per 100,000
Grade 2 (vaccine)	225,000	25
Grades 1 and 3 (no vaccine)	725,000	54
Grade 2 (no consent)	125,000	44

The experiment was later repeated as a randomized controlled double-blind experiment. This data is shown in the second table below:

Table 2: Table 2: Follow-up study results.

	Size	Polio rate per 100,000
Treatment (vaccine)	200,000	28
Control (salt injection)	200,000	71
No consent	350,000	46

(a) Describe each of the two studies (e.g., their design) and comment on the differences between them. For each study, explain whether it helps measure what was intended to be estimated.

The NFIP study was not randomized: all students in grades 1 and 3 did not get the vaccine, while the 2nd graders did. In that sense, the study was not blinded, as both treatment and control groups knew their assignment prior to treatment. Using this design, it is impossible to detect to a greater level of confidence the effects of the vaccine. At least two sources of bias can be identified for this design:

1. Students in 2nd grade are no necessarily comparable to younger or older students, even from the same school. Differences can be related to exposure to the virus but also to other confounders like gender distribution, parents age and education, among other. This could imply these students have

different chances of getting polio, regardless the vaccine, which will bias the results. In fact, comparing groups from grades 1 and 3, with those from the no consent group, can lead us to conclude these groups are not similar.

2. Being polio an infectious disease, peer effects can be substantial in confounding the effects of the vaccine. This implies that students from second grade that did not consent to the vaccine got protected by their schoolmates by a weaker version of herd immunity. This could also affect the rates of polio of 1st and 3rd graders if these students are continuously sharing spaces at school. This could also be important if students from the control and treatment groups both belong to the same school.

On the contrary, the follow-up experiment was double-blinded and randomized. In this case, each student was randomly assigned to a treatment group (and got the vaccine) or a control group (and got a placebo). Observational data was obtained from those students that did not consent to participate (the No consent group). A design like this one is better suited to estimate the effects of the vaccine, as potential confounders are now (in average) equal between both groups. However, the second source of bias is not completely eliminated if treatment is not randomized at school level. That is, if within the same school there are children that belong to both treatment and control groups, then the vaccine effect is biased downwards (i.e. a lower bound of its efficacy is estimated) due to peer effects. In that case, vaccinated children indirectly protect those that only receive a salt injection.

(b) Which numbers show the effectiveness of the vaccine? Explain why.

The numbers capable of showing the effectiveness of the vaccine are those in Table 2. However, which of these actually allow to test the hypothesis depends on how the experiment was designed. If the randomization occurred after asking for consent to participate, then we would like to compare the rates of polio between treatment and control groups. The caveat is that the sample that consented participating in the study may have selected on particular characteristics, that could bias the results in two possible ways:

1. If those that consented are people that could potentially benefit more from the vaccine (e.g. a family with previous close cases of polio) then the effect would be larger (biased upwards) than in absence of selection.

2. If those that consented benefit less from the vaccine (e.g. more educated people, that have generally better hygiene and less risk of infection), then the effect would be smaller (biased downwards) than if absence of selection.

On the other hand, if randomization occurred before asking for consent, then we would need to compare the original groups, that is, we would need to separate the No consent group into those assigned to the treatment and those assigned to the control group. However, if the randomization was correctly realized in the first place, then the people from each group that did not consent should be (in average) similar. In particular, the amount of people from the No consent group that belong to the treatment group should be similar to the amount of people that belong to the control group. Moreover, the two possible biases presented above should be distributed equally in the No consent group, making the comparison between the first two rows of Table 2 closer to the effectiveness of the vaccine.

Note, however, that since polio is infectious, then if randomization did not occur at school level, then the results will be biased downwards. This, following the previous argument that students in the control group are indirectly protected by their vaccinated counterparts.

(c) In the two studies neither the control groups nor the no-consent groups got the vaccine. Yet the no-consent groups had a lower rate of polio. What could be some of the underlying reasons?

As discussed in the previous question, there are at least two reasons that could explain this lower polio rate.

It could be the case that the group of people that did not consent to participate where those who felt less at risk from contracting polio, because they did not have close events of contagion. This can happen if these people live in better conditions, with more access to clean water and food and in cleaner, more hygienic neighborhoods. These conditions would make them less prone to being infected by the virus.

Another option I also discussed before is that a less intensive form of herd immunity is working behind these results. This is particularly true for the first study, where children that did not consent to get a vaccine where indirectly protected by their schoolmates that did get a shot. This effect in fact could happen, at a lower scale, for the 1st and 3rd graders in the NFIP study. For the follow-up experiment, this effect may still be tampering the results, although at a much smaller scale. This, given that randomization should distribute the No consent individuals evenly among the treatment and control groups.

(d) Polio is an infectious disease. The NFIP study was not done blind. Could this bias the results? If yes, to what extent?

As discussed earlier, the infectiousness of the disease can alter the results in general. However, regarding the blindness of the study, there could be behavioral changes in the subjects in at least two ways:

1. Vaccinated children (or their families or teachers) could lower the safety measures against the virus, expecting the vaccine to work. This can imply a higher probability of contracting the virus.

2. On the other hand, unvaccinated children (or their families or teachers) participating in the study could be more aware of the risks of polio just by being part of the experiment. This could decrease their chances of getting polio.

Overall, this two effects bias the results because treatment and control groups are no longer comparable. In fact, if the two hypotheses above are true, then the estimated effectiveness of the vaccine is a lower bound on the real effect.

Nevertheless, it is arguable to which extent these effects are present in the study, particularly the first. Since only the children are getting vaccinated, the rest of the members of the family must continue their safety measures for their own protection. For example, if the vaccinated children has a sibling in 1st or 3rd grade, or if there is an elderly relative in the house. In class, there are 2nd graders that did not get the vaccine because they did not consent to participate in the study. For this reason, it is unlikely that teachers would lower the protective measures towards these children just because their schoolmates are vaccinated.

(e) In the randomized controlled trial the children whose parents refused to participate in the trial got polio at the rate of 46 per 100,000. On the other hand, the children whose parents consented to participate got polio at a slighter higher rate of 49 per 100,000 (treatment group and control group taken together). On the basis of these numbers, in the following year some parents refused to allow their children to participate in the experiment and be exposed to this higher risk of polio. Were they right? And why so? Please explain your reasoning process.

There are two possible arguments to make here.

At first glance, it might be the case that the average rate of polio for children that participate in the study is lower than the ones that do not. That is, is possible that the rates obtained in the study correctly reflect the underlying distribution of polio rates between these two groups. In that case, the parents would be right to not allow their children to be part of the study.

However, the previous argument relays in two assumptions that will possibly not hold in a second RCT. First, those rates where obtained in a situation where parents made their decisions without previous

knowledge of results from a similar design experiment. Hence, their selection into consenting or not consenting to participate is driven by a different set of characteristics that for this second time. Second, and most importantly, the previous discussion suggested that the lower rate of contagion for students in the No consent group could be driven by an indirect protection from their schoolmates. This, in particular, depends on people consenting to participate. Otherwise, the expected rates of contagion could be as high as the ones obtained for the control group.

What is more, the herd immunity effect alone could explain the similarities between the two rates. Consider the null hypothesis $H_0 : rate_{\text{Consent}} = rate_{\text{No consent}}$ against the alternative $H_A : rate_{\text{Consent}} > rate_{\text{No consent}}$ and the statistic T reflecting the number of contagions in the Consent group. Then the probability of observing this number is

$$\mathbb{P}_{H_0}(T = 198) = \frac{\binom{400,000}{198}\binom{350000}{161}}{\binom{750,000}{359}} = 0.033$$

with a p-value of 0.77. Hence, the null hypothesis is not rejected and the rates of contagion between the two groups are considered statistically equal. This implies the parents of the children that did not consent were not correct.

Problem 1.2: NASA Compton Gamma Ray Observatory Data (source: Rice, Ch.8)

The file `gamma-ray` contains a small quantity of data collected from the Compton Gamma Ray Observatory, a satellite launched by NASA in 1991 http://cossc.gsfc.nasa.gov/. For each of 100 sequential time intervals of variable lengths (given in seconds), the number of gamma rays originating in a particular area of the sky was recorded. You would like to check the assumption that the emission rate is constant.

(a) What is a good model for such data?

