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Master studies in Bioanalitical technologies – Instructions for lecturers

INTERNACIONALNI UNIVERZITET U SARAJEVU

MASTER STUDIES IN BIOANALITICAL TECHNOLOGIES - INSTRUCTIONS FOR LECTURERS

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Sadržaj

1 Introduction

The International University of Sarajevo (hereinafter: IUS), in cooperation with the Catholic University of Lublin (hereinafter: KUL), the Republic of Poland, has initiated activities to establish a joint master's study in the field of bioanalytical technologies. The new Master study program aims to educate highly sought-after experts in the field of bioanalytical technologies, internationalize higher education through joint study in Bosnia and Herzegovina and Poland, and to create conditions for broader cooperation between two related institutions.

The launch of a joint master's study is a part of a central activity within the scope of an international project called "CATAMARAN", which is funded by the Polish National Agency for Academic Exchange (NAWA). The initiated master's study, in principle, relies on the already existing study programs of the first and second cycle of studies in Genetics and Bioengineering, which exist both atKUL andIUS. Both institutions meet high staffing standards and have significant laboratory resources to carry out such endevor. This is particularly true for KUL,whose teaching materials, laboratory equipment, as well as diagnostic technology available to students was recently renewed and expanded by use of EU member states funds for higher education. Value of the available equipment and facilities is measured in tens of millions of euros and provides students with the opportunity to be trained on technologically most recent platforms and laboratories. This bolsters our hopes for the success of the new master's degree and opens perspectives for further connection of IUS with universities in the countries of the European Union.

This publication represents the set of detailed instructions for IUS part of classes in the aforementioned joint master program (the classes are taught by IUS and KUL in non-overlaping manner). According to the master curriculum, twelve courses are to be offered and taught at IUS within the master program. The instructions provided in this publication define the topics and class activities for each class (course). These also cover activities in tutorilas. In addition, the literature and resources info are given.

The main purpose of the publication is to help instructors to conduct the coures in the way that will support the learning outcomes and objectives of the master program. Although the topics and activities for each lecture are defined, this is not done in a narrow way which could limit a space for leturers to be inovative in their teaaching methods. The instructions presented

here are intented to help and support the lecturers rather than to strictly impose the practice and topics within the courses. We believe that the publication will help to achive the learning outcomes of the master programe, to harmonize the educational processes that are conducting in two different educational institutions, to ensure quality of teaching and lecturing and finally to ensure that the joint master program becomes recognizable on the local and international markets.

2 Lecture and course outlines

2.1 Molecular Diagnostics

Prepared by Dr. Daria Ler

Hours/credits: 60

Semester: II

Course format:

1. Method of presentation of course material:

   presentation, discussion, theoretical/practical classes, literature review

2. Form of assessment:

   quizzes, assignments and projects and student presentations

Prerequisites:

Principles of Molecular Biology, Biochemistry, Genetics, Molecular Biology Techniques

Course objectives:

- Identify the fundamentals and important parameters in the design of laboratory biomedicine and genetics to conduct the most commonly used molecular diagnostic procedures and tests.
- Identify the important parameters in the design of a quality system for molecular analyses.
- Become proficient with the techniques required to perform the most commonly used molecular diagnostic protocols in biomedical practice.
- Identify the components of well-controlled diagnostic test.
- Use critical thinking skills to troubleshoot problems as they occur and determine possible causes.

Learning outcomes:

1. Explore the fundamental principles of molecular methods and their implications in biomedical diagnostics, as well as disease treatment.
2. Knows the fundamental principles of testing methodology, quality assurance and the application of molecular methods to the clinical and research laboratory.
3. The students are exposed to aspects of statistics, quality control, regulatory issues and applications of these methods to the diagnosis and prognosis oh human disease.
4. The student follows and apply related protocols and tools in clinical and pre-clinical research.

5. Comprehend current laboratory diagnostic approaches through applying biochemical and molecular biology principles.
6. Utilize tools used in clinical research with biomedical applications on different level of genetic information.
7. Is able to recognize the importance of strong work ethics, persistence and intellectual integrity.
8. Understands step-by-step the important role of good laboratory and clinical practice.
9. Successfully develop plans and implement them; evolve to successfully incorporate to new working environments.
10. Is ready to work as a team member, be responsible, confident, independent and able to actively participate in all discussions and tasks.

