



CZECH TECHNICAL UNIVERSITY IN PRAGUE
Faculty of Nuclear Sciences and Physical Engineering



Estimating patient's life expectancy after a successful kidney transplant using machine learning methods

Odhad délky života pacienta po úspěšné transplantaci ledviny pomocí metod strojového učení

Bachelor's Degree Project

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ZADÁNÍ BAKALÁŘSKÉ PRÁCE

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Pokyny pro vypracování:

- 1) Prozkoumejte současný přístup k transplantacím ledvin, jeho problémy a výzvy. /
Investigate the current approach to kidney transplantation, its problems and challenges.
- 2) Prozkoumejte příslušné metody strojového učení a metody pro hodnocení přesnosti modelu. /
Explore applicable machine learning methods and model accuracy evaluation methods.
- 3) Vyčistěte, předzpracujte a rozšiřte stávající datovou sadu. /
Clean, preprocess and extend the existing dataset.
- 4) Vytvořte prediktivní model strojového učení pro odhad délky života pacienta a ohodnoťte jeho přesnost. /
Create a predictive machine learning model estimating a patient's life expectancy and evaluate its accuracy.
- 5) Navrhněte úpravy skórovacího algoritmu pro transplantace ledvin na základě výsledků prediktivního modelu. /
Design an updated kidney matching compatibility scoring algorithm based on the prediction model.
- 6) Prozkoumejte možnost integrace dosažených výsledků do nástroje pro správu transplantací TX Matching. /
Evaluate the possibility of integrating achieved results into kidney transplantation management tool TX Matching.

Doporučená literatura:

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Author's declaration:

I declare that this Bachelor's Degree Project is entirely my own work and I have listed all the used sources in the bibliography.

Prague, August 2, 2023

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Název práce:

Odhad délky života pacienta po úspěšné transplantaci ledviny pomocí metod strojového učení

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Chapter 1

Introduction

The goal of this paper is to explore fields of kidney transplantation and machine learning, create and apply machine learning model in real-world application.

Chapter 2

Medical Background

2.1 Why kidney fail

2.2 The history of kidney transplantation.

2.2.1 Early Animal Experiments

Advancements in surgical methods and techniques at the beginning of the 20th century eventually led to experiments with organ transplantation. On March 1st, 1902, Emerich Ullman, a physician at the Vienna Medical School, performed the first recorded organ transplantation. He performed an autograft, meaning the transplantation where the donor and the recipient are the same individual. Ullmann utilized the method of vascular suturing developed by Ervin Payr, to connect the dog's kidney to the vessels of its neck. The transplant was successful - the kidney produced urine. The dog was presented the same day to Vienna medical society eliciting significant interest and discussion.

The same year other similar transplantations were made. Another physician, Alfred von Decastello, performed a dog-to-dog kidney allograft at the Institute of Experimental Pathology in Vienna. The kidney produced urine for a while but then stopped working. Later Ullman performed a dog-to-goat kidney xenograft (cross-species transplant), and to his surprise kidney produced some urine, but later stopped.

In Lyon in the department headed by Mathieu Jabourday, his assistants Carrel, Briau and Villard were working on new methods of vascular suturing. In 1902, Alex Carrel published the method of vessel anastomosis now referred to as Carrel's seam. This technique represented a significant improvement over existing methods and effectively addressed the common issues of thrombosis, hemorrhage, stricture, and embolism[13].

Later Carrel moved to the United States where he continued his research on vessel suturing and organ transplantations at The Rockefeller Institute for Medical Research. There he perfected his method and while performing autografts and allografts documented what later would be recognized as "rejection". For his works in 1912, he got the Nobel Prize in Medicine. By this time, his method of suturing had been widely adopted in human surgeries[6].

2.2.2 Early Human Transplantation

The first recorded human renal xenograft was performed by Mathieu Jaboulay in 1906. He chose a pig and a goat as donor animals and performed two xenografts. One kidney was transported to the arm and the second to the thigh. Each kidney functioned for one hour[14, 4].

The second and third human transplants performed by Ernst Unger were far more known. On December 10, 1909, he performed a kidney transplant from a stillborn baby to a baboon. Even though the kidney produced no urine, the postmortem showed that vascular anastomosis (connection of vessels) was performed successfully. This inspired Unger to perform another transplantation that same month, but this time monkey-to-human xenograft. The kidney was transplanted from an ape to a dying young woman from renal failure. The kidney never worked.

These early experiments demonstrated that technically kidney transplantation was possible, but the mechanism of rejection was not yet fully understood. Carrel in his famous lecture about the future of transplantation (1914) to the International Surgical Society mentioned that the works of his colleague at the Rockefeller center J.B. Murphy might seriously impact the development of the field. Murphy found that irradiation and benzol treatment increased the graft survival of cancer in mice. This observation inspired Carrel to conduct his own experiments, wherein he irradiated recipients and found prolonged graft survival, but these experiments were never formally published[11].

The period of the 1930s and 1940s was rather stagnant compared to the beginning of the century. European surgical centers that studied transplantology before were in decline. Mayo Clinic in the US was conducting some cautious experiments without considering Carrel's works and attempts at immunosuppression.[13] However, there was a notable event during this period - the first human-to-human transplantation. It was performed by Yurii Voronyi (in literature for some reason he is referred to as Voronoy) on March 3, 1933, in Kherson, Ukraine. The recipient was a 26-year-old woman admitted to the hospital on March 3, 1933, with mercury chloride poisoning induced by a suicide attempt the previous day that resulted in acute renal failure. Transplantation seemed the only viable option. It was known from previous experiments by other scientists that no xenograft ever was successful so human-to-human transplantation was the only feasible choice. The option of injuring a living person by organ removal was not even considered. It was known from the physiology that kidneys save their function a couple of hours after the reperfusion with ringer-solution and that organs keep some sterility a couple of hours after the host's death. So temporary cadaver transplantation until the woman's own kidneys would regenerate seemed to be a reasonable option. The transplantation was performed to the thigh's artery and vein using Carrel's seam with some modifications. After some time the kidney started to produce urine for a while but then eventually the allograft failed and 48 hours after the surgery the patient dies. The reason for graft failure was blood group mismatch and too long warm ischemia time - 6 hours, so the kidney began to degrade, resulting in an immune reaction to dead kidney cells and kidney blood cells. Voronyi performed another 5 such transplantations, which he considered as a bridge therapy until the recipient's own kidneys would recover. Kidneys produced urine for different durations from 1 to 7 days with 2 patients eventually recovering and living normally thereafter[12].

2.2.3 First Successes

In 1946, at the Peter Bent Brigham Hospital in Boston, a group of surgeons: Hufnagel, Hume, and Landsteiner performed kidney transplantation under local anesthetic on the arm vessels. The short period of kidney functioning may have helped the patient to recover from acute renal failure. It ignited the hospital's interest in renal transplantation.

Simonsen in Denmark, Dempster in London, and Küss in Paris concluded that it is preferable to place the kidney in the pelvis. Further, both Simonsen and Dempster deduced that the immune response was responsible for graft failure and both hypothesized that the humoral mechanism of rejection was probable.

In the early 1950s, two groups of surgeons based in Paris and Chicago performed pelvic kidney transplants without immunosuppression. In Paris, Jean Hamburger reported the first live-related kidney

transplant between a mother and her child. the transplanted kidney began to function immediately. It functioned for 22 days until it was rejected.

A series of nine transplantations with the thigh position of the allograft was closely studied in Boston and the first usage of hemodialysis for the preparation was recorded in Boston by David Hume in 1953. In some of these cases, mild successes were achieved using the adrenocorticotrophic hormone (more known as cortisone). It was hypothesized that the endogenous immunosuppression of uremia was responsible for the results rather than the drug regimen. Hume's findings were substantial as he concluded that prior blood transfusions, blood group matching between the donor and recipient, and host bilateral nephrectomy could be beneficial for the success of the transplant. These conclusions were later confirmed by subsequent studies.

These attempts in the early 1950s taught technical aspects of kidney transplantation and with increased confidence on December 23, 1954 in Boston Joseph Murray performed kidney allograft from one identical twin to another, bypassing the rejection barrier. From that time many similar surgeries were performed in Boston. This caused a lot of talks and predictions but all of them were negated when one of such recipients got pregnant and gave birth to a completely normal infant. However, in retrospective, it didn't bring anything new scientifically, because the technical possibility of kidney transplantation was evident and the cases of successful skin allografts between identical twins were known for decades, but nonetheless it was an important milestone that aroused the interest in further experiments [14, 4].