The number of events (in this case, γ ray emissions) during a certain timeframe could be modeled as following a Poisson distribution. Specifically, if we call x_i to the number of events during time interval t_i, then the proposed model is $x_i \sim Poisson(\lambda_i t_i)$, where λ_i is an unknown parameter. Here, we are making three assumptions: 1) Emissions occur independently from each other; 2) emissions do not happen at the same time, and; 3) the average rate ($\lambda_i t_i$) is constant.

(b) Describe the null hypothesis H_0 and the alternative H_A.

Following the model in the previous question. The null and alternative hypotheses are:
$H_0 : \lambda_i = \lambda_1 \quad \forall\, i \in \{2, \ldots, 100\}$
$H_A : \exists i \in \{2, \ldots, 100\} : \lambda_i \neq \lambda_1$

(c) What is(are) the most plausible parameter value(s) for the null model given the observations? Calculate the maximum likelihood estimate(s) (MLE) of the parameter(s). Compute the estimator(s) for these parameter(s) from the data and report the resulting value(s).

Since λ represent the rate under which events occur, then the most plausible parameter value should be to count the total number of events occurred and dividing it over the total amount of time in which they occurred, which is equal to `0.0039`.

To formally compute this parameter, note that the probability of observing this data, under the null, is:

$$p\left(\{x_i\}_{i=1}^{100}, \{t_i\}_{i=1}^{100}; \lambda\right) = \prod_{i=1}^{100} \frac{(\lambda t_i)^{x_i} e^{-\lambda t_i}}{x_i!} = \lambda^{\sum_{i=1}^{100} x_i} \cdot e^{-\lambda \sum_{i=1}^{100} t_i} \cdot \prod_{i=1}^{100} \frac{t_i^{x_i}}{x_i!}$$

Taking *log* and differentiating with respect to λ, we obtain

$$\frac{\partial \log p\left(\{x_i\}_{i=1}^{100}, \{t_i\}_{i=1}^{100}; \lambda\right)}{\partial \lambda} = \frac{1}{\lambda} \sum_{i=1}^{100} x_i - \sum_{i=1}^{100} t_i$$

which implies that the MLE for λ is

$$\hat{\lambda} = \frac{\sum_{i=1}^{100} x_i}{\sum_{i=1}^{100} t_i} = \frac{\overline{x_i}}{\overline{t_i}}$$

(d) What is(are) the most plausible parameter value(s) for the alternative model given the observations? Calculate the MLE(s). Compute the estimator(s) for the parameter(s) from the data (you do not need to provide the value(s)). Hint: You should carefully define the space for the parameter(s) of your model.

In this case, the MLE estimator allows λ_i to vary from observation to observation. In this case, following the calculations from the previous part, then we have that the probability of observing the data under the alternative is:

$$p\left(\{x_i\}_{i=1}^{100}, \{t_i\}_{i=1}^{100}; \{\lambda_i\}_{i=1}^{100}\right) = \prod_{i=1}^{100} \frac{(\lambda_i t_i)^{x_i} e^{-\lambda_i t_i}}{x_i!}$$

After taking log and computing partial derivatives with respect to each λ_j we obtain

$$\frac{\partial \log p\left(\{t_i\}_{i=1}^{100}; \{\lambda_i\}_{i=1}^{100}\right)}{\partial \lambda_j} = \frac{x_j}{\lambda_j} - t_j = 0$$

Which implies that the MLE for λ_i is

$$\hat{\lambda}_i = \frac{x_i}{t_i}$$

(e) Define a test statistic and plot its distribution under H_0 using the software of your choice.

Given that we already computed the MLE under the null and alternative hypotheses, we could perform a likelihood ratio test for H_0. The likelihood ratio for this situation is given by:

$$L\left(\{x_i\}_{i=1}^{100}, \{t_i\}_{i=1}^{100}\right) = \frac{\max_{\lambda} p\left(\{x_i\}_{i=1}^{100}, \{t_i\}_{i=1}^{100}; \lambda\right)}{\max_{\{\lambda_i\}_{i=1}^{100}} p\left(\{x_i\}_{i=1}^{100}, \{t_i\}_{i=1}^{100}; \{\lambda_i\}_{i=1}^{100}\right)}$$

The statistic of interest is the transformed likelihood ratio:

$$\Lambda\left(\{x_i\}_{i=1}^{100}, \{t_i\}_{i=1}^{100}\right) = -2 \log L\left(\{x_i\}_{i=1}^{100}, \{t_i\}_{i=1}^{100}\right)$$

Which asymptotically distributes:

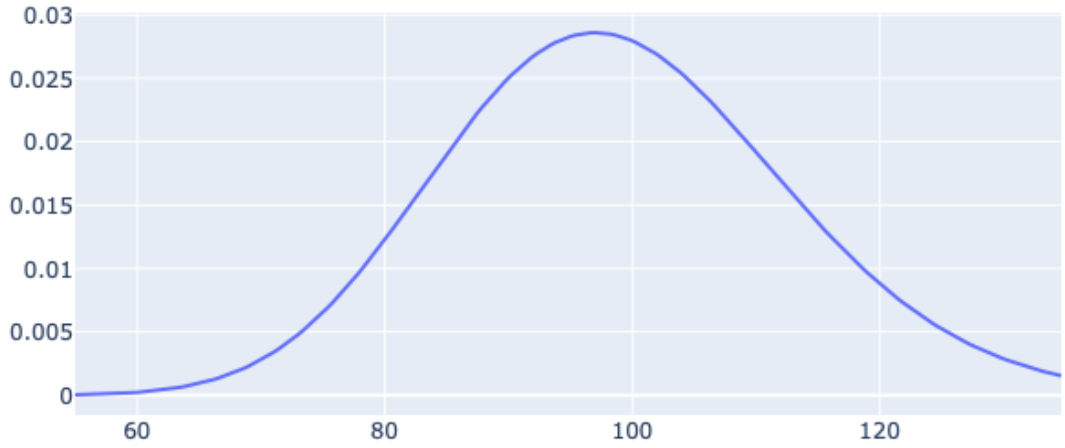
$$\Lambda\left(\{t_i\}_{i=1}^{100}\right) \sim \chi_d^2$$

with

$$d = 100 - 1 = 99$$

since the total parameter space has dimension 100 and the null parameter space has dimension 1. Thus, the distribution of the test statistic is:

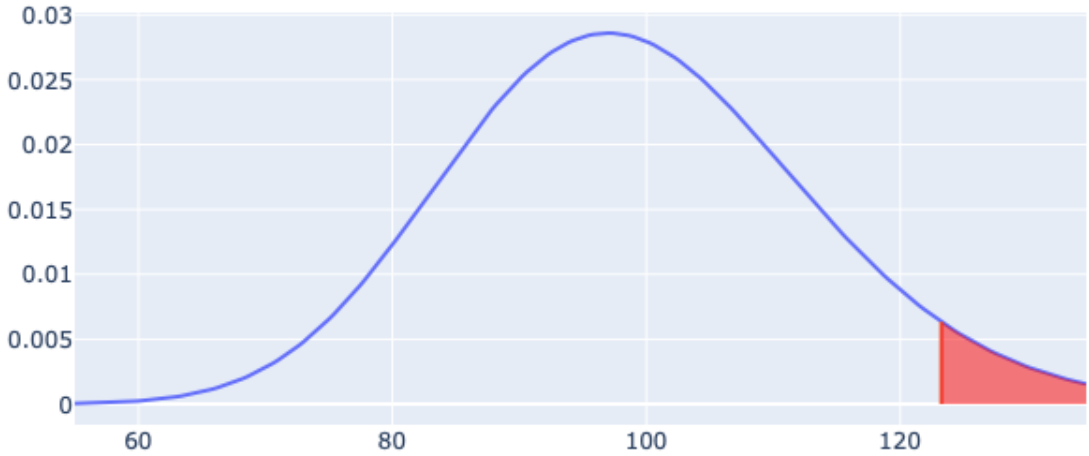
Figure 1: Approximate distribution of the test statistic Λ for a likelihood ratio test. Under the null hypothesis, $\Lambda \dot{\sim} \chi^2_{99}$.



(f) Determine the rejection region at a significance level of 0.05. Depict it in the previous plot.