Lecture 1

Topic: Classification of neoplasms, molecular basis of cancer; oncogenes, tumor-supressors.

The students will learn to identify the checkpoints in the cell division cycle (G1, G2 - cell growth, S – DNA synthesis and chromosomes replication, M – mitosis and cytokinesis) that are critical for regulated cell proliferation. The gatekeeper genes, oncogenes and tumor suppressor genes, will be explained, along with apoptosis, gain-of-function mutations, and loss-of-function mutations, respectively.

Lecture 2

Topic: Analytical targets of molecular testing; gene and chromosomal mutations in solid tumors: HEGF receptor, EGF-receptor, Ras proteins, Ewing sarcoma.

List of molecular targets that are useful for diagnosis and monitoring of solid cancers will be introduced and processed in detail. Following gene and chromosomal mutations in solid cancers will be presented: HEGF receptor 2, HER/neu/erb-b2 1 (17q21.1), EGFR (7p12), K-ras (12p12), N-ras (1p13), H-ras (11p15), and Ewing sarcoma EWS (22q12).

Lecture 3

Topic: Analytical targets of molecular testing; gene and chromosomal mutations in solid tumors.

Continued explaining and describing of additional analytical targets of molecular testing useful for diagnosis and monitoring of solid cancers such are synovial sarcoma translocation t(X;18)(p11.2;q11.2), PAX3-FKHR, PAX7-FKHR, t(1;13), t(2;13), ATM (11q22), TP53 (17p13) and BRCA1 (11q21), BRCA2 (13q12).

Lecture 4

Topic: Von Lippen-Hindau Gene, V-myc, Ret protooncogene, other molecular abnormalities, Microsatellite Instability, Loss of Heterozygosity.

In the second part of gene and chromosomal mutations in solid tumors, more analytical targets, also useful in solid cancers diagnosis, prognosis and therapy will be introduced. This

part will cover following gene/chromosomal mutations: Von Lippen-Hindau gene, VHL (3p26), V-myc or n-myc oncogene, MYCN (2p24), RET protooncogene (10q11), IDH1 (2q33.3) and IDH2 (15q26.1), as also other molecular abnormalities. In addition, it will be explained how microsatellite instability (MSI) can be detected. Loss of heterozygosity (LOH) will be described and its detection, together with gene expression patterns and tissue of origin to contrast cell-specific and tumor-specific molecular targets.

Lecture 5

Topic: Leukemia and Lymphoma: Molecular targets in haematological malignancies. Starting with a new section where an introduction of gene rearrangements associated with haematological malignancies that can be used for molecular testing will be described.

Lecture 6

Topic: Gene rearrangement in Leukemia and Lymphoma; VDJ recombination.

In this part the students will learn to analyze how the normal intra-chromosomal rearrangements in B- and T-lymphocytes as well as the abnormal inter-chromosomal translocations can occur in any cell type. It will be explained how antibody diversity can develop.

Lecture 7

Topic: Ig-heavy and light chain gene rearrangement in B cells; TCR gene rearrangement.

Here the antibody structure will be explained and it will include heavy and light chains, as also each type of segment V, D, J. Allelic exclusion, somatic hypermutation, affinity maturation along with correlated examples will be introduced to the students. The composition and the rearrangement of T-cell receptor gene segments will be described as also the recombination between VDJ and C elements resulting in deletion of the TCR gamma gene.

Lecture 8

Topic: Case study; Detection of clonality, translocations in hematological malignancies.

In this section examples and case study will be given to the students where clonality will be discussed with the respect to the rearranged genes. In addition, different techniques and analyses (Southern blot, PCR amplicon banding patterns etc.) will be introduced to describe how the immunoglobulin heavy and light chain, as also T-cell receptor rearrangements can be detected.

Lecture 9

Topic: Gene mutations in haematological malignancies, test panels, additional abnormalities.

Following gene mutations in haematological malignancies will be described and discussed: FMS-related tyrosine kinase, FLT3 (13q12), nucleophosmin/nucleoplasmin family, member 1, NPM1 (5q35), CCAAT/Enhancer-binding protein-alpha, CEBPA (19q13.1), and Janus kinase 2, JAK2 (9p24). Furthermore, testing of group of mutations or panels rather than single abnormalities will be discussed, as it becomes more practical and the number of diagnostically/prognostically important molecular abnormalities grows. Case studies and additional chromosomal abnormalities will be included in this part of the lesion too, since the chromosome irregularities are target for diagnosis of the associated diseases.