2.2.4 Attempts in Immunosuppression

In 1948 at Mayo Clinic patients handicapped by rheumatoid arthritis were given already mentioned cortisone, adrenal cortical hormone with mild immunosuppressive properties, that relieved their condition. This popularized the research on adrenal cortical hormones, but later it was concluded that the steroid effect was clinically insignificant for transplantation. After that, the experiments with irradiation, abandoned by Carrel and Murphy, were revitalized. Joan Main and Richmond Prehn showed that weakening of the immune system of adult mice by radiation and consequent skin and bone marrow transplantation from the same donor resulted in skin transplant acceptance. This encouraged teams in Boston and Paris to pursue the similar approach in humans.

In 1958, Murray's team transplantation on humans utilizing the Main-Prehn method conducted lethal total body irradiation (TBI) on two patients with additional bone marrow transplant. Ten more recipients were irradiated with sub-lethal TBI, but without donor bone marrow transplant. As a result 11 patients passed away within a month, the only survivor had sub-lethal TBI without transplanted bone marrow and he got kidney from his non-identical twin brother. This was rather revolutionary - for the first time kidney was not rejected from non-identical twin. The kidney functioned for 20 years. Jean Hamburger and his team performed another fraternal twin transplant utilizing the same irradiation technique. The transplant functioned for 26 years finishing with the recipient's death for rejection-unrelated reason.

Between 1960 and 1962 Kuss and Hamburger performed four successful transplantations between non-twin patients with following TBI. This gave promise that the transplantations could be done in non-twins and potentially between anybody. The research continued.

It was obvious that TBI is not the best choice and that it is necessary to find a substitution. In 1959, Schwarz and Dameshek from Tufts University published paper that described how an anticancer drug 6-mercaptopurine (6-MP) lowered immune response to foreign proteins in rabbits. Roy Calne, a training surgeon at Royal Free Hospital, London, dissatisfied with TBI in prolongation of kidney allograft survival in dogs, noticed Schwarz and Dameshek's paper and performed his own experiment in dogs and found that it significantly prolonged dog's survival. Charles Zukoski and David Hume found the same outcomes.

6-MP was used in three transplantations at Royal Free Hospital, but without success. However Kuss and associates reported one prolonged graft survival from a nonrelated donor. The TBI was main agent and intermittent usage of azathioprine and prednisone was used as an additional therapy.

Gertrude Elion and George Hitchings provided Roy Calne with the 6-MP derivative - azathioprine. Calne showed even longer graft survival with azathioprine. Both Elion and Hitchings were awarded with the Nobel Prize for the development of 6-MP and azathioprine. In 1961 Azathioprine became available for human use.

2.2.5 Gloom Then Revolution

In 1963 National Research Council organized a small conference consisting of 25 transplant clinicians and scientists to review the status of kidney transplantation at the moment. 'the discussion was quite depressive. Clinicians presented their results, that were rather discouraging: less than 10% of hundreds performed transplantations survived for more than three months, from patients with TBI only six got to the one year mark. Murray reported that from his first ten patients on 6-MP one survived for a year, others passed away within 6 months, so it was concluded that drugs were not more effective than radiation.

The gloom continued until Tom Starzl, until then unknown, did his presentation where he described his protocol that allowed graft survival for more than one year in 70% of cases. He was not believed at first, but then he showed medical records of his patients and he was eventually believed. The only thing that differed from other protocols with 6-MP was that addition of prednisone. This was a sensation. In the first year after the presentation, 50 new transplantation programs were founded in US alone. And his protocol became medical world standard for the next 20 years.

2.2.6 Plateau

During the period from 1964 to 1980 nothing groundbreaking had happened, although the steady development was seen. Dialysis became available and thanks to the accumulated experience the dosages became more precise. The brain death was accepted and the body was supported for a while to save organs for transplantation.

Hemodialysis for renal failure was created by Willem Kolff from Holland during WWII. But it couldn't be used for chronic renal failure until 1960 when was invented Teflon arteriovenous conduits for long-term vascular access.

Acceptance of brain death as a real death. Before the mid 60s the cadaver transplantation was limited by the ischemic damage. Now the additional organs were available from "heartbeating cadavers".

Cold for organ preservation. This was suggested in 1905 by Carrel's colleague Charles Guthrie. Initially, Starzl used total body hypothermia to protect donor organs, but by 1960 switched to infusing cold solution into the portal vein to protect donor livers. In 1963 the infusion of cold solution intravenous in the transplanted kidney has become a standard.

As the organ preservation for more than 6 hours was achieved in mid 60s the exchange of organs between centers has become practical. Initially sharing was local and informal, that roused the worry that the organs could be distributed unequally and that they could be transported outside of the US. This led to Congress passing the National Transplant Act in 1984. The Southeastern Organ Procurement Foundation (SEOPF), founded in 1969 and eventually composed of 12 hospitals in several cities, served as the template for the United Network of Organ Sharing (UNOS) that controls organ allocation and placement, monitors performance of transplant centers and organ procurement organizations, collects data, and controls quality. They kindly provided us with data for this paper.

2.2.7 Tissue Typing

Although tissue typing was suggested by Alexis Carrel in the beginning of 20th century it could not be proven and used until 1958 when Jean Dausset discovered the first human leukocyte antigen (HLA). Testing for antibodies was not reliable until 1964 when Paul Terasaki invented a microcytotoxicity assay. Test included mixing donor's lymphocytes and recipient's serum and quickly has become the standard and was named crossmatch. For a couple of years Terasaki performed typing for most of U.S. transplant centers and found a couple of observations: 1) Positive cross-match test predicts hyperacute rejection. 2) matching can reliably identify optimal donor within a family. It was assumed that the same would work for non-related recipients.

However, when in 1970 Terasaki reviewed his large database of cadaver renal allografts he found no correlation with the typing. This raised a lot of agitation in tissue typing community and his grant even was temporarily suspended until others didn't report the same. Now it is concluded that the

2.2.8 Antilymphocyte Serum

Next mark was cyclosporine, a fungal derivative with immunosuppressive properties discovered in 1976 by Jean-François Borel. It revolutionized the renal and extrarenal transplants, proving to be much better than the previous drug azathioprine. However it also had to be combined with prednisone to gain those results. It was used until 1989 when even more potent drug was discovered - Tacrolimus. It helps even when the cyclosporine with prednisone has no effect.

Tom Starzl discovered that donor leukocyte chimerism was present in patients who had maintained successful kidney or liver grafts for up to three decades.

chimerism is an important cause (not the consequence) of successful transplantation, successful engraftment is the result of the responses of coexisting donor and recipient cells each to the other causing reciprocal clonal exhaustion followed by peripheral clonal deletion

2.2.9 Conclusion and challenges of the field

The ultimate goal is immunosuppression without drugs because drugs are often toxic and the proper dosing might be tricky.

2.3 Immunology

The immune system is a sophisticated defense mechanism that evolved to protect multicellular organisms from pathogens such as bacteria, fungi, viruses, and parasites. It consists of many cells and tissues that compose a complex system that detects, evaluates, and responds to the invader. The immune system is divided into humoral and cell-mediated immunity. Humoral is mediated by soluble immunoglobulin proteins referred to as antibodies, while cell-mediated involves pathogen-specific T Lymphocytes that either destroy the invader or assist other cells in doing so. Both are essential for a complete immune response.

Lymphocyte is a type of white blood cell that is responsible for both humoral and cell-mediated immune responses. There are two types of lymphocytes: T lymphocytes (T cells) and B lymphocytes (B cells). B cells mediate humoral response by producing antigen-specific antibodies. An antigen is any molecular structure that binds to an antibody or specific surface T cell receptor, triggering an immune response. Once B-cell encountered an antigen it starts to produce antibodies specific to it, antibodies then bind to it, marking the invader for destruction. T cells when encountering an antigen start to proliferate

forming an army of T cells that will eliminate the invader and will form long-term memory about the pathogen.

Physical barriers: epithelia and mucous membranes constitute the first line of defense. To activate the immune system the pathogen must first breach physical barriers. The immune system categorizes pathogens by common characteristics and designs its response accordingly. Pathogen detection and categorization rely on the interaction between pathogen and T-cell receptors, as well as soluble antibodies. Binders for T cell receptors and antibodies can be the whole pathogen's body, its part, or molecules excreted by it.

Pathogens are recognized and categorized by molecular patterns that are associated with a particular pathogen and are referred to as pathogen-associated molecular patterns (PAMPs). Pathogen recognition receptors (PRRs), which are excreted by white blood cells, bind to PAMPs initiating the cascade of events that will mark a pathogen for destruction.