In this case, the rejection threshold is given by:

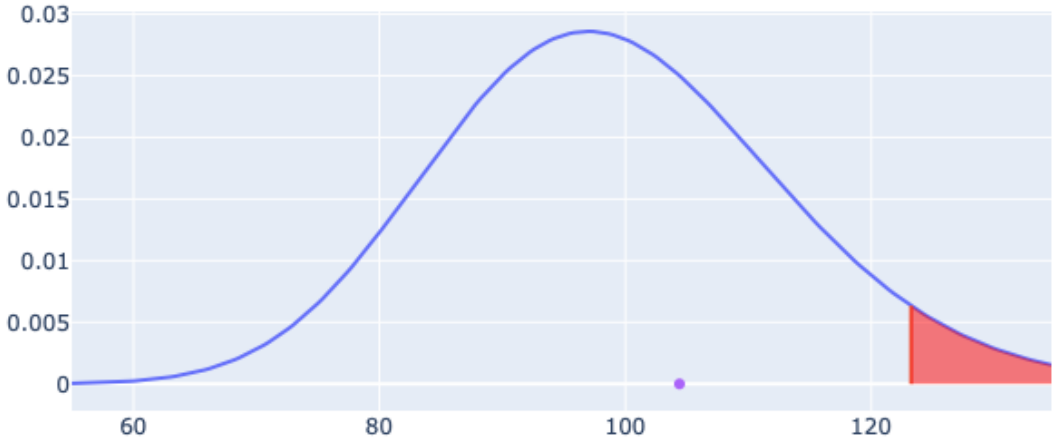
Figure 2: Rejection region (red) for the likelihood ratio test with significance level $\alpha = 0.05$.



(g) Also show the value of the test statistic in the previous plot. What is its p-value? Based on the data collected by the observatory and the analysis that you have conducted, does the emission rate appear to be constant?

The value of the test statistic is `104.40`,which in the previous plot falls outside the rejection region

Figure 3: Rejection region (red) for the likelihood ratio test with significance level $\alpha = 0.05$. The value of the statistic Λ is shown in the purple dot.



The p-value associated with this value is `0.34`. Hence, under this assumptions, the null cannot be rejected and thus the emission rate appears to be constant.

Problem 1.3: p-values

Read the statement by the American Statistical Association about p-values (Wasserstein and Lazar: The ASA's statement on p-values: context, process, and purpose) and respond to the following scenarios.

(a) A friend looking at your notes from the first lecture saw that there's a p-value of 0.0012 for the HIP study. They ask you, does that mean there's a 99.88% chance that offering a mammography decreases the risk of death from breast cancer? Explain to your friend exactly what this p-value means, including any assumptions that were made.

According to Wasserstein and Lazar (2016), for a certain statistical model, the p-value is "the probability (...) that a statistical summary of the data (...) would be equal to or more extreme than its observed value." In that sense, the interpretation of my friend is incorrect. To understand what this p-value means, first note that the HIP was based on two assumptions:

- That a person dying from breast cancer follows a Bernoulli distribution with parameter π.
- That a person dying from breast cancer is independent of other people dying (or not) from breast cancer.

Under that model, a randomized control trial was designed and the participants assigned randomly to treatment and control groups. Only the first were offered mammographies. The p-value in questions arises when testing the (null) hypothesis that the probability of dying of breast cancer (the π parameter of the Bernoulli distribution) is the same for both groups. If that hypothesis were true, then a certain test statistic (namely, the number of deaths in the treatment group) follows a Hypergeometric distribution and the probability of the test statistic being lower that the obtained value is 0.12%. In other words, there is a 99.88% of probability that this statistical summary is greater that its observed value. Additionally, it means there is at most a probability of 0.12% for the null hypothesis being true, although we rejected it being so.

An additional (and hidden) assumption made to obtain that p-value is that the number of deaths in the study was known beforehand.

(b) Your colleague in education studies cares about what can improve the education outcome in early childhood. He thinks the ideal planning should be to include as many variables as possible and regress children's educational outcome on the set. Then we select the variables that are shown to be statistically significant and inform the policy makers. Is this approach likely to produce the intended good policies? What other approach to this problem could you suggest?

There are multiple problems with this approach. First, given a certain significance threshold it is highly likely to obtain significant results if testing multiple hypothesis without correction. However, even if the tests are corrected fro multiple hypothesis testing, other problems arise. As mentioned in the Wasserstein and Lazar (2016), at least four caveats can be mentioned for this approach:

1. The statistically significance of the variables is "only a measure about data in relation to a specified hypothetical explanation", which in this case is the coefficient of the variable not being zero. This is, we have evidence to reject the idea that the variable in particular is not helpful in linearly predicting the outcome, albeit there is no idea of causality involved.

2. If we present the policymakers only the statistically significant variables and do not report how the results were obtained, it is impossible to draw clear and useful conclusions for policymaking. Like the paper mentioned, p-values are uninterpretable in absence of the models that produced them. After all, p-values are by definition tied to a certain statistical model and assumptions.

3. The variable being statistically significant does not mean the effect it could have on the outcome is big, or cost-effective to be a good public policy. As mentioned by the authors: "[s]maller p-values do not necessarily imply the presence of larger or more important effects(...)". In this case, finding a statistically significant variable does not mean their effect on education is large enough to become a good policy.

4. Finally, the statistical significance of the variables is not an indicator of the underlying model being right. This, because the test was realized assuming the model was right. In other words, testing whether a variable is statistically significant in a certain model is not a test about the model assumptions. Wasserstein and Lazar (2016) elaborate on this mentioning that "[b]y itself, a p-value does not provide a good measure of evidence regarding a model or hypothesis." Since we are only testing one of the infinite possible hypothesis, there is a chance another completely different model or hypothesis could explain better the data we have.

In light of these problems, a better framework could be combining statistical methods with experiment design improvements. First, and drawing from the paper, we could combine testing for significance with confidence intervals, likelihood ratios or Bayesian methods. We could also incorporate decision-theoretic modeling and false discovery rates. This way, we could deviate our attention from testing and focus on the estimation and the size of the effects that each feature has on the outcome. Another approach would be designing good RCTs that could shed more light on the effects that some variables can have on education. Evidently, this is a long and costly process and should be done with most caution and care, in order to draw correct conclusions and avoid bias.

(c) An economist collects data on many nationwide variables and surprisingly finds that if she runs a regression between chocolate consumption and number of Nobel prize laureates, the coefficient is statistically significant. Should she conclude that there exists a relationship between Nobel prize and chocolate consumption? Explain why.

As mentioned in caveat 1 of the previous question, the fact that the coefficient is statistically significant only means that chocolate consumption is useful at predicting the number of Nobel prize laureates. However, no relationship is elicited this way. There could be other variables not taken into account like

investment on science or research in general, quality of schools and universities, easiness of migration, among others, that could explain better the number of Nobel prize laureates by country.

(d) Your lab collects individual-level data on 50,000 humans for 100 features, including IQ and chocolate consumption. They find that their initial hypothesis about the relation between chocolate consumption and IQ has a p-value higher than 0.05. However, they find that there are other variables in the data set that have p-value less than 0.05, namely, a subject's family income and number of siblings. They therefore decide to not write about chocolate consumption, but rather, report these statistically significant results in their paper, and provide possible explanations. Is this sound scientific practice? Please discuss.

Exploratory studies may prove useful to discover suggestive relationships in the data. However, these are not meant to be conclusive about relationships between outcome variables and possible predictors. As mentioned before, if 100 features are tested then, in average, under a 0.05 significance threshold we should expect to find around 5 variables to be statistically significant, just by chance alone. This can happen even if we correct our p-values for multiple hypothesis testing. Consequently, this is not an ethical way to produce scientific knowledge, less make decisions based on these discoveries.

The adequate way to move forward after an exploratory analysis is finding good experiments (like RCTs or natural experiments) that could allow us to test independently these hypotheses. Afterwards, we could also provide explanations and try to test whether these are consistent with the data.

(e) A neuroscience lab runs a randomized experiment on 100 mice by adding chocolate in half of the mice's diet and another food of the equivalent calories in another half's diet. They find that the difference between the two groups' time in solving a maze puzzle has a p-value lower than 0.05. Should they conclude that chocolate consumption leads to improved cognitive power in mice? Explain why.

This may not be a right conclusion to make after this experiment. Note that, since this is a randomized experiment, the problem in this case is not its statistical design, but in its conclusions. Strictly speaking, they just proved that replacing half of the diet of the mice with chocolate improved their maze solving time but not necessarily their skills. There may be other explanations for this difference that are not the mice improving their cognitive skills.

For example, since chocolate contains sugar, then is natural that mice are more active (e.g. run faster) and thus take less time than their counterparts that did not have a diet change. In order to test an improved cognitive power there should be used test that rely less on time and more on other expression of cognition.

Problem 1.4: Published research findings are false

Read the paper by Ioannidis (PLoS Medicine, 2005) on why most published research findings are false and summarize the paper in your own words.