Lecture 10

Topic: Molecular detection of inherited diseases: Molecular basis of inherited diseases;

chromosomal abnormalities; patterns of inheritance in single-gene disorders.

In this chapter the student will get familiar with Mendelian patterns of inheritance, as also with non-Mendelian inheritance; examples of these types of inheritance, such as mitochondrial disorders and trinucleotide repeat expansion disease, will be given and discussed. Molecular and cytogenetic analyses are critical component of diagnostic testing, so in this section the students will learn how to identify molecular or chromosomal abnormality as direct observation of the source of some diseases. In addition, examples of clinical laboratory tests commonly performed in molecular genetics will be presented.

Lecture 11:

Topic: Lysosomal storage diseases; Molecular basis of single-gene disorders.

Single-gene disorder will be described, how these affects structural proteins, cell surface receptor proteins, growth factors/regulators, and enzymes. Examples of diseases resulting from such disorders will be shown, as well as molecular methods that have been or could be used to detect these gene lesions.

Lecture 12:

Topic: Thrombophilia risk factors, Factor V Leiden, CS, hemochromatosis, Cyt450.

Molecular diagnosis of single- gene disorders will be presented. Detection methods such are hybridization/amplification methods and nucleotide sequencing will be described and correlated examples of some frequently tested genes will be given and carefully discussed (ie. Factor V Leiden, Cystic fibrosis (CS), hemochromatosis, Cytochrome P-450 and Methylenetetrahydrofolate reductase (MTHFR).

Lecture 13:

Topic: Single gene disorders with non-classical patterns of inheritance; mutations in Mt genes.

Explanation of disorders which do not follow Mendelian rules of inheritance like mitochondrial mutation, genomic imprinting and gonadal mosaicism. Examples of diseases resulting from mutations in mitochondrial genes will be given.

Lecture 14:

Topic: Techniques in the clinical laboratory: DNA polymorphisms and Human identification: RLFP, STR typing.

Compare and contrast different types of polymorphism, define restriction fragment length polymorphisms and discuss how they are used in genetic mapping, parentage testing, and human identification. Short tandem repeat structure, and nomenclature, will be described, as well as gender identification, matching probabilities and the contribution of allele frequencies to the certainty of matching, and use of Y-STR in forensic studies respectively.

Lecture 15:

Topic: Bone marrow engraftment; testing using DNA polymorphisms, linkage analysis.

In this section the students will learn how STR may be used for bone marrow engraftment monitoring and for quality assurance of histological section. Case studies will be presented and discussed.

Tutorial 1

Topic: qRT-PCR detection of inherited risk factors, genotyping, viral-DNA/RNA copy-number quantification.

Quantitative PCR (qPCR) is used to detect, characterize and quantify nucleic acids for numerous applications. Commonly, in RT-qPCR, RNA transcripts are quantified by reverse transcribing them into cDNA first, as described above and then qPCR is subsequently carried out. As in standard PCR, DNA is amplified by 3 repeating steps: denaturation, annealing and elongation. However, in qPCR, fluorescent labeling enables the collection of data as PCR progresses. This technique has many benefits due to a range of methods and chemistries available. In dye-based qPCR (typically green), fluorescent labeling allows the quantification of the amplified DNA molecules by employing the use of a dsDNA binding dye. During each cycle, the fluorescence is measured. The fluorescence signal increases proportionally to the amount of replicated DNA and hence the DNA is quantified in “real time”. The disadvantages to dye-based qPCR are that only one target can be examined at a time and that the dye will bind to any ds-DNA present in the sample. In probe-based qPCR, many targets can be detected simultaneously in each sample but this requires optimization and design of a target specific probe(s), used in addition to primers. There are several types of probe designs available, but the most common type is a hydrolysis probe, which incorporates the use of a fluorophore and quencher. Thus, the fluorescence signal from a probe-based qPCR reaction is proportional to the amount of the probe target sequence present in the sample. Because probe-based qPCR is more specific than dye-based qPCR, it is often the technology used in qPCR

diagnostic assays. Students will work practical on identifying different microroganisms (bacterias, viruses and funghi), genotyping of HPV viruse genotypes (14 high - and 2 low risk), amplifying various viral sequences on DNA and RNA level, as well as quantifying the copy number of related pathogen, identifying gene mutation and hetero- homozygosity.