Pathogen-host interaction is a continuous arms race, as pathogens usually have a short life cycle and can modify their DNA to elude the host's recognition systems. The generation of diversity in developing cells is designed to combat this. When lymphocytes are developing in bone marrow random PRRs are generated, then cells are tested on non-reactivity to host cells. If the test is passed the cell is released into circulation. The principle of recognizing self vs. non-self is called tolerance.

There are two interconnected systems of response: innate and adaptive. Innate includes primitive built-in cellular and molecular mechanisms aimed at preventing infections and quickly demolishing common pathogens. It consists of physical and molecular barriers as well as PRRs that are encoded in DNA and therefore are inherited. Innate immunity provides a fast and effective response which however is not very specific and cannot differentiate small differences. Adaptive immunity is constituted by both humoral, where antibodies neutralize and eradicate extracellular microbes and toxins, and cell-mediated immunity, where T lymphocytes exterminate intracellular invaders.

Adaptive immunity is much slower but more able to recognize small differences. It typically starts to act within 5 to 6 days after initial exposure. Because it takes time to create an army of cells with specific receptors. After pathogen extermination, some of the lymphocytes with the specific receptor become memory cells, making it easier to fight this type of pathogen.[13]

In conclusion, the immune system is a complex network of molecules, cells, tissues, and organs that cooperate in protecting the organism from pathogens. The system can be divided into two main branches: innate and adaptive, which cooperate in protecting the host from infections while developing long-term immunity to specific pathogens. Understanding the mechanisms of the immune system is essential to understanding the domain of kidney transplantation.

2.4 Immunology of kidney transplant

The process of transplantation inevitably includes termination of blood flow, and, as a result, oxygenation. Therefore cell is unable to generate sufficient amount of energy to maintain homeostasis, leading to damage or death. Damage or death is associated with DAMP release that might be detected by both innate and adaptive immunity.

2.4.1 Immune system activation Peritransplant

The process of transplantation inevitably includes termination of blood flow, and, as a result, oxygenation. Therefore cell is unable to generate sufficient amount of energy to maintain homeostasis, leading to damage or death. Damage or death is associated with DAMP release that might be detected

by both innate and adaptive immunity. Mostly it is the ancient innate immunity that is activated with its soluble arm - complement system.

Damage Signals Many DAMPS are recognized by the same PRRs that mediate response to PAMPs. These DAMPS include molecules that are normally hidden from the immune system and are produced during ischemia, such as extracellular ATP, heat shock proteins (HSPs), uric acid, etc. Likewise, oxidative stress and decline in intracellular potassium may act as intracellular damage signals.

Complement Complement system is comprised of series of protein kinases that are sequentially activated resulting in membrane attack complex (MAC) formation. MAC include complement components C5 to C9, which are inserted into pathogen cell membrane resulting in compromising cell integrity leading to cell death.

There are three pathways of complement system activation: the classical pathway, the alternative pathway, and the mannose-binding lectin (MBL) pathway. The classical pathway is activated by IgM and IgG antibodies and participates in antibody-mediated rejection, that will be discussed further. Alternative complement is always active and therefore must be controlled by a regulatory proteins, to prevent inadequate responses. The MBL pathway is activated by damaged endothelium, a cell tissue that covers organs and vessels, and carbohydrates present on pathogens. Either pathway results in C3 convertase that cleaves C3. This cleavage leads to a cascade of reactions that culminate in MAC formation.

Long ischemia time results in endothelial cell damage that is associated with ischemia-reperfusion injury (IRI). IRI activates MBL and alternative complement pathways.

Gene silencing using small interfering RNA (siRNA) might be a promising instrument in organ transplantation, because it can be applied to an allograft during cold reperfusion and it has been shown to mitigate IRI in animal models. Other strategies of suppressing local complement activation would also be useful.

2.4.2 Stimulation of Adaptive Alloimmunity

Immune response to a graft occurs in two main stages: afferent and efferent arms. In afferent stage, recipient lymphocytes are stimulated by donor antigens and start to proliferate and send signals to other cells. In efferent arm, leukocytes migrate to the transplanted organ and donor specific antibodies are produced.

For the immune system to be activated graft must express antigens that will be considered by the host's immune system as foreign. These include ABO antigens, human leukocyte antigens (HLA), and polymorphic non-HLA "auto-antigens".

ABO Blood Group Antigens

ABO system is used to group blood into groups, based on presence or absence of antigens on a blood cell surface. There are four major blood groups: A, B, O and AB.[7]

When allocating an organ to transplant the first thing that is considered is ABO blood group antigens compatibility. ABO antigens are expressed almost by any cell in the allograft, and if the transplantation to be carried out in ABO-incompatible donor and recipient it would result in a hyperacute antibody-mediated rejection.

Donors with blood group O are so called "universal donors". Organs from them can be safely transplanted to recipients with any ABO blood group. Whereas, recipient with AB group can safely receive organ from recipient with any ABO blood group and is called a "universal recipient".[9]

Table 2.1: MHC class division

MHC class I	MHC class II
HLA-A	HLA-DR
HLA-B	HLA-DP
HLA-C	HLA-DQ

HLA

Histocompatibility antigens are genetically encoded antigens that cover cell surfaces. They differ between individuals of the same species and therefore trigger an immune response in case of allograft. In all vertebrates histocompatibility antigens are divided into single major histocompatibility complex (MHC) and numerous minor histocompatibility (miH) systems. In case of either MHC or miH incompatibility the result is an immune response to the graft, more severe in case of MHC than miH. Rejection in MHC-compatible donor-recipient pair is usually delayed, in some cases forever. Although, sometimes miH mismatch might be so severe that it would be comparable to full MHC mismatch.

MHC antigens are proteins that cover cell surfaces to help the immune system to recognize self vs. non-self. Major histocompatibility complex is divided into MHC class I and MHC class II. MHC class I cover surfaces of most cells and are liable for activation of cytotoxic CD8 cells, that help to find and destroy infected cells. MHC class II are found on certain immune cells and play crucial role in immune response coordination. In humans MHC class I are divided into three subgroups each, as can be seen on table

In clinical practice, clinicians assess and try to match donors and recipient according to the number of HLA-A, -B, and -DR mismatches, ranging from zero mismatches (0-0-0) to a maximum of 6 mismatches (2-2-2). Generally more emphasis is placed on DR loci due to capability of CD4 T cell activation, which might trigger both humoral and cellular adaptive immune responses.

Minor histocompatibility proteins can act as antigens, although weaker than MHC. However if prior sensitisation exists it could result in severe immune response that might result in graft loss.

2.4.3 T Cell-mediated rejection

T cell-mediated rejection or TCMR is the most common type of allograft rejection, as it still happens in 20% of transplantations mostly within first 6 months posttransplant. Immune system cells migrate through vessels to the graft, become activated and start to attack the organ. Complement may also play role in it.

2.4.4 B Cell-mediated rejection

B cells are immune system cells that produce antibodies. Alloantibodies are antibodies that react to donor-specific HLA antigens and might cause hyperacute rejection, acute antibody-mediated rejection (ABMR), and chronic ABMR. About 30% of patients have sensitivities and have certain HLA antibodies. It might cease transplantation or require antibody suppression strategy. Even low amount of antibodies below crossmatch cutoff doubles the risk of ABMR and increases the risk of graft failure by 76%. Additionally, donor specific antibodies might develop posttransplant and cause an acute ABMR.

Acute AMBR is rarely seen in patients without prior sensitization and is highly difficult to treat. AMBR is characterized by decline in allograft function, presence of DSA and signs of acute vascular injury. A progressive reduction in graft function over time is observed almost universally.

2.4.5 Transplant Tolerance

Taking into account the detrimental effect of long-term immunosuppression one of the primary objectives in transplantation is the induction of immunologic non-responsiveness (tolerance) to an allograft. There are a couple of pathways of immune non-responsiveness generation described in literature, however it hasn't gone further in animal models yet.

2.4.6 Factors Influencing Rejection Beyond the Graft - Microbiome

Human body is a very complex system where every subsystem influences other subsystems and the whole system in general. It is clear that gut microbiome has a profound influence on the immune system. It is possible that microflora on the allograft might cause rejection. Immunosuppression, prophylactic antibiotics, diet changes and other restrictions associated with organ transplantation result in a decrease in gut microbiome diversity that results in systematic inflammation, that might contribute to alloimmunity, as well as autoimmunity.