What is the most important lesson you learned from reading this paper? Explain the computations going into Table 1, Table 2, and Table 3. How does Ioannidis get to the conclusion that a research finding is more likely true than false if $(1-\beta)R > \alpha$ (at the beginning of page 697)? What does this mean?

The author proposes a simple theoretical framework to explain why many research findings in science could in principle be false. The three models Ioannidis proposes focus primarily on three parameters:

- R, the fraction of "true relationships" to "no relationships" among the relationships tested in a given field. From this, he computes the pre-study (ex ante) probability of a relationship taken at random being true: $\frac{R}{R+1}$.

- α, the significance threshold (i.e., the probability of claiming the existence of a relationship where is none).
- β, the statistical power of the study (i.e., the probability of finding a true relationship).

In his first model, the author compares in a contingency table (Table 1 in the paper) the expected number of studies that belong to each of the 4 groups given by: finding or rejecting a relationship, and the actual existence (or not) of a relationship. Under this simple model is that he proposes that a research finding is more likely true than false if $(1-\beta)R > \alpha$.

This arises from the following calculation. If c studies are conducted in a field, then a fraction $(1-\beta)\frac{R}{R+1}$ of them are true findings (computed as the probability of finding a true relationship times the probability of that finding being true). Also, a fraction $\alpha\frac{1}{R+1}$ of the studies are false research findings (computed as the probability of falsely claiming a finding times the probability of not being in presence of a relationship). Consequently, a fraction $\frac{\alpha+(1-\beta)R}{R+1}$ of the studies are research findings (the sum of both previous ratios), and if one is taken at random, its more likely to be true than false if and only if the fraction of true findings is greater than the fraction of false findings:

$$\frac{(1-\beta)R}{R+1} > \frac{\alpha}{R+1}$$

which translates to $(1-\beta)R > \alpha$. This condition is equivalent to the positive predictive value (PPV) being greater than 0.5, where

$$PPV = \frac{\text{fraction of true research findings}}{\text{fraction of research findings}} = \frac{\frac{(1-\beta)R}{R+1}}{\frac{\alpha+(1-\beta)R}{R+1}} = \frac{(1-\beta)R}{\alpha+(1-\beta)R}$$

Indeed,

$$PPV > 0.5 \iff (1-\beta)R > 0.5\alpha + 0.5(1-\beta)R \iff (1-\beta)R > \alpha$$

Note that the PPV is nothing more than the ex post probability of a relationship being true. Hence, the Ioannidis' claim translates to: we could expect that a given research finding is more likely false than true if the probability of being true, after being tested is strictly greater than a 50%. Of course, we could aim for a more strict threshold, but 50% is the minimum necessary to make the appearance of true findings more likely.

Later in the paper the author makes more complex assumptions and incorporates, separately, two variations:

1. Presence of bias, that is, the probability that a given study was passed as a research finding, although there was none.
2. Presence of multiple independent studies, that is, the fact that many independent research teams are testing the same relationship simultaneously.

These new models are summarized in Tables 2 and 3, respectively. These tables follow the same logic as the first one, where studies are split in four groups and the expected values computed based on the probabilities of belonging to each group, now including bias and multiple independent testing.

The main contribution of the paper is showing using a very simple framework that finding true relationships from published research findings is not as probable as we may expect. Moreover, the author shows to how extent different aspects of the studies are affecting the ex post probability of the finding being true. In this line, Ioannidis shows that the ex ante probability is one of the main drivers of the veracity of research findings. Statistical power and bias also have a important effect. In his closing remarks, the author

provides at least three solutions: better evidence (e.g. large-scale studies in relationships with high ex ante probability of being true), pre-register studies to reduce bias (or at least adhering to a scientific protocol), and better understand the range of R values for each field (and promote fields where R is bigger).

In that sense, the lesson I learned from the paper is that we have to be very critical when interpreting results from studies. Biased fields can have many false results posing as true, especially if the study design did not achieve high power. The same can be said about questions that draw a lot of attention from the scientific and social community, in particular those that fight to produce a highly significant or strong result (although there may be none). For example, due to the pandemic a lot of interest was drawn towards questions about the effects that some policies could have on the pandemic control or the effects than the pandemic can have in different aspects of our lives. It is possible that the R value for this field may be large (as there are a lot we do not know yet on pandemics), but there may also be a lot of bias in which relationships want to be answered and which pre conceived answers are expected. Moreover, many teams are tackling simultaneously similar questions, which as mentioned can produce false results. Last but not least, there is possible that for these questions is not possible to design good experiments and we must have to relay on natural experiments or country-or-state-level quasi-experiments, which have much less power.

Problem 1.5: Detecting Leukemia types

The data set `golub`[1] consists of the expression levels of 3,051 genes for 38 tumor mRNA samples. Each tumor mRNA sample comes from one patient (i.e., 38 patients total): 27 of these tumor samples correspond to acute lymphoblastic leukemia (ALL), while the remaining 11 correspond to acute myeloid leukemia (AML).

How many genes are associated with the different tumor types (meaning that their expression level differs between the two tumor types) using (i) the uncorrected p-values, (ii) the Holm-Bonferroni corrected p-values, and (iii) the Benjamini-Hochberg corrected p-values? Feel free to use existing libraries for multiple hypothesis testing, in `R` or `python`. You can use $\alpha = 0.05$ for the significance threshold.

In order to determine which genes had different expression leves between the two tumor types, for each gene a t test of means between each group was performed. This test has a null hypothesis that both ALL and AML samples have the same mean, against the alternative hypothesis that the means are different. This test is equivalent to estimating, for each gene g, the linear model

$$y_{gi} = \beta_{g0} + \beta_{g1}\text{tumor}_{gi} + \varepsilon_{gi},$$

where $y_g i$ is the expression level for gene g in patient i, and tumor_{gi} is the tumor class for sample i of gene g. Here, the null hypothesis $\beta_{g1} = 0$ against $\beta_{g1} \neq 0$ is equivalent to the mean t-test.

For more robustness, the test was made without the assumption that variances across groups are equal. The results are as follows:

- Number of relevant genes without correction: 1078.
- Number of relevant genes using the Holm-Bonferroni correction: 103.
- Number of relevant genes using the Benjamini-Hochberg correction: 695.

As expected, the Holm-Bonferroni correction is the most conservative, as it tries to minimize the FWER. The Benjamini-Hochberg is less conservative, categorizing almost 35% of the rejected hypothesis as false discoveries.

[1] **Source of data:** Golub et al. (1999). *Molecular classification of cancer: class discovery and class prediction by gene expression monitoring*, Science, Vol. 286:531-537.

Problem 1.6: Regression and Gradient Descent

In this problem, we will look at OLS and the gradient descent algorithm.

(a) Read in the synthetic data matrix `syn_X.csv` and the vector `syn_y.csv` of "observations". Compute the OLS estimator $\hat{\beta}$ by matrix inversion.

The OLS estimator $\hat{\beta}$ is obtained from the following formula:

$$\hat{\beta} = \left(X^T X\right)^{-1} X^T y$$

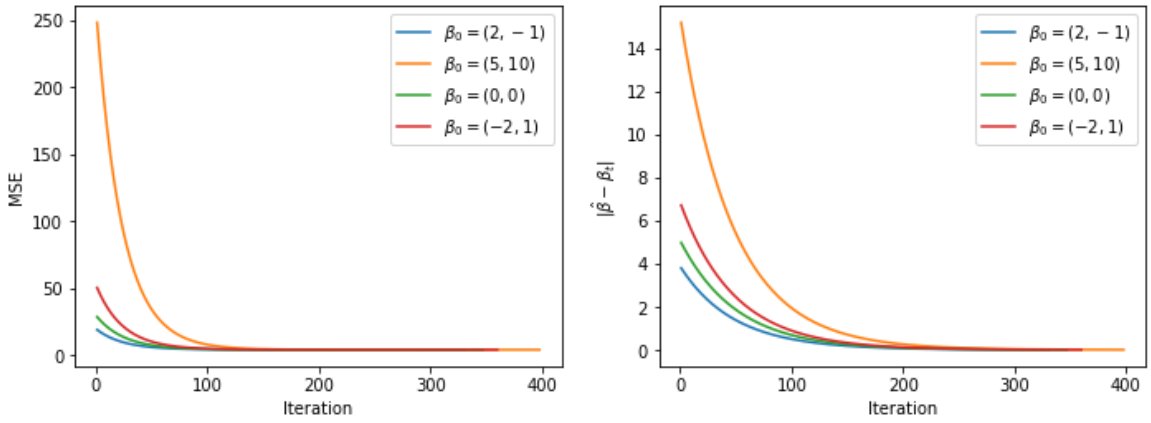
In this case

$$\hat{\beta} = \begin{pmatrix} 1.45 \\ -4.75 \end{pmatrix}$$

(b) Implement gradient descent for the least squares problem and run it on the synthetic test data loaded in the previous question. As a function of the iteration t, plot the mean squared error (MSE) and the distance $\|\beta^t - \hat{\beta}\|$ of your current iterates (in separate plots). Play with different initializations β^0 and different step sizes. What do you observe? Explain. Based on your observations, what would be an optimal step size?