Tutorial 2

Topic: ELISA techniques- serological analyses of different human pathogens.

ELISA (enzyme-linked immunosorbent assay) is a plate-based assay technique designed for detecting and quantifying soluble substances such as peptides, proteins, antibodies, and hormones. Other names, such as enzyme immunoassay (EIA), are also used to describe the same technology. In an ELISA, the antigen (target macromolecule) is immobilized on a solid surface (microplate) and then complexed with an antibody that is linked to a reporter enzyme. Detection is accomplished by measuring the activity of the reporter enzyme via incubation with the appropriate substrate to produce a measurable product. The most crucial element of an ELISA is a highly specific antibody-antigen interaction. In this pratical section, student will work on detection of antibody indexes of various microorganisms, autoimmune diseases etc. Following antibodies and/ antigens will be performed: antibodies against Rubella, Toxoplasma, HSV i and II viruses, Citomegalo virus (CMV), Epstein Barr Virus (EBV), ENA 6-profiles, Antids DNA, ANA-screen, Helibacter pylorii, anti-Gliadine and anti-Tranglutamine etc.

Tutorial 3

Topic: Blotting techniques - detection of specific Immunoglobulins (IgG, IgA, IgM, IgE).

Based upon the observation that allergic responses typically affect the skin, gut, and respiratory tract, the major sites of parasitic invasion, it is thought that IgE evolved as a defense mechanism against parasitic infestation. Helminths stimulate a vigorous IgE production, including parasite-specific IgE antibody. However, another hypothesis for the beneficial function of IgE antibodies is that they play a key role in very early recognition of foreign material ("gate keeper function") or a general potentiation of the immune system response by improved antigen presentation. Actually, allergy triggered by IgE may provide a beneficial function to the host; the typical allergic reactions of mucus secretion, sneezing, itching, coughing, bronchoconstriction, tear production, inflammation, vomiting and diarrhoea are all mechanisms that expel allergenic proteins from the body. The measurement of allergen specific IgE antibodies in serum is of similar diagnostic value to that of skin tests but has a much higher reproducibility and is not influenced by ongoing symptoms or treatment, eg, antihistamines or anti-inflammatory therapy. In some instances, especially in food allergic individuals where, in rare cases, even skin prick testing with minute amounts of allergen might cause an anaphylactic reaction, in-vitro tests using blood samples is a safe method to determine levels of specific IgE antibodies. In-vitro tests are also preferred for individuals who have widespread eczema, which precludes skin prick testing. For the purpose

of detectin levels of IgE, students will perform different alergen panels such as nutritive (20 alergens), inhalatory (20 alergens), antibiotics and milk-gluten detection.

Textbooks and suggested reading materials:

1. George Patrinos, Wilhelm Ansorge, Phillip B. Danielson: Molecular Diagnostics, 3rd Edition, Academic Press-Elsevier (2017)
2. Lela Buckingham PhD MB DLM(ASCP): Molecular Diagnostics, Fundamentals, Methods and Clinical Applications, 3rd Edition, F.A. Davis Company (2019)
3. The World of the Cell by Hardin, Bertoni, Kleinsmith (PEARSON) (2012)
4. Biochemistry. 5th edition, Berg JM, Tymoczko JL, Stryer L, New York: W H Freeman (2002)

2.2 Biostatistics

Prepared by Asst. Prof. Emin Tahirovic, PhD

Hours/credits: 60 / 6

Semester: II

Course format:

1. Method of presentation of course material: presentation, discussion, theoretical/practical classes, literature review
2. Form of assessment: quizzes, tests, assignments and small projects/student presentations

Prerequisites:

1. Introduction to Probability and Statistics

Course objectives:

1. have a deeper appreciation for how to interpret and visualize data
2. understand how statistics and probability apply to real-world problems
3. be able to critically evaluate the statistics in medical studies

Learning outcomes:

1. The student understands overall goal and the role of statistical analysis in bio-medical research, recognizes when and why it is necessary to apply statistical concepts in their research.
2. The student understands how type of the data determines applicability of different statistical methods.
3. The student understands different types of association measures between variables and different types of study design.
4. The student knows about and is able to define common data visualization techniques.
5. The student understands and can interpret confidence intervals and p-value in the context of statistical hypothesis testing.
6. Student proficiently uses statistical notation and statistical language to the level that allows consummation of biomedical literature and critical appraisal of it.
7. The student can determine which study design is appropriate for which research question.
8. The student can interpret statistical graphs and can decide which visualization technique to use to represent which data.
9. The student correctly interprets results section and understands to a certain extent statistical methods section in articles published in renowned biomedical journals.
10. The student understands the importance of data privacy in the collection and subsequent phases of data analysis.

Lecture 1

Topic: Course introduction; Introduction to statistics

Students will be introduced to the syllabus, means of communicating with the instructor and the teaching assistant, times and venues for lectures and tutorials, grading criteria and weighting factors of different evaluation components. We will generally talk about what statistics is, its history, what it means to think as a statistician and what is its relation to mathematics using the article by Chris Wild "What is Statistics". Additionally, we will talk about "shapes and forms" of data that a statistician can encounter and how different objects in our environment and their characteristics become variables and observations with which statisticians work.

Lecture 2

Topic: Data presentation and visualization techniques; Population and Sample;

In this lecture we will cover different ways to present different types of data covered in the previous week. We will discuss how to visually present categorical data and which univariate and bivariate graphs will do that for us. In particular we will talk about definitions and intricacies of bar plots, pie charts, grouped bar plots and mosaic plots. In continuation, we will introduce different ways to present quantitative (continuous and discrete) variables through graphs. Here we will define and understand which graphs are best suited for particular applications and purposes. In particular, we will introduce histograms, box-plots, time-series graphs. As a second part, we will introduce the foundational concepts of a population and a sample and discuss different ways of collecting samples of observations from a population. This will allow us to introduce concepts of a population parameter and a sample statistic. We will then circle back to two visualization techniques inherent to population (probability distribution) and a sample (empirical probability distribution or a histogram).

Lecture 3

Topic: Measures of central tendency, variability and shapes of distributions. (normal distribution).

Here we will talk about 3 parameters describing the central tendency of data: the mean, the median and the mode and how their relationship is governed by the shape of the distribution of the data. In addition we will mention the definitions and interpretation of prominent percentiles. Besides these, we will introduce measures of variability: range, inter-quartile range, standard deviation and variance. We will then go into different shapes univariate distributions of continuous variables can have and how these are reflected in the measures of central tendency and variability. We will then introduce normal distribution and its parameters and talk about its mean, variance, shape and standardisation to arrive at standard normal distribution and Z-scores. We will give insight in rules based on normality of the data

that say how much data falls in 1, 2, and 3 standard deviations from the mean in the case of a normal distribution. This will lead us to prominent quantiles of normal distribution that will later be used to

Lecture 4

Topic: Basic probability, sampling distribution, quantile and probability plots, sampling distribution of the mean and standard error of the mean.

We will start with intuition for probability and answer the questions of how to model events in our surroundings by means of random variables and their distributions. This will be a nice introduction for defining a sampling distribution of a sample statistic. After we define what it is, we will introduce graphical ways of checking if a certain data that we sampled behaves according to some theoretical (sampling) distribution. These are qq-plots and we will describe how to read and interpret this type of diagnostic plots. We will then talk about central limit theorem and how it determines the sampling distribution of the mean. To end this lecture we will define and explain what standard error of the mean is and how it relates to the sampling distribution of the mean.

Lecture 5

Topic: Variability of the mean and T-distribution (interval estimation, confidence interval around the mean, one-sided and two-sided)

We will talk about errors in estimating the mean and how the random interval, that comes with some (higher) guarantees to contain the mean, is more useful in practice. We will discuss how one estimates such intervals and based on what theory this is done. We will explain concrete calculations involved in determining boundaries (width) for confidence intervals and how confidence level impacts these calculations. We will go in detail on how and when to calculate one-sided and when to calculate a two-sided confidence interval. We will then explain how the theory behind these calculations breaks down for small samples and this will motivate the introduction of the T-distribution. We will motivate its use and explain how it contributes to "honest" confidence intervals and tests in cases when we cannot use. We will conclude with introduction of the concepts of margin of error in estimating the mean and how margin of error, sample size, confidence interval and confidence level relate to each other.