2.5 Conclusion

Chapter 3

Machine Learning Background

Machine learning is a subfield of computer science that consists of building algorithms capable of processing large amounts of data, finding patterns, and performing actions such as predictions or generating new data. Machine learning is an intersection of many fields of science, such as statistics, the theory of probability, linear algebra, calculus, and, of course, computer science.

Machine learning excels in problems that are either overly complex or have no known algorithm.[9] It can help us learn. We can extract previously unknown correlations from the data and create knowledge. It might have fewer errors in decision-making than humans.

Based on the problem and, therefore, on our approach to building a dataset and the model, machine learning can be divided into four sub-fields: *supervised*, *semi-supervised*, *unsupervised*, and *reinforcement learning*. *Supervised learning* means that data are labeled, and we want to predict labels from the unlabeled data. What is labeled data is explained in the following section dedicated to supervised learning. Unsupervised learning deals with unlabeled data.

Semi-supervised learning deals with partially labeled data, and we need to label the rest of them either manually, or using techniques such as *clustering*.

In *reinforcement learning*, we create an environment, set up rewards for performing certain actions and punishment for others, and let the machine (actor) perform actions that produce the highest reward.

Every field suffers from human errors, and medicine is no exception. Machine learning also makes mistakes, but if we manage to get at least 1% less error than human error, this will be a success. The human body is a complex system it is very hard to comprehend everything happening and how it relates to each other. Also, it can help us gain insights from accumulated data and make discoveries.

In this chapter, we will cover all theoretical backgrounds that might prove useful for solving our problem, including classical machine learning, deep learning, statistical survival analysis, basic steps that are required to create machine learning systems, and how to preprocess data. We will begin by exploring supervised learning.

3.1 Supervised Learning

Supervised learning is the process of training a model on data where the outcome is known to make predictions for data where the outcome is not known[12]. *Classification* and *regression* are common supervised learning tasks. In this section we will define these problems, necessary terminology and describe commonly used algorithms that are used to solve these types of problems.

In supervised learning the *dataset* is the collection of labeled examples $\{(\bar{x}_i, y_i)\}_{i=1}^N$, where each individual \bar{x}_i is called a *feature vector*. A feature vector is a vector that in each its dimension $j = 1, \dots, D$ contains a value that describes an example in some way. This value is called a *feature* and is denoted as

$x^{(j)}$. The *label* y^i might be either a finite set of classes $\{1, 2, \dots, C\}$, in case of classification task, or a real number, a vector, a matrix or graph, in case of a regression. The goal of supervised learning algorithm is to create a model using the dataset that will take the feature vector as input and produce label or more complex structure as an output.

Classification is a problem of assigning a label to unlabeled example. This problem is solved by a classification learning algorithm that takes a labeled set of examples as an input and produces a model that takes unlabeled example as input and outputs a label, a number associated with it or a probability of belonging to a certain class out of which it is easy to deduce the class. If the set of labels has only two classes we talk about *binary classification*. Consequently, if the set of labels has three or more classes it is a *multiclass classification*. Some algorithms are binary classifiers by definition, while others are multiclass classifiers. It is possible to create an *ensemble* out of binary classifiers that will be able to perform multiclass classification. Ensemble is a combination of algorithms that are connected together to perform one task. More on that in subsection 3.1.5 talking about random forests.

Regression is a problem of predicting a *target value* given an unlabeled example. The problem is solved by regression learning algorithm that takes a set of labeled examples as inputs and produces a model that takes unlabeled example as input and outputs a target value.

In the following subsections we are going to explore some techniques for supervised learning. Classification and regression tasks are similar in many ways and often for each classifier there is an equivalent regressor, and vice versa. More on that in the following sections.

3.1.1 Performance Metrics

- mean square error (MSE)
- confusion matrix
- precision/recall
- area under the ROC curve

3.1.2 Linear Regression

Linear regression is a popular regression learning algorithm. The model it produces is a linear combination of all features.

The problem formulation we are trying to solve is as follows: Given a collection of labeled examples $\{(\bar{x}_i, y_i)\}_{i=1}^N$, create a model

$$f_{\bar{w},b}(\bar{x}) = \bar{w}\bar{x} + b \quad (3.1)$$

. Where N is the size of the collection, \bar{x}_i is a *feature vector* of D dimensions of example $i = 1, \dots, N$, every feature $x_i^{(j)} \in \mathbb{R}$, $y_i \in \mathbb{R}$ is the target value. \bar{w} is a D -dimensional vector of parameters and $b \in \mathbb{R}$. Notation $f_{\bar{w},b}(\bar{x})$ means that f is parametrized by \bar{w} and b .

To train the linear regression means to find optimal values (\bar{w}^*, b^*) of parameters \bar{w} and b so that the model makes as accurate predictions as possible. In graphical terms, it means finding such a hyperplane that fits data points from the training set as well as possible, as can be seen in image 3.1.

To find optimal parameters we need to minimize the following expression:

$$\frac{1}{N} \sum_{i=1 \dots N} (f_{\bar{w},b}(\bar{x}_i) - y_i)^2. \quad (3.2)$$

It is called *mean squared error (MSE)*, the *loss function* that comprises of *squared error loss* $(f_{\bar{w},b}(\bar{x}_i) - y_i)^2$, another loss function that evaluates individual predictions. The loss function measures model's overall performance (MSE) or evaluates each prediction (square error loss).

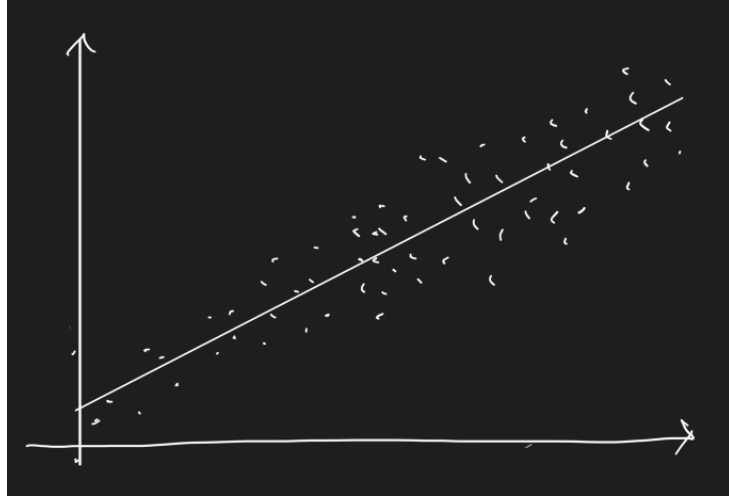


Figure 3.1: Linear regression for two-dimensional data

There is a *closed-form solution* for finding the optimal values (\bar{w}^*, b^*) . A closed-form solution is a simple algebraic expression that gives the result directly. In the case of linear regression, it is the *normal equation*, and it looks like the following:

$$\bar{\mathbf{w}}^* = (\mathbf{x}^T \mathbf{x})^{-1} \mathbf{x}^T \mathbf{y}. \quad (3.3)$$

Where x^T means transposed feature matrix x .

We could select another loss function, but according to Andriy Burkov, it would be a different algorithm. For example, we could take the absolute difference between $f(x_i)$ and y_i . But that would create problems as the derivative of absolute value is not continuous, and therefore the function is not smooth. Non-smooth functions create unnecessary complications during the optimization process.

Linear models are usually resilient to overfitting because they are simple. Overfitting is when the model learns the intricacies of the training dataset so well that it remembers actual values rather than learn underlying pattern. Overfit model is unable to make accurate predictions when confronted with the unseen data. More on overfitting in section 3.6.

3.1.3 Logistic Regression

Logistic regression is a binary classifier that estimates the probability of an example belonging to a particular class. If the predicted probability of the instance belonging to a class is greater than 50%, then the model concludes that it does belong to the class (referred to as positive class and labeled as 1). Otherwise, it predicts that the example does not belong to that class (but belongs to the negative class, labeled 0). Logistic regression comes from statistics, where its mathematical formulation is similar to a regression, hence the name. Multiclass classification is available in softmax regression, a multiclass variant of logistic regression.

As with linear regression, in logistic regression, we want to model y as a linear combination of \bar{x} , but in this case, it is not that straightforward.