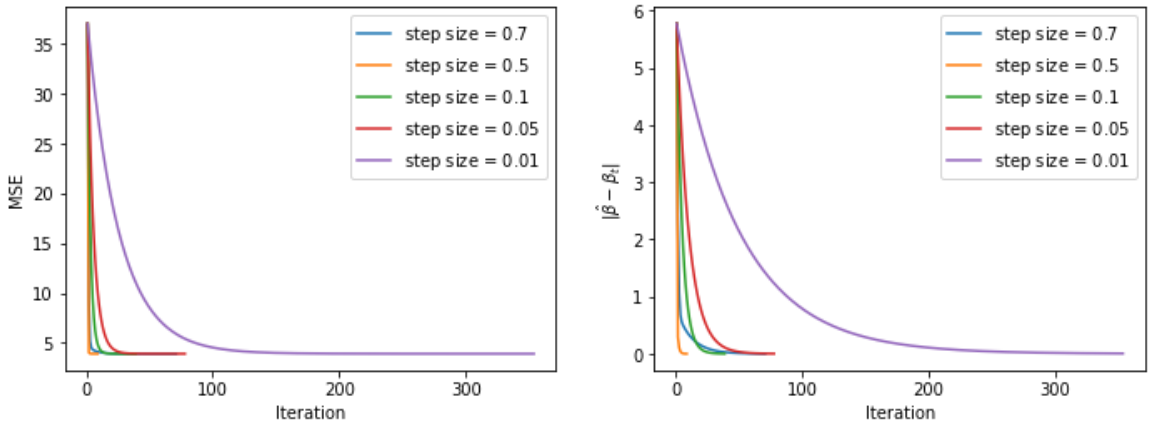
As expected, the closer the initial β_0 is from $\hat{\beta}$, the faster the algorithm converges to it. In the figure below, the faster convergence happened with $\beta_0 = \begin{pmatrix} 2 \\ -1 \end{pmatrix}$, which is extremely close o $\hat{\beta}$ computed before.

Figure 4: MSE and distance to true estimate for different initial vectors β_0. Step size = 0.01.



In terms of step sizes, smallest values take more iterations to converge. However, values close to 1 have problems converging, because gradients tend to explode. In the figure below, a step size of 0.7 gave the fastest convergence, but albeit a very steep one. On the other hand, the value of 0.01 gave a slower convergence but more controlled. All in all, it appears that an optimal value could be 0.05 or lower, in order to prevent numerical instabilities.

Figure 5: MSE and distance to true estimate for different step size. Initial vector $\beta_0 = (1,1)$.



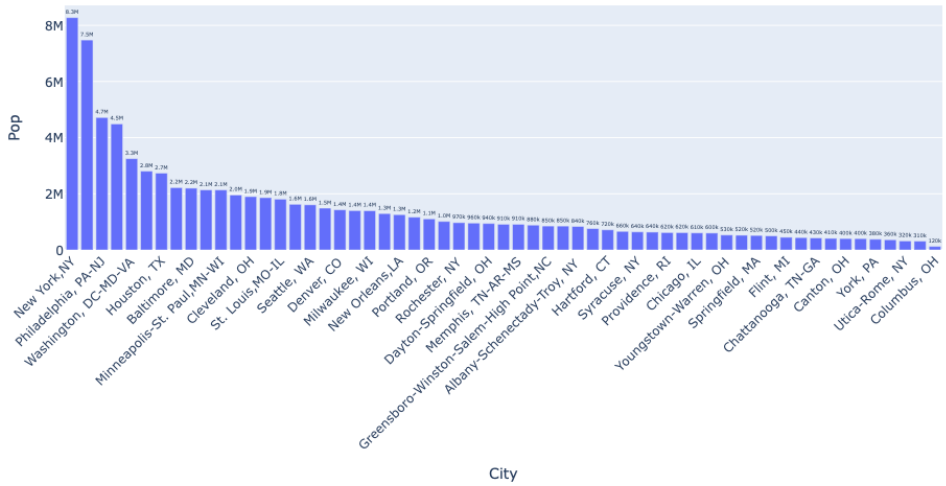
Next, we look at some real data. General Motors collected data (found in `mortality.csv`) from 60 US cities to study the contribution of air pollution to mortality. The dependent variable is the age-adjusted mortality (`Mortality`). The data include variables measuring climate characteristics (`JanTemp`, `JulyTemp`, `RelHum`, `Rain`), variables measuring demographic characteristics of the cities (`Educ`, `Dens`, `NonWhite`, `WhiteCollar`, `Pop`, `House`, `Income`), and variables recording the pollution potential of three different air pollutants (`HC`, `NOx`, `SO2`).

(c) Get an overview of the data and account for possible problems. Which cities stand out? Which of the variables need to be transformed? When applicable, which transformations would you apply?

One the first problems with the data is the lack of descriptions over the variables. Even if statistical assumptions hold and the other problems (I will mention below) are not present, it is impossible to interpret quantitatively the results obtained.

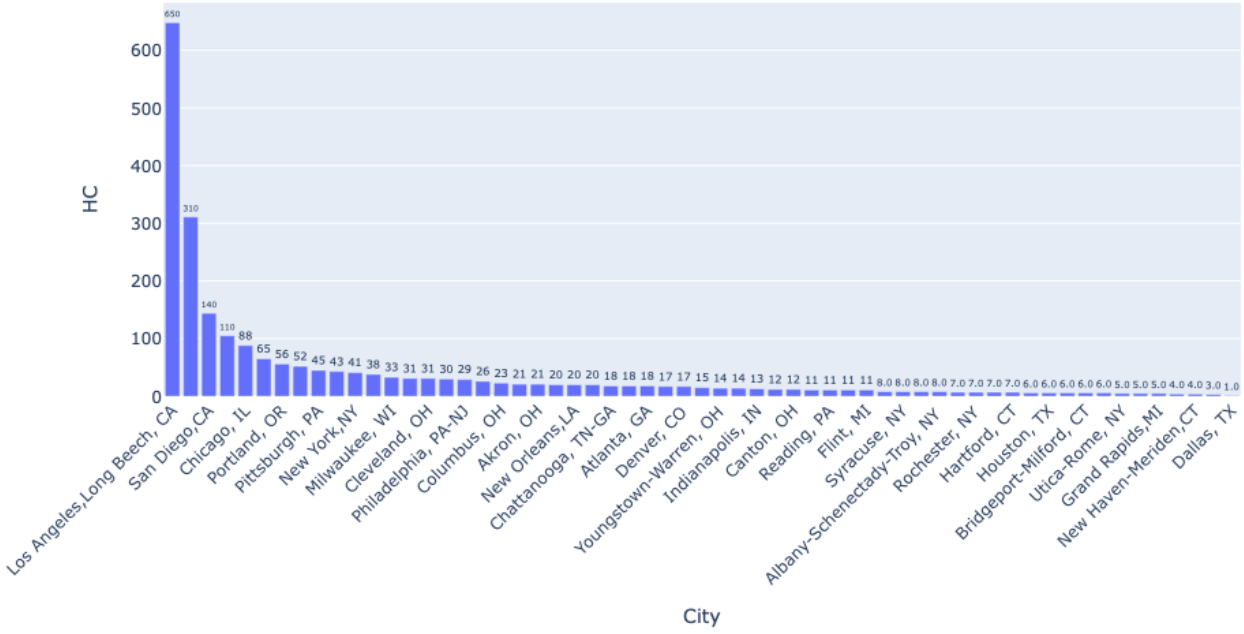
Nevertheless, there are potential problems with the data that may bias our results. First of all, looking at the population chart, is clear that two cities are considerable bigger than the others: New York and Los Angeles (see Figure 6).

Figure 6: Population chart of different cities in the database. Some cities with smaller populations are omitted.