Lecture 6

Topic: Interval estimation around a difference between means and interval estimation for proportions.

We continue with interval estimation which this time involves two random samples from two independent populations. We describe intervals based on the central limit theorem and those based on the Student's T-distribution. We discuss versions of "T-based" intervals when variance is similar in the two populations and when it is different. We describe the notion of a "conservative" statistical approach using the concept of the choice of degrees of freedom for the T-distribution. In addition we switch to binary outcomes and notion of proportion as an

analogous measure of average behaviour for binary outcomes. We describe how to calculate confidence intervals for population proportions based on the central limit theorem. For confidence interval calculation and margin of error for proportions we introduce the relationship between sample size, confidence level and width of the interval (margin of error).

Lecture 7

Topic: General concepts in statistical hypothesis testing and related types of errors

We will start this lecture by illustrating the necessity and opportunity for correct decision making by utilizing data. With all the concepts covered so far we will be able to explain how to stage probability calculated using data and assumptions on their distribution as a weight of evidence for something we have a preconception about. We will introduce null and alterative hypothesis and how statistical test determines which one is more reliable as judged by the data we collected. We will go into two types (Type I and Type II) of errors we can make when conducting formal tests of hypothesis. We will define test statistic, as well as rejection region of the test. In conclusion, we will talk what power and significance level of the test are and how sample size affects power of the test. This will tie in nicely with notions of positive and negative study and how power of the test relates to these.

Lecture 8

Topic: Preparation and discussion of the midterm exam

We will discuss the solutions for the midterm exam.

Lecture 9

Topic: One-sample and Two-sample tests of the mean, p-values and duality of statistical hypothesis tests and confidence intervals.

We will talk about a formal test for testing the hypothesis about a single mean and about difference between the means in two independent populations. We will describe the concept and the use of the p-value for purposes of hypothesis testing, in particular how a p-value can be understood as the weight of evidence in favour of the NULL hypothesis. In addition, we will discuss interdependency between sample size, power of the test, significance level of the test and the hypothesized difference for one- and two-sample test of the mean.

Lecture 10

Topic: Correlated data – correlation vs. causation, paired T-test, test of equality of variances

We will start by review of statistical independence and what it means for two variables to be statistically independent. We will discuss correlation as a measure of linear association of two variables. The concept of confounding will be introduced together with the notion of independent and dependent variables. We will distinguish linear and non-linear association, and show how non-linear one is sometimes not detected by a simple correlation coefficient.

We will then introduce the paired T-test and discuss why repeated observations from the same individual / object are correlated and not independent.

Lecture 11

Topic: Introducing F-distribution: F-test for equality of variances and ANOVA – analysis of variance

We will introduce F-distribution, its shape, purpose, area under the curve … Subsequently we will introduce a formal test for equality of variances, describe the test statistic, define the rejection region and background logic for this F- test. We will circle back to the two-sample T-test and explain when to use a formal test of equality of variances to decide which version of the two-sample T-test we should use. In addition we will introduce the test of equality of population means in more than two populations. We will describe the formal F-test of equality of the means in ANOVA type of analysis going into sum of squares between and sum of squares within the groups. We will then problematize the pairwise comparisons in the context of ANOVA.

Lecture 12

Topic: Basic design of epidemiological studies – clinical trial, observational study (prospective, retrospective), case-control, diagnostic accuracy (PART I)

Using the concepts of confounding and bias we will introduce different types of study design and name their advantages and disadvantages. Each study type will be introduced using a realistic example and realistic data coming out of the domain of bioanalytical studies. Each type will feature its own measure of association, hence we will define odds-ratio, risk-ratio, risk-difference and mean difference. This lecture will extend over 2 weeks.

Lecture 13

Topic: Basic design of epidemiological studies – clinical trial, observational study (prospective, retrospective), case-control, diagnostic accuracy (PART II)

Using the concepts of confounding and bias we will introduce different types of study design and name their advantages and disadvantages. Each study type will be introduced using a realistic example and realistic data coming out of the domain of bioanalytical studies. Each type will feature its own measure of association, hence we will define odds-ratio, risk-ratio, risk-difference and mean difference. This lecture will extend over 2 weeks.