The logistic regression model looks like the following:

$$f_{\bar{w}, b}(\bar{x}) \stackrel{\text{def}}{=} \frac{1}{1 + e^{-(w\bar{x} + b)}}. \quad (3.4)$$

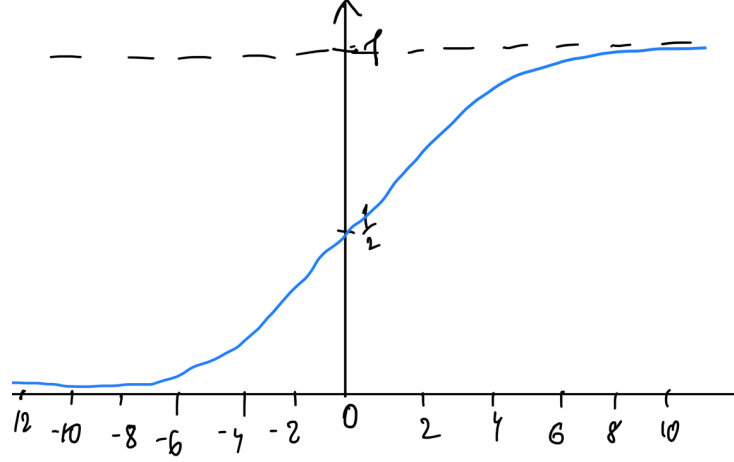


Figure 3.2: Logistic function

Similar to linear regression, our task is to find optimal values (\bar{w}^*, b^*) for parameters \bar{w} and b .

Once we found (\bar{w}^*, b^*) for the 3.4, in other words, we trained the model, we can apply the model 3.4 on features x_i from an example (x_i, y_i) . The output value lies in range $0 < p < 1$. If y_i is a positive class, the probability of being a positive class is given by p . If it is negative, the probability is given by $1 - p$.

In the figure we can see that if the y has a value less than $\frac{1}{2}$ it has negative x values and will be marked as negative and positive if it is greater than $\frac{1}{2}$. Although, the threshold may be different, depending on the context.

Instead of *minimizing* MSE, in logistic regression, we are trying to *maximize* the *likelihood function*. In statistics, the likelihood function tells how likely the example is according to our model. The objective function in logistic regression is called *maximum likelihood*. It looks like the following:

$$L_{\bar{w}, b} \stackrel{\text{def}}{=} \prod_{i=1 \dots N} f_{\bar{w}, b}(\bar{x}_i)^{y_i} (1 - f_{\bar{w}, b}(\bar{x}_i))^{(1-y_i)}. \quad (3.5)$$

Because of the exponential function in 3.5, it is better to use the *log-likelihood* instead to make calculations easier. As *Log* is a strictly increasing function, maximizing it is the same as maximizing its argument. The solution to this optimization problem is the same as the solution to the original problem. The log-likelihood function looks like the following:

$$\text{Log} L_{\bar{w}, b} \stackrel{\text{def}}{=} \ln(L_{\bar{w}, b}(\bar{x})) = \sum_{i=1}^N y_i \ln f_{\bar{w}, b}(\bar{x}) + (1 - y_i) \ln(1 - f_{\bar{w}, b}(\bar{x})). \quad (3.6)$$

Unfortunately, there is no closed-form solution for this optimization problem. But the function is convex, so gradient descent (or any other optimization algorithm) more or less guarantees the finding of the global minimum, provided not too large a learning rate and given enough time.

3.1.4 Support Vector Machines

Support vector machine (SVM) is a widely-used and powerful machine learning algorithm that can perform a wide range of tasks, including linear and nonlinear classification, regression, and outlier detection on small- to medium-sized datasets.

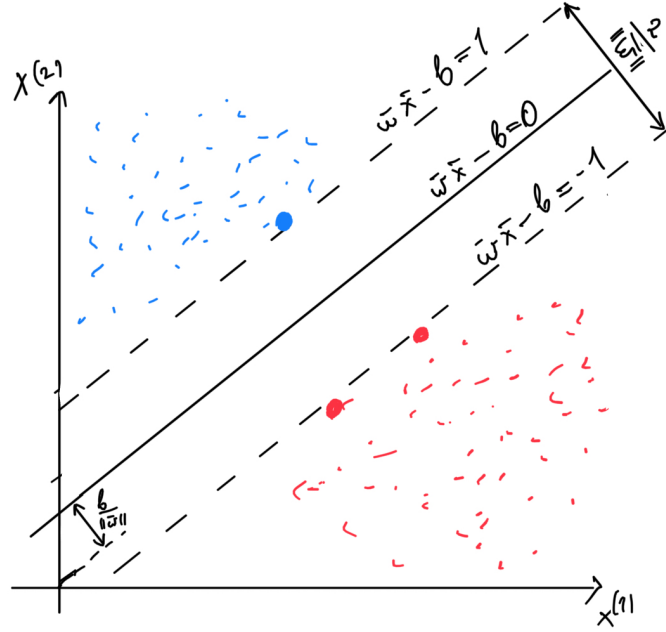


Figure 3.3: SVM demonstration for two-dimensional dataset

Linear SVM

In its classical formulation, the support vector machine is a binary classifier. Classes are called positive and negative and are labeled +1 and -1, respectively.

The model is described by the equation

$$f(x) = \text{sign}(\bar{w}x - b).$$

The function *sign* returns +1 if the input is positive, and -1 if it is negative. Train the SVM means to find optimal values (\bar{w}^*, b^*) of parameters \bar{w} and b so that the model makes as accurate predictions as possible. The process of finding (\bar{w}^*, b^*) is called training.

The concept behind support vector machines is demonstrated in Figure 3.3. The image consists of two classes represented by the red and blue dots, divided by a solid line termed the *decision boundary* $\bar{w}x - b = 0$ with two dashed lines by its sides known as *support vectors* $\bar{w}x - b = 1$ and $\bar{w}x - b = -1$. Support vectors are defined by the closest instances of a class to the decision boundary. These instances are emphasized in the figure.

The distance between the closest instances of two classes is called *margin* and is equal to $\frac{2}{\|\bar{w}\|}$, where $\|\bar{w}\|$ is the Euclidean norm and \bar{w} is a parameter vector of the same dimensionality as the feature vector. So the smaller the norm, the larger the margin is. The larger the margin, the better model generalizes. The primary objective of the model is to find the largest possible margin $\frac{2}{\|\bar{w}\|}$, so, to do that we need to *minimize* the Euclidean norm defined by the expression

$$\|\bar{w}\| = \sqrt{\sum_{j=1}^D (w^{(j)})^2}.$$

The fundamental assumption of support vector machines is that classes are linearly separable, implying their instances can be separated by a hyperplane (decision boundary) with no examples of one class

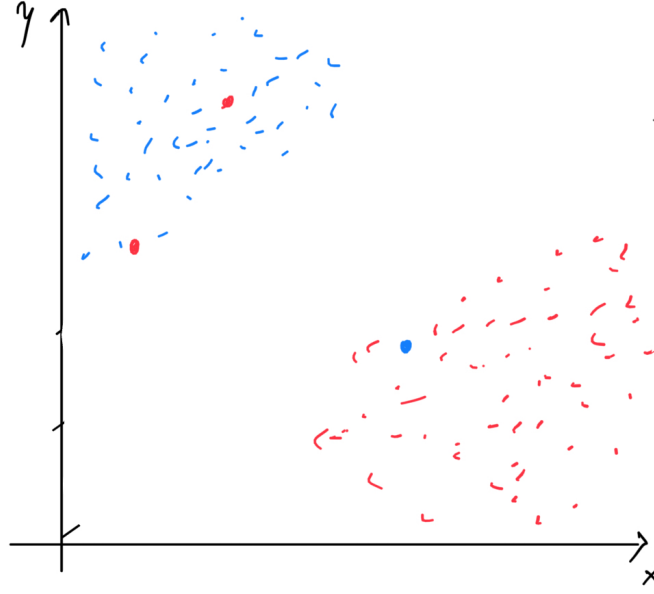


Figure 3.4: Linearly non separable dataset

lying among the ones of the opposite class. It is illustrated in the figure 3.4. In this case, the algorithm won't be able to find an optimal solution with no instances lying between the support vectors and the decision boundary. Consequently, the model is highly sensitive to outliers.

Every optimization problem requires constraints, and for the support vector machine, they are the following:

1. $\overline{wx}_i - b \geq +1$ if $y_i = +1$
2. $\overline{wx}_i - b \leq -1$ if $y_i = -1$.

These two equations can be reduced to one $y_i(\overline{wx} - b) \geq 1$.