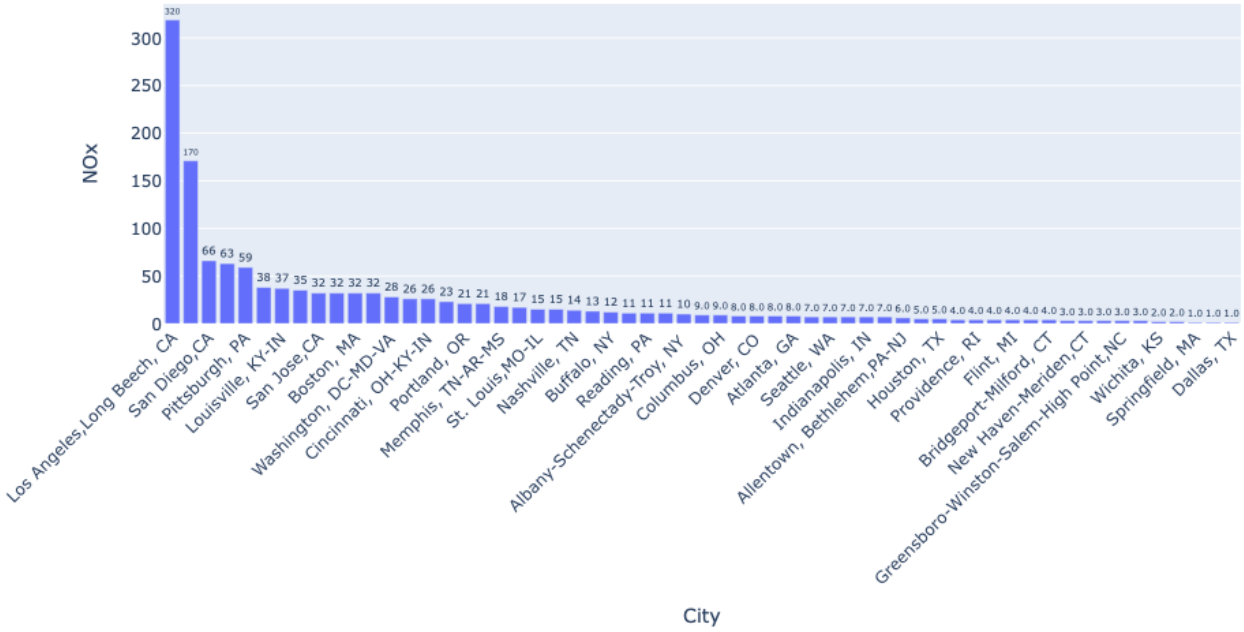


Something similar happens when looking at the `HC` and `NOx` variables, where Los Angeles and San Francisco stand out from the others (see Figures 7a and 7b, respectively).

Figure 7: Pollutants chart of different cities in the database. Some cities with smaller values of pollutants are omitted.



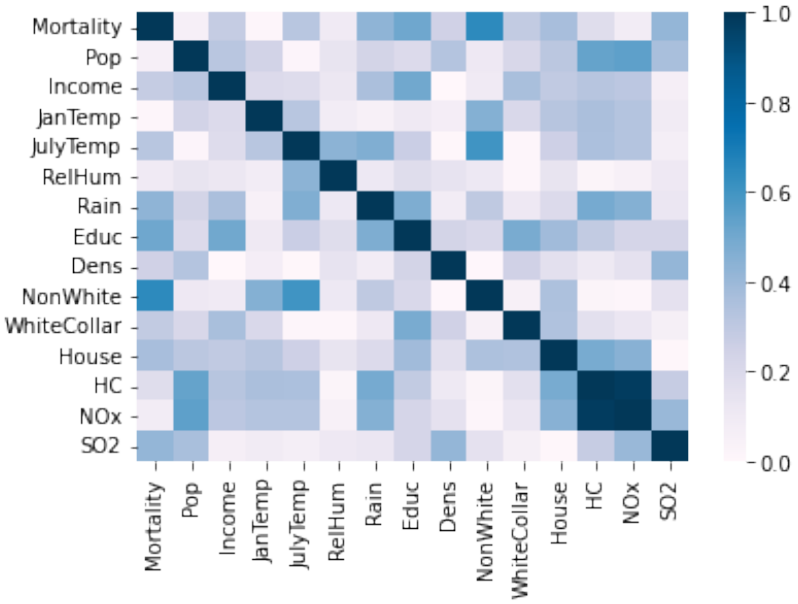
(a) HC



(b) NO_x

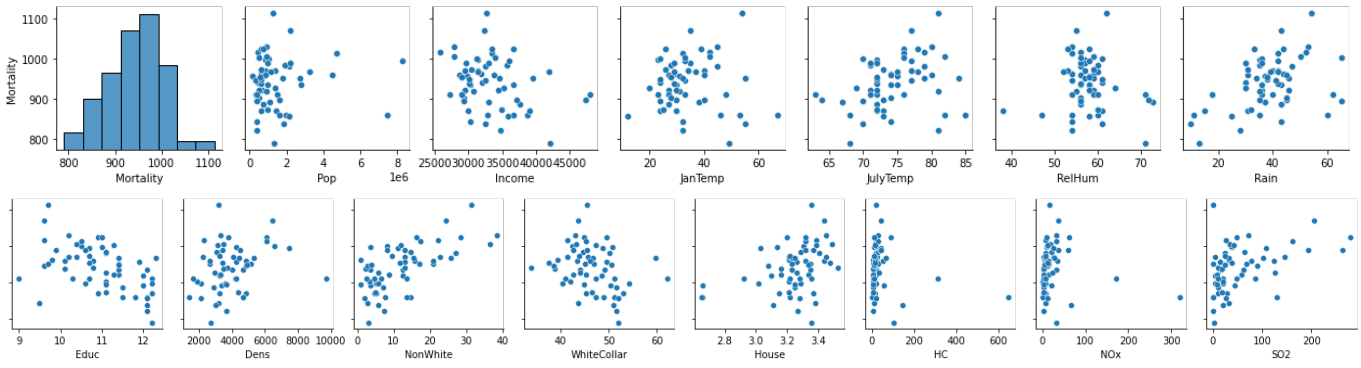
Another potential issue with the data is that `HC` and `NOx` are highly correlated (see **??**), with a Pearson correlation of 0.98). This may be due to cars or coal plants emitting both HC and NO_x contaminants in a similar fashion. In order to estimate the effect of contaminants over mortality, only one of these two variables should be included in the regression model.

Figure 8: Matrix of absolute values of Pearson correlation coefficients, for the numeric variables in the dataset. A darker color implies a higher correlation.



Finally, the pair grid between `Mortality` and other control variables does not present visual evidence that the latter need to be transformed in order to include them in a regression model. However, to avoid scale issues, variables `Pop` and `Income` could be normalized to million of people and thousands of dollars, respectively.

Figure 9: Pair grid for mortality and its potential predictors. The first graph is the histogram of `Mortality` and the others are scatterplots with `Mortality` as dependent variable and the corresponding independent variable indicated on the X axis of each graph.



(d) Run your gradient descent algorithm for least squares on the raw data and on the transformed data, with different step sizes as before. What do you observe?

The GD algorithm applied in the raw data does not converge. This is most likely happening due to

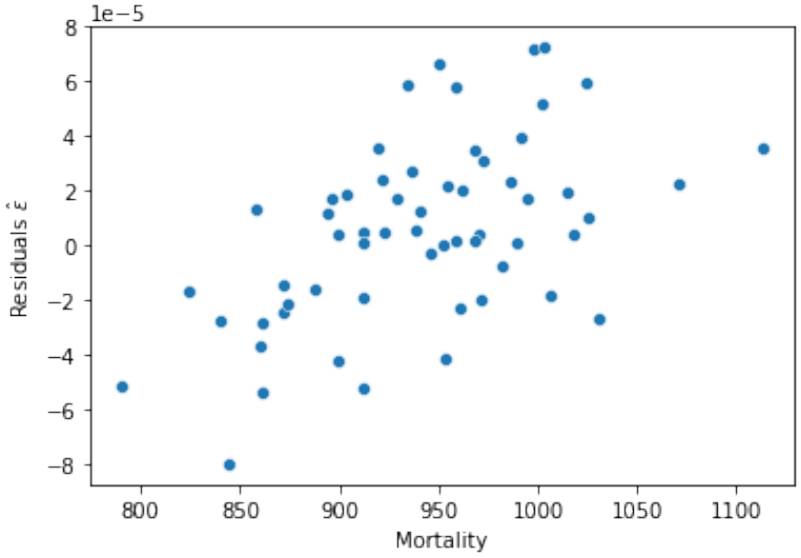
numerical instability issues driven by the variables with large numbers or the highly correlated variables `HC` and `NOx`.