Lecture 14

Topic: Student's final project presentations

Lecture 15

Topic: Student's final project presentations

Tutorial 1

Topic: Introduction to R statistical software and RStudio – integrated development environment for R

In the first tutorial students will go through series of slides and demonstrations on what R is and how to use it to import, do basic manipulation and export data. This class will be mainly about getting started with R, since it has a steep learning curve, students will be engaged through lot of code examples and comments to gain a big picture what statistical software is and how it helps us in practice to gain very quickly a picture on the structure, components and types of data. The tutorials in this class are hands on, learning by doing, and in this first students will learn R functions necessary for importing, inspecting and basic manipulation and exporting and permanently saving their data. All exercises will involve a realistic data set with data coming from a prominent bioanalytical context / study. First half (1.5 hours) of the tutorial will be reserved for introduction of the new R functions and functionalities, while the second half will be allocated for students autonomous work under the supervision of the teaching assistant who will help, answer questions and help in understanding and solving errors that the R-software produces on the way to successfully solving the exercise.

Tutorial 2

Topic: Basic R functions for inspecting and

We will introduce some very useful R-functions like “seq()”, “rep()”, “str()”. Subsequently we will discuss how are different types of data (categorical (ordered and unordered), continuous, and discrete data) are represented and called by R-statistical software. Further, we will learn how to produce all the statistical graphs we introduced in the lecture using a realistic data set. Among others, students will learn how to produce histograms, boxplots, line-graphs, time-series graphs, basic and grouped bar plots and mosaic plots, under supervision and later reusing and slightly modifying the code on their own. We will then emulate the relationship between a population and a sample by introducing R function “sample()” . Students will then find out about the functions for calculating different measures of central tendency and variability in the data using a realistic data set: “mean()”, “median()”, “var()”, “sd()”, “range()”, “quanitile()” ... We will then demonstrate all these concepts (mean, median, prominent percentiles) for the normal distribution using R. In conclusion students will produce qq-plots

Tutorial 3

Topic: Sampling distribution and demonstration of the CLT with standard error of the mean as the consequence

In this tutorial we will provide students with the code that they can use to visualize the behaviour of the sampling distribution of the mean for different sample sizes. Students will be able to play with different settings and this will visualize and exemplify the theoretical

concepts related to central limit theorem. We will then calculate the standard error of the mean for different sample sizes. Subsequently, students will be taught how to calculate confidence intervals for the population mean based on normal and T-distribution. Here students will be introduced to “qnorm()”, “pnorm()”, “qt()” and “pt()” functions and their purpose in calculating confidence intervals.

Tutorial 4

Topic: Sampling distribution and demonstration of the CLT with standard error of the mean as the consequence

In this tutorial we will provide students with the code that they can use to visualize the behaviour of the sampling distribution of the mean for different sample sizes. Students will be able to play with different settings and this will visualize and exemplify the theoretical concepts related to Central Limit Theorem. We will then calculate the standard error of the mean for different sample sizes. Subsequently, students will be taught how to calculate confidence intervals for the population mean based on normal and T-distribution. Here students will be introduced to “qnorm()”, “pnorm()”, “qt()” and “pt()” functions and their purpose in calculating confidence intervals. We will demonstrate the correct use of these functions for calculation of one-sided and two-sided intervals for different confidence levels. Subsequently, using some binary data, we will demonstrate how to do all these calculations for confidence interval for population proportion.

Tutorial 5

Topic: One – sample and two – sample T-test for the mean, correlation and paired T-test

Students will learn how to use R function “t.test()” with all its parameters and how different settings implement different versions of the T-test : one sample, two sample, one-sided, two-sided. Students will get a closer look at the list returned by the function “t.test()” and read off among other results the p-value “t.test()” produces. Students will manipulate the confidence level of the test and find out how sample size and significance level of the test relate to each other. We will introduce the R function “cor()” for calculation of the correlation between two variables measured on same set of individuals / objects. In conclusion, we will demonstrate how to use “t.test()” function to test paired observations keeping the significance level at the nominal level.

Tutorial 6

Topic: F- distribution, test of equality of variances and ANOVA

In this tutorial students will visualize F-distribution using R-functions “qf()”, “pf()” and “df()”. We will use then the the F-test of equality of variances in two samples and Bartlett’