The optimization problem we want to solve is the following: Minimize $\|\overline{w}\|$ subject to constraint $y_i(\overline{wx}_i - b) \geq 1$ for $i = 1, \dots, N$, where N is the number of features. This problem can be modified so that the quadratic programming techniques could be used in the optimization process. The modified formula is $\frac{1}{2}\|\overline{w}\|^2$, and minimization of it would also mean minimization of $\|\overline{w}\|$. The updated optimization problem looks like this:

$$\min \frac{1}{2}\|\overline{w}\|^2 \text{ such that } y_i(\overline{wx}_i - b) \geq 1, i = 1, \dots, N \quad (3.7)$$

Handling Noise

To introduce the ability of SVM to handle nonlinearly separable data (but not to the extreme), we define the hinge loss function: $\max(0, 1 - y_i(\overline{wx}_i - b))$. It is zero if the constraints 1 and 2 are satisfied. If it is not, the data point does not lie on the right side of the decision boundary. The function value is proportional to the distance from the decision boundary. The resulting cost function looks like the following:

$$C\|\bar{w}\|^2 + \frac{1}{N} \sum_{j=1}^N \max(0, 1 - y_i(\bar{w}x_i - b)), \quad (3.8)$$

where C is the hyperparameter that determines the tradeoff between increasing the size of the decision boundary and ensuring that each x_i lies on the correct side of the decision boundary. Its value is chosen experimentally. C handles the tradeoff between classifying the training data well and classifying future examples well (generalization). For higher values of C , the misclassification error will be almost negligible, so the algorithm will try to find the highest margin without considering it. For lower values of C , the algorithm will try to make fewer mistakes by sacrificing the margin size. A larger margin is better for the generalization. (Smaller values lead to wider streets and more margin violations, larger values lead to narrower streets and fewer margin violations.)

SVM with the hinge loss function is called *soft-margin SVM*, while the original formulation that optimizes the Euclidian norm is referred to as *hard-margin SVM*. *Soft margin classification* tries to mitigate the downsides of the *hard margin classification* by trying to find a balance between keeping the margin as large as possible and mitigating the margin outliers (instances that lie on the margin or the opposite side).

Handling Non-linearity

We can adapt SVM to work with nonlinearly separable datasets by applying the kernel trick. The kernel trick means transforming the original space to a higher dimensional one during the cost function optimization with the hope that, in higher dimensional space, it will become linearly separable. In mathematical language: the kernel trick is mapping $\varphi : \bar{x} \rightarrow \varphi(\bar{x})$, where $\varphi(\bar{x})$ is a vector of higher dimensionality than \bar{x} . The kernel trick allows us to save a lot of non-necessary computations.

There are multiple kernel functions. The most widely used are linear, polynomial, radial basis function (RBF),

3.1.5 Decision Trees and Random Forests

- highly interpretable model
- builds trees that can be visualized and show the model's reasoning
- The concept of an ensemble:
- Stacking:
- (some other technique)
- Base learner of the random forest:
- How it all works together:
- Benefits: potentially interpretable model.

3.2 Unsupervised Learning

Unsupervised learning deals with a dataset that does not have labels. It proves useful during *exploratory data analysis (EDA)*, *dimensionality reduction*, and *anomaly detection*.

I will cover this part briefly, as it is not closely related to our task. Although, certain elements might be used during exploratory data analysis or a data preprocessing step.

There are three main branches of supervised learning: clustering, dimensionality reduction, and anomaly detection. Clustering is a method that identifies similar instances and groups them into groups of similar instances - clusters. It has applications in data analysis, customer segmentation, dimensionality

reduction, and anomaly detection. Clustering might be either soft, where an instance has a score of belonging to a particular cluster, or hard, where an instance belongs to only one class. The score might be the distance from the cluster centroid or an affinity (similarity score).

Dimensionality reduction is useful for visualization and for acceleration of learning. Datasets often have a lot of redundant data or it might be the case that the task requires a lot of features. A lot of algorithms, such as linear model, SVMs, decision trees, might have its performance compromised due to high-dimensional data. So called *curse of dimensionality* states that high dimensional data can cause slow learning and prevent us from getting an optimal model. Consequently, the reduction of the data dimensionality might be a good idea. However, it is worth noting that dimensionality reduction algorithm might loose some useful information. A lot of modern algorithms, such as neural networks or ensemble algorithms, handle high dimensional data very well, and dimensionality reduction techniques are used less than in the past. However, they are still used for data visualization and for cases when we need to build an interpretable model, while we are limited in number of algorithms we can use.

Anomaly (outlier) detection involves the detection of instances strongly deviating from the norm. These instances are called *outliers* or anomalies, while regular ones are referred to as *inliers*. Anomaly detection is useful in many applications. It can be used as a data preprocessing step - to remove outliers from the dataset, which might improve the performance of the resulting model. Also, it can be used in the *fraud detection* task and the detection of faulty products in manufacturing facilities.

Novelty detection is a closely related task to anomaly detection. The only thing different about them is that novelty detection assumes that the dataset, the model was trained on, was not contaminated by outliers, while anomaly detection does not make this assumption.

3.2.1 KMeans

Finding optimal numbers of clusters:

Advantages of kmeans

Limitations of KMeans:

3.2.2 Principal Component Analysis (PCA)

Principal components are vectors that define a new coordinate system. The first vector goes in the direction of the highest variance. The second vector is orthogonal to the first one and goes in the direction of the second highest variance, and so on. If we were to reduce dimensionality to $D_{new} < D$, we would pick D_{new} largest principal components and *project* instances onto them.

(Create images)

It is not advised to choose the number of dimensions arbitrarily. Usually, such a number of dimensions is chosen that preserves a large amount of variance (e.g. 95%), or in the case of visualization we reduce the number of dimensions down to 2 or 3. There are different versions of PCA; kernel PCA, Incremental PCA (online or batch PCA), and Randomized PCA. But covering those lies beyond this paper.

3.2.3 Gaussian Mixtures

Gaussian mixtures is a common algorithm that can be used for anomaly detection. Gaussian Mixtures assume that the dataset is generated by several Gaussian distributions. Any instance lying in a region of low density is an anomaly. The density threshold has to be specified. If one gets too many false positives (good products labeled as faulty) they need to decrease the threshold. Consequently, if we get too many false negatives (faulty products labeled as good) the threshold has to be increased. Gaussian mixtures

belong to soft clustering. Gaussian mixtures require the number of clusters to be specified. It needs to be run a couple of times to avoid suboptimal solutions.

3.3 Data Preparation

Due to factors such as the curse of dimensionality and inherent noise, we cannot load raw data to an algorithm and expect good performance. More often than not, the raw data has too many features, and most of them have very little predictive power. We need to build a dataset first. *Feature engineering* is responsible for transforming raw data into a dataset. It is a labor-demanding process that requires creativity and, most importantly, domain knowledge.

The objective of this stage is to create *informative* features or features with *high predictive power*. For example, in our task of predicting survival time, donor-recipient blood group compatibility or recipient age is likely to have much higher predictive power than the donor's or recipient's citizenship.

Moreover, it is possible to create new features with higher predictive power out of those with low predictive power. For example, the calculation of the *estimated Glomerular Filtration Rate (eGFR)*, the metric of kidney function estimated on a patient's age, gender, and serum creatinine level, could potentially give more information to the learning algorithm than all those features separately.

In the following subsections, we will cover some popular feature engineering techniques.

3.3.1 Handling Categorical Features

The majority of machine learning algorithms primarily operate with numerical features. To handle categorical features (the ones with only a couple of possible values), such as age group or blood group, we can use *one-hot encoding* to convert it to several binary ones. For instance, consider four primary blood groups: A, B, AB, and O. We can convert a single feature into a vector of four numerical values:

$$A = [1, 0, 0, 0]$$

$$B = [0, 1, 0, 0]$$

$$AB = [0, 0, 1, 0]$$

$$O = [0, 0, 0, 1]$$

This technique will increase the dimensionality of the dataset, but this is a trade-off we have to make. Because if we were to assign a number to each group (1 to A, 2 to B, etc.), that would imply gradation or ranking among these categories, while there is none.

However, if the categorical feature does suggest some gradation, for example, university marks as "fail", "average", "good", or "excellent", an enumeration of each value would be appropriate. This practice of assigning a number to categories that have ranking is called *ordinal encoding*.

Binning (or *bucketing*) is the technique used for converting numerical values into multiple binary features, called *bins* or *buckets*. For example, a patient's age can be transformed into age-range bins: 0 to 18 years old, 18 to 25 y.o., 25 to 40 years old, and so on. This technique might help an algorithm to learn better, particularly with smaller datasets.