On the other hand, the algorithm converges for the transformed data, albeit with a step size several orders of magnitude smaller than the ones used in the previous exercise. For this reason, only one experiment with step size equal to 10^{-8} was performed. The most likely explanation for this could be numerical issues driven by the different units the variables are expressed in. Additionally, this could be due to the presence of the outliers mentioned before. In order to induce the convergence of the algorithm in less iterations, we would need to normalize the variables (using standarization or min-max normalization) and dropping the outliers, if necessary.

(e) Carry out a multiple linear regression containing all variables with the necessary transformations (with gradient descent as in d) or with matrix inversion). Does the model fit well? Check the residuals and comment on what you observe.

After fitting the model (with a constant), the goodness-of-fit, given by the R^2 coefficient is almost 1, which is close to a perfect prediction for all the data points in the sample. This is also confirmed by the residuals, with magnitudes of 10^{-9}. However, by looking at **??**, the residual plot evidences a trend, with lower errors for cities with large mortality and higher errors for cities with low mortality.

Figure 10: Residuals of the regression model fitted on Mortality against all other numeric variables in the database.



The first problem could be related to a violation of the assumptions on the normality of the error. There could be omitted variables that could explain the mortality that we are not including in the model. Regarding the second issue, the problem could be the prescence of outlier cities. For these cities, a certain margin of error reuslts in a greater increase in the loss function for them than for others with lower mortality overall. This may induce the model to predict better the mortality of those cities.

(f) ***Gradient descent for other functions:*** **A popular regression model for binary observations y is given by the following estimator:**

$$\hat{\beta} = \arg\min_{\beta} \sum_{i} \log\left(1 + \exp\left(-y_i \beta^T x_i\right)\right)$$

How would you solve this via gradient descent? Derive the corresponding gradient and write down the steps of the algorithm.

First, note that log is a non-decreasing convex function, and $1 + \exp(w)$ is convex. Hence, each of the terms in the summation are convex and the loss function is convex as well. This implies that the gradient descent algorithm will converge, given an adequate step size.

Now, in order to describe the algorithm we need to compute the gradient of this loss function. Let $L(\beta)$ be the loss function. Then

$$\frac{\partial L}{\partial \beta_j} = \sum_i -y_i x_{ij} \frac{\exp\left(-y_i \beta^T x_i\right)}{1 + \exp\left(-y_i \beta^T x_i\right)}$$

Consequently, for step size α, the update of the algorithm for coordinate j of iteration β_t is

$$\beta_{t+1,j} \leftarrow \beta_{t,j} - \alpha \frac{\partial L}{\partial \beta_j}$$

Problem 1.7: Computational Aspects of Regression

In this problem, we will consider some computational challenges that arise in practice when performing linear regression.

(a) Suppose you have a problem in which the feature matrix, X, has 100 million rows and 200 columns. What challenge will arise when you try to apply either the matrix inversion method or the gradient descent method to compute the regression coefficients as in the previous problem? *Hint: if each entry is a 64-bit float, how much memory will be required to store X?*

A matrix X of that size would have $2 \cdot 10^{10}$ entries. If every entry is a 64-bit float, then each entry needs 8 bytes of memory to be stored. Consequently, to store the matrix X would be needed:

$$\frac{2 \cdot 10^{10}}{10^9} = 20\, GB$$

of memory. This, without considering matrix additional matrix operations needed to invert X or compute the gradient and the update of gradient descent algorithm.

Hence, for a problem like this we would need a different mechanism to compute the regression coefficients.

(b) Suggest one method that will allow you to compute the linear regression coefficients for this problem. Be specific. Discuss pros and cons of your proposed approach.

An option would be to use the stochastic gradient descent (SGD) algorithm. For this algorithm, we have the following steps:

1. Define batch size `batch_size`. Also define initial state β_0, initial loss function value L_0 (large), step size α and tolerance ϵ for the GD algorithm.
2. Sample randomly `batch_size` many numbers between 0 and 100 million (with replacement). Load the sampled rows of X (including all columns) into dataset `df`.
3. Compute gradient using `df` and update $\beta_t \to \beta_{t+1}$ using step_size α.
4. Compute loss function L_{t+1} with β_{t+1}.

5. If $|L_{t+1} - L_t| \leqslant \epsilon$, define $\hat{\beta} = \beta_{t+1}$ and terminate. Otherwise, return to step 2.

Assuming the loss function is convex, then SGD will converge given a correctly specified step size, even if `batch_size` is small. An advantage of using SGD is that the process is much more efficient, even if the necessary memory to run GD is available. However, it is possible that SGD takes much more steps if the loss function is not smooth enough.

Now, suppose we are in a setting in which the number of data points, n, is much smaller than the number of variables, p, i.e., X has many more columns than rows. This situation occurs often in biological applications, for example, in which the features may represent the expression levels of various genes. This is often referred to as the "high-dimensional" regime. (Assume X is small enough that it can fit in memory.)

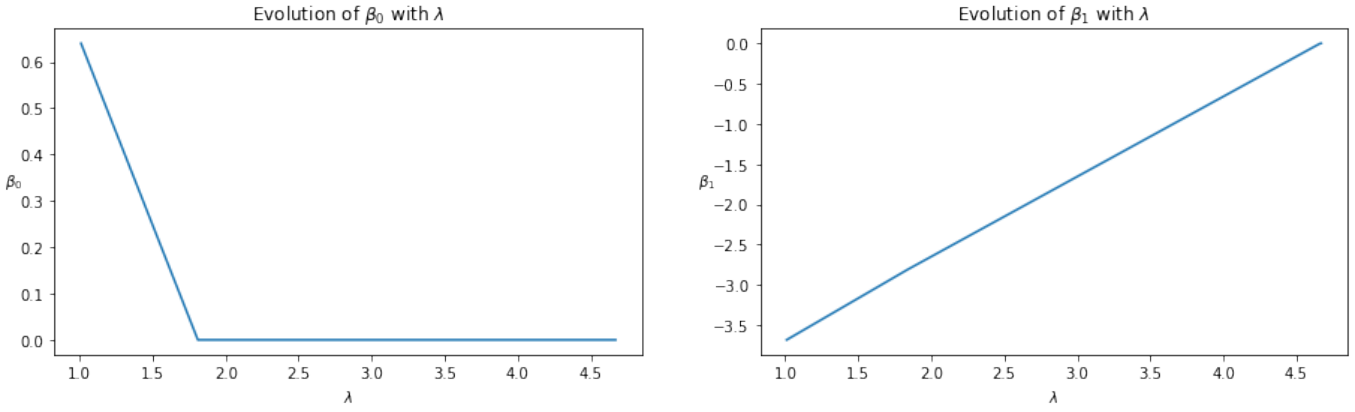
(c) Can we run gradient descent to compute the regression coefficients? What do you think about the solution? Why? *Hint: what is the maximum rank of the matrix $X^T X$?*

In this setting, there are infinite solutions to the problem of minimizing the MSE. In that sense, running GD on the MSE alone may not converge. Moreover, even if it converges, the solution will vary between different runs of the algorithm if the initial state or the step size are changed. Consequently, there is no possible way of making conclusions about the solution unless we impose some kind of regularization.

(d) Load the data from the previous question, `syn_X.csv` and `syn_Y.csv`. Compute the regression coefficients by solving the LASSO problem for various values of λ. What happens to the solution as λ increases? Choose λ such that only one component of the coefficient vector is nonzero. What is the value of λ? Which coefficient is it? (For this problem, feel free to use a package that performs LASSO regularization, such as `scikit-learn` in `python` or `glmnet` in `R`.)

The results are presented in **??**. As λ increases, the size of the coefficient vector shrinks towards 0 linearly. The first component to become zero is β_0, which achieves this value with $\lambda = 1.81$. The second coefficient becomes zero with $\lambda = 4.67$.

Figure 11: Evolution of each coefficient of linear regression `syn_y` $=$ `syn_X`$\beta + \varepsilon$ as a function of the Lasso parameter λ.