3.3.2 Feature Scaling

Different ranges of feature values might pose a problem to some machine learning algorithms, as they don't handle them very well. It might result in slowed training time or worse performance. This problem is solved by *normalization* and *standartization* scaling techniques.

Normalization (also known as *min-max scaling*) is a technique of converting an actual range of numerical feature values into a standard range of values: $[-1, 1]$ or $[0, 1]$ without losing any information. The normalization formula for value $x^{(j)}$ for feature j , looks like following:

$$\bar{x}^{(j)} = \frac{x^{(j)} - \min(j)}{\max(j) - \min(j)},$$

where $\min(j)$ and $\max(j)$ are minimal and maximal values of feature j .

Standardization is a scaling technique that scales numerical data in such a way that after scaling it has properties of *standard normal distribution* with the mean μ (average value) equal to zero and the standard deviation from the mean σ equal to 1. The standardization formula for value $x^{(j)}$ for feature j , looks like following:

$$\hat{x}^{(j)} = \frac{x^{(j)} - \mu^{(j)}}{\sigma^{(j)}}.$$

Typically, standardization is used for supervised learning (it works better with standardization), in case, feature values are formed by standard distribution (bell-curve) or feature has outliers. In other cases normalization is preferred.

3.3.3 Handling missing feature values

Datasets frequently have missing values, and to handle them, we have one of the following options:

1. **Removal of rows with missing values.** The most direct and straightforward approach to managing missing data. If missing values are sparse or the dataset is large enough, the usage of this technique would be appropriate.
2. **Feature removal.** If the dataset has an excessive amount of missing values relative to its size, it is better to remove the feature altogether.
3. **Regression imputation.** Imputation means filling in the missing value. Using machine learning regression algorithm to predict missing feature values.
4. **Mean/median imputation.** This method involves filling missing feature values with their mean or median value.
5. **Constant value imputation.** This technique entails filling missing values with clearly too-high or too-low values. The motivation is for the algorithm to discern the value as an outlier while considering other features. This method is not recommended, as it can introduce bias.

It is often impossible to tell which data imputation method would work the best and it should be checked experimentally.

3.4 Model Training and Hyperparameter Tuning

It is a common practice to divide the data set into three parts

- Training set (constitutes about 70% of the dataset)
- Validation set (15% of the dataset)
- Test set (15% of the dataset)

The training set, being the largest of them, is employed to train the machine learning model. Validation and test sets, which are of identical sizes and often called hold-out sets, are used in subsequent stages of model evaluation.

The rationale behind the use of separate training and validation sets is to prevent overfitting - a situation when the model performs well on training data but poorly on unseen data. Overfitting can occur if the model is tested and evaluated on the same dataset. As a result, the model may memorize the training examples and fail to make accurate predictions on unseen data. To alleviate this, we use the validation set to fine-tune the model and the test set to assess its performance before deploying it to production.

A typical workflow involves training the model on the training set, validation on the validation set using the selected metric, then adjusting the model's parameters to improve its performance. This process is repeated until no substantial improvement is observed. Finally, the model's performance is assessed on the test set. This iterative process is referred to as hyperparameter tuning.

An alternative to the three-sets technique is k-fold cross-validation. This technique involves splitting the dataset into k subsets, or folds, of equal size. One fold is used as a validation set, while the other k-1 folds constitute a training set. The model is trained exactly k times, with each fold serving as a validation set only once. The only drawback is that it is highly computationally expensive, particularly with a high k value and larger datasets, as the model will be trained k times.

A hyperparameter is a parameter specified before model training, in contrast to regular parameters, that are calculated during training. Each model possesses a different set of hyperparameters, and they profoundly influence the model's performance. For example, the number of trees in Random Forest or the C hyperparameter in Support Vector Machines. The task of finding the optimal combination of hyperparameters is called hyperparameter tuning. One strategy would be manually select hyperparameters and observe their impact on performance. However, a better way is to utilize grid search.

Grid search is a standard way of performing hyperparameter fine-tuning. It includes defining hyperparameters to experiment with, providing values for each hyperparameter to be tested, and training a model for each possible combination of hyperparameters. The performance of each individual model is assessed using k-fold cross-validation, and the best combination of hyperparameters is selected. This approach is used in sci-kit-learn's implementation - GridSearchCV.

Grid search proves to be effective when dealing with relatively few hyperparameter combinations. However, with larger number of hyperparameter combinations, it is advisable to use RandomizedSearch (RandomizedSearchCV in sci-kit-learn). This method is very similar to grid search, but instead of trying every possible combination of provided values, it tests only a specified number of randomly selected hyperparameter combinations. This method's primary advantage over grid search lies in more control over computational power and the time one wants to dedicate to hyperparameter tuning.

3.5 Survival Analysis

Definition: *Survival analysis*, also known as *time-to-event analysis*, is a statistical method used to analyze the time until an event of interest occurs. Its name originates from the clinical and biological research, where these methods are used mostly to analyze survival time, hence the name. These methods, however, found their uses in areas far beyond clinical setting: in business to analyze the time until the customer "churns" from a subscription, in engineering, to estimate the longevity of certain products, or its parts. In social sciences, estimate the longevity of a marriage or a student dropout rate in academic setting.

Censoring: The most pronounced feature of these methods is the ability to handle censored data. Censoring is a situation when the information about the survival time is known only partially. For exam-

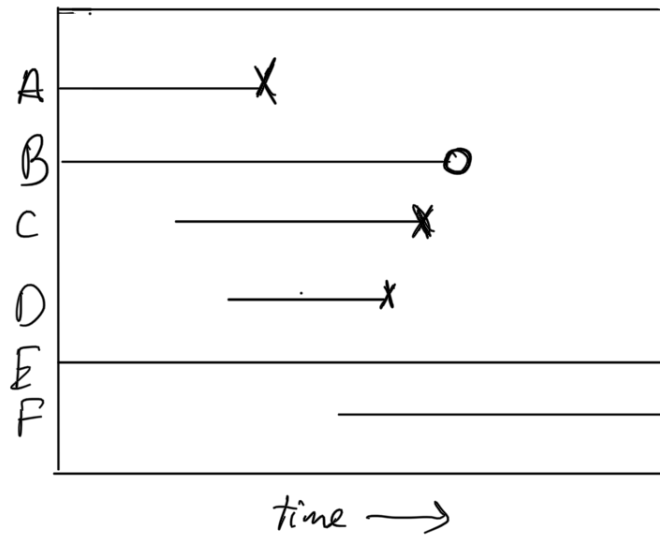


Figure 3.5: caption

ple, in the dataset used in this work there are (**number of patients**) that were still alive until last date of observation (**date of observation**). And we do not know what happened to them after that date — they are censored.

Look at the figure 3.5. On the y axis we can see individual patients. x axis corresponds to timeline of the study (right side is the end of the study). Cross (X) denotes an occurrence of the event, circle (O) corresponds to subject's exit from the study.

Left and right censoring: There are two types of censoring: left and right censoring. Right censoring, the most common one, happens when we know that event did not happen up to a certain point — the patient didn't attend follow-ups after a certain time or the study ended when he was still alive. Lets look at the figure 3.13.5, E and F are obviously right censored, as the event didn't happen during study and B is also right censored, as the subject dropped out of study. Left censoring, being much less common, describes the situation when the subject's survival time is unknown, but we know that it is less than a certain time. For example, in epidimiology studies we may not know when exactly the patient was infected. but we know that he is infected.

Censoring assumptions: They are very similar, however, they have very subtle differences that we are going cover in the following paragraphs.

-Random: censored subjects are representative of the remaining subjects provided the same survival experience.

-Independent: censoring is independent if it is random within any subgroup

Random an independent censoring assume that those who left the study are no different from those who stayed and therefore the percentage of survival is the same in both groups with respect to their survival experience. They are the same if assumed in one group. Censoring is *independent* if the censoring percentage in one group differs from the censoring percentage in the other group. In contrast, if the censoring percentages are the same, the censoring is *random*.

-Non-informative censoring: distribution of survival times T provides no information about the distribution of censorship times C .

Relation to machine learning: Because we are predicting a numerical value (rather values), from the machine learning point of view, survival analysis might be considered a regression, but instead of one numerical value we predict a continuous value - survival function or hazard function, and, obviously, the dataset is censored. *Survival function (also survivor function)* $S(t)$ shows us the probability of patient *surviving (event doesn't happen)* at a given time t and can be denoted as

$$S(t) = P(T > t). \quad (3.9)$$

Where t is any specific *time* of interest, T is random variable for subject's survival time. For instance, if we want to know if a patient is going to live for more than 5 years after kidney transplant, t is equal to 5 and we ask whether T is greater than t (probability question). The function is declining in the range from 0 to infinity. As it is a probability, the function value ranges only from 0 to 1. Theoretically, the graph of the survival function must be smooth, but in reality it is represented by a step function.

Hazard function $h(t)$ tells us the probability of given event *happening* at a given point of time t , provided the event did not happen before time t , and is denoted as

$$h(t) = \lim_{\Delta t \rightarrow 0} \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t}. \quad (3.10)$$

Subject's survival time T lies between t and $t + \Delta t$ provided that survival time T is greater or equal than t . Sometimes, the hazard function is called a *conditional failure rate*. It is a rate because it is a conditional probability per unit of time Δt . As it is not a probability, but a rate, the scale for this ratio is from 0 to infinity — depends on the measure of time in days, weeks or years. When we consider the limit of the expression as the time interval approaches zero we basically get the instantaneous potential of failing at time t per unit time, given survival up to time t .

Cumulative hazard function: This is basically area under the hazard function that allows to say which group has a greater risk.

The relationship between the two: There is a clear relationship between the survival function $S(t)$ and the hazard function $h(t)$ — if we know one, we can determine the other. The relationships are the following:

$$S(t) = \exp \left[- \int_0^t h(u) du \right] \quad (3.11)$$

Equation ... tells that the survival function $S(t)$ is equal to the exponential of the negative integral of the hazard function from zero to t .

$$h(t) = - \left[\frac{dS(t)/dt}{S(t)} \right] \quad (3.12)$$

Equation ... tells us that the hazard function is equal to the negative derivative of the survival function $S(t)$ with respect to t divided by $S(t)$.

Considering the facts that survival function describes the probability of patient surviving to a given point of time t and hazard function shows us the probability of person dying at any given point of time t , we can say that they provide complementary information about survival and risk over time. Of the two discussed functions the survival function is used much more often as it is more appealing in the context of survival analysis and in the practical part of this paper (bachelor project/thesis) I am going to estimate exactly the survival function.

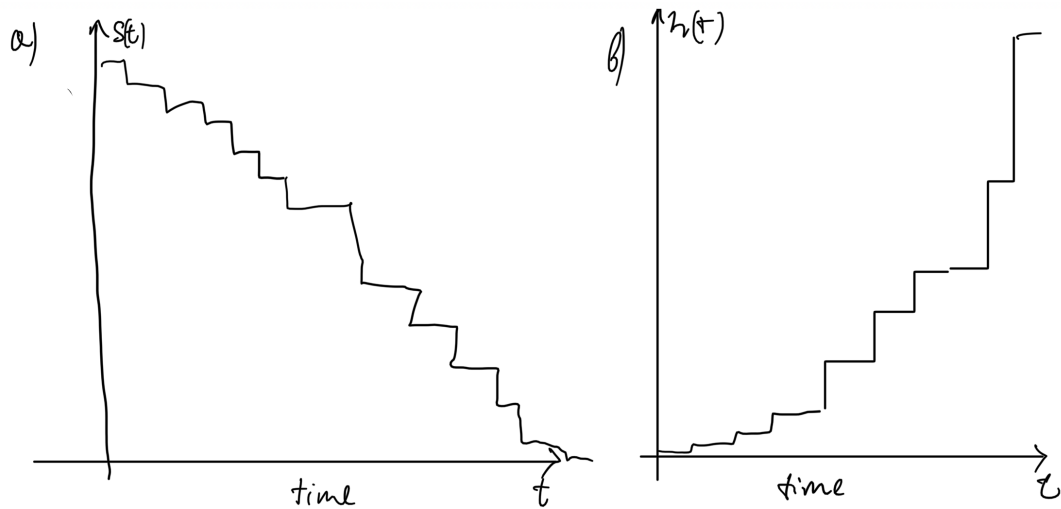


Figure 3.6: (Don't forget to provide example images both for the survival and hazard functions for some random patient from the dataset)

Take a look at figure 3.6. a) shows us a graph of the estimated survival function and b) shows us a graph of the estimated hazard function for a random patient from the dataset used. As we can see the survival function is declining over time, while the hazard function increases.

Kaplan-Meier Survival Curves:

it is one of the ways to create a survival function.

non-parametric - does not take covariates into account.

"The main assumption of the Kaplan-Meier estimator is that censored data has the same probability of survival as uncensored data. "

Log-Rank Test: It is a way to compare two survival functions. Often used in studies, where there is a target group and a placebo (control) group to assess the efficacy of the studied thing by comparing the survival curves of the two groups.

3.5.1 Performance Metrics

documentation scikit-survival

c_index: Begins to be biased at high levels of censoring

Uno's c_index: Handles high levels of censoring (provide a number) very well

Time-dependent Area under the ROC:

Time-dependent Brier Score:

3.5.2 Survival Gradient Boosting

mention it is an ensemble model and the way it is implemented in the scikit-survival.

—

Survival analysis methods

- CoxPH

- Regularized Cox

3.5.3 Cox Proportional hazards method

Survival Trees

3.5.4 Random Survival Forests

useless with large amounts of data

3.6 Machine Learning Workflow

0. define problem type and what objectives you want to achieve.
 1. gather data
 2. Analyse data
 3. Create dataset: feature engineering
 4. Train a lot of models for the given problem type on the reduced dataset, shortlist a couple of the most promising ones.
 5. Fine tune the most promising ones using the validation set until no significant improvements are seen.
 6. Assess on the test set
 7. Run on the whole dataset and/or modify the dataset
 7. Deploy

3.7 Overview of Machine Learning Libraries

3.7.1 Sci-kit learn

- pros
- cons
- where it is used

3.7.2 Keras

3.7.3 Tensorflow

- pros
 - cons
 - where it can be used
- it is more corporate driven

3.7.4 PyTorch

- pros
 - cons
 - where it can be used
- it is more research driven

3.7.5 Comparison

3.8 Conclusion

Chapter 4

Data Preparation and Analysis

4.1 Exploratory Data Analysis

- how many transplantations we have
- median age
- age distribution
- survival time distribution
- box plots

4.1.1 ...

4.2 Data preparation

4.2.1 Feature selection

4.2.2 Handling Numerical Values

4.2.3 Handling Categorical Values

Chapter 5

Machine Learning Model

5.1 Problem Formulation

Predicting the survival time after a successful kidney transplant can be approached in three ways: as a regression problem, classification problem, or through survival analysis.

A *regression* model may seem an intuitive choice, as we want to predict a numerical value – the survival time. But it is not the best option for the following reasons:

1. **The censored dataset.** The dataset has a high level of censoring – 76%. The dataset contains the number of days survived, along with the survival status. Including both living and deceased patients would introduce too much noise to the model, making it highly inaccurate. It is impossible to predict the number of days survived with regression methods based on a dataset comprised of both living and deceased patients.

2. **Censoring removal would produce bias and significantly reduce the dataset.** We could remove all censored instances, but that would reduce the dataset from 500 000 to roughly 120 000 examples. It would also introduce significant bias, as the dataset would contain only deceased patients, and most of them passed away before the introduction of modern techniques for treating the rejection. As a result, the model created from such a dataset would be highly inaccurate.

3. **Regression predicts only one single number.** It poses a problem, especially over extended time frames, as there are too many factors that we can't account for, leading to incorrect predictions.

Another way of formulating the problem is *classification*. We can theoretically divide the dataset into groups: "less than one year", "one to five years", "five and more", or even more groups and train a classifier based on them, as it was done by et al.. And again, we would face problems of censoring and bias mentioned above. So the classification is also not the best option.

A more appropriate way of problem formulation is in terms of *survival analysis*. Survival analysis methods handle censoring and provide a better form of prediction: survival function or hazard function, which represents survival probability or the failure rate at each moment in time, respectively.

5.2 Model selection

- bottleneck in a number of instances each model can train on. +

- different groups of people have different expected life expectancy -> separate models for different groups of people for the result maximization.

-

- Create an ensemble of a couple of learners.

5.3 Model comparison

5.4 Final Model

5.5 Scoring algorithm

the cumulative hazard suits the place of score very well

5.6 Limitations

5.7 Further work

Chapter 6

Applications

txmatching is something totally different, so it was decided to create separate application for accesing the model.

6.1 Existing Solutions

6.1.1 Txmatching

6.2 KidneyLife

6.2.1 Frontend

6.2.2 Backend

6.2.3 MLOps

Conclusion

Text of the conclusion...

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