Problem 1.8: Likelihood ratio test for a Gaussian model

In this problem, we will analyze the likelihood ratio statistic for the model $X \sim \mathcal{N}(\mu, \sigma^2)$ with unknown mean and unknown variance and null hypothesis $H_0 : \mu = 0$ versus alternative hypothesis $H_A : \mu \neq 0$.

(a) What is the likelihood function for n independent and identically distributed (iid) Gaussian random variables (with mean μ and variance σ^2)? The likelihood function for n iid Gaussian random variables with mean μ and variance σ^2 is

$$p_{\mu,\sigma^2}(x_1,\ldots,x_n) = \prod_{i=1}^{n} \frac{1}{\sigma(2\pi)^{1/2}} \exp\left(\frac{1}{2\sigma^2}(x_i-\mu)^2\right) = \frac{1}{\sigma^n(2\pi)^{n/2}} \exp\left(\frac{1}{2\sigma^2}\sum_{i=1}^{n}(x_i-\mu)^2\right)$$

(b) What is the likelihood ratio statistic for the hypothesis test specified above? (You should simplify the statistic so it only involves the realizations $x_1,\ldots,x_n$.) The test statistic for the likelihood ratio test is given by

$$\Lambda(x_1,\ldots,x_n) = \frac{\max_\sigma p_{0,\sigma}(x_1,\ldots,x_n)}{\max_{\mu,\sigma} p_{\mu,\sigma}(x_1,\ldots,x_n)}$$

For the denominator, we have that taking logs and differentiating with respect to μ and σ, the first order conditions are

$$\frac{n\,(\overline{x}-\mu)}{\sigma^2} = 0$$

$$-\frac{n}{\sigma} - \frac{1}{\sigma^3}\sum_{i=1}^{n}(x_i-\mu)^2 = 0$$

Hence,

$$\hat{\mu} = \overline{x}$$

$$\hat{\sigma}^2 = \frac{1}{n}\sum_{i=1}^{n}(x_i-\hat{\mu})^2$$

For the null hypothesis, since $\mu = 0$, the first order condition for σ is just

$$-\frac{n}{\sigma} - \frac{1}{\sigma^3}\sum_{i=1}^{n} x_i^2 = 0$$

And thus

$$\hat{\sigma}_0^2 = \frac{1}{n}\sum_{i=1}^{n} x_i^2$$

Consequently, the test statistic for this likelihood ratio test is

$$\Lambda(x_1,\ldots,x_n) = \frac{\hat{\sigma}^n}{\hat{\sigma}_0^n}\exp\left(\frac{1}{2\hat{\sigma}_0^2}\sum_{i=1}^{n} x_i^2 - \frac{1}{2\hat{\sigma}^2}\sum_{i=1}^{n}(x_i-\overline{x})^2\right) = \frac{\hat{\sigma}^n}{\hat{\sigma}_0^n}\exp\left(\frac{n}{2}-\frac{n}{2}\right) = \frac{\hat{\sigma}^n}{\hat{\sigma}_0^n}$$

Moreover, using the definitions of $\hat{\sigma}^n$ and $\hat{\sigma}_0^n$ we obtain

$$\Lambda(x_1,\ldots,x_n) = \left(\frac{\sum_i (x_i-\overline{x})^2}{\sum_i x_i^2}\right)^{n/2}$$

(c) What is the rejection region for a one-sample (two-sided) t-test for the same hypothesis test?

Under the null, we have that

$$\frac{\overline{X_n}}{\hat{\sigma}/\sqrt{n}} \sim t_{n-1}$$

where $\overline{X_n}$ is the sample average of the observations,

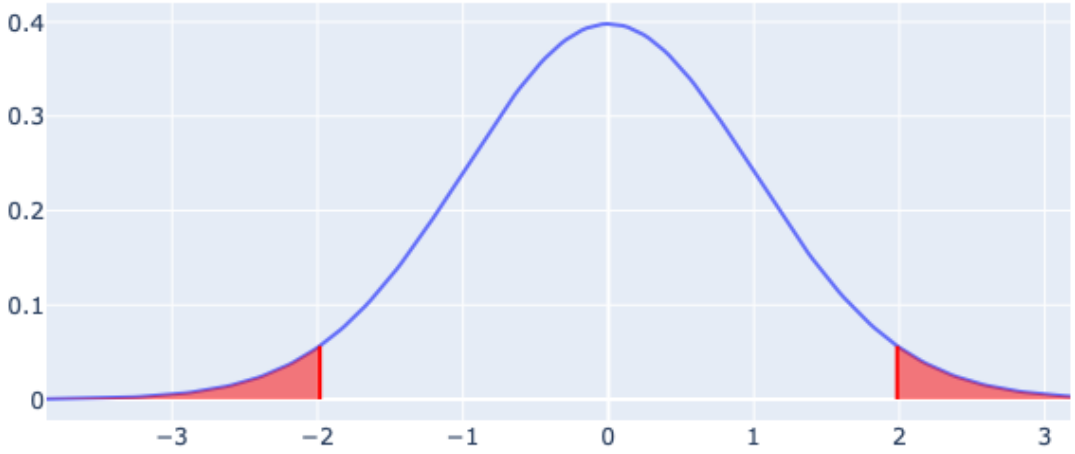
$$\hat{\sigma} = \frac{1}{n-1} \sum_{i=1}^{n} \left(X_i - \overline{X_n}\right)^2$$

is the sample variance and t_{n-1} is the t-student distribution with $n-1$ degrees of freedom. Consequently, the rejection region with significance α for the two-sided t-test for this hypothesis test is given by

$$\left| \frac{\overline{X_n}}{\hat{\sigma}/\sqrt{n}} \right| > t_{n-1,\alpha}$$

where $t_{n-1,q}$ is the q quantile of the t-student distribution with $n-1$ degrees of freedom, and α is the significance level. The figure below shows the rejection region for a sample size $n = 100$ and $\alpha = 0.5$.

Figure 12: Rejection region (red) for the two-sided t test with significance level $\alpha = 0.05$.



(d) How is the likelihood ratio test related to the one-sample t-test? Show that the exact rejection region of the likelihood ratio test (without approximation by the χ^2-distribution) has the same form as the rejection region of the t-test.

Observe that given $\Lambda(x_1, \ldots, x_n)$, we reject the null hypothesis if, for some value $k \in (0, 1)$,

$$\Lambda(x_1, \ldots, x_n) = \left(\frac{\sum_i (x_i - \overline{x})^2}{\sum_i x_i^2} \right)^{n/2} < k$$

which occurs if and only if

$$\frac{\sum_i x_i^2}{\sum_i (x_i - \overline{x})^2} = \frac{\hat{\sigma}^2 + \frac{n}{n-1}\overline{x}^2}{\hat{\sigma}^2} > k^{-2/n} =: k'$$

which can be rewritten as

$$\frac{\overline{x}^2}{\hat{\sigma}^2/n} > (n-1)(k'-1) =: k''$$

and since both sides are greater or equal than zero (because $k' > 1$), this occurs if and only if

$$\left| \frac{\overline{x}}{\sqrt{\hat{\sigma}^2/n}} \right| > \sqrt{k''}$$

which is the same rejection region as above. Hence, the exact distribution of the likelihood ratio is the same as the t test and, consequently, both test are equivalent.

(e) Analyze either by simulation or by computation how large the error is if you use the asymptotic distribution of the likelihood ratio statistic versus the exact distribution as in (d).

The error the asymptotic distribution is making is quite large, compared to the aimed confidence level.

By simulating 5000 samples of size 100 from a standard normal distribution, I tested the null hypothesis $H_0 : \mu = 0$ against $H_A : \mu \neq 0$ using the exact distribution and the approximate one, for a significance level $\alpha = 0.05$. For each of these samples, the Λ and t statistics were computed and then confronted to their respective rejection thresholds. After the simulation, the exact distribution rejected H_0 around 5% of the time, as expected from the confidence level. On the contrary, the asymptotic distribution rejected 30% of all the hypothesis tested. Moreover, the error was increasing in the sample size, with 44% of null hypothesis rejected when sample size equals 1,000 and 48% when the sample size was 10,000.

Another aspect to consider is that these tests are highly susceptible to the underlying standard deviation and the type-I error is increasing in its value. The approximate distribution, moreover, is the most affected by this behaviour. Increasing the standard deviation from 1 to 1.1 only affects the type-I error of the exact test by 1 percentage point (from 5% to 6%). However, the asymptotic test increases is false rejection rate up to 79%. Increasing σ again in one tenth ends up with an useless aymptotic test, with a false discovery rate of 100%, against a 7% of the exact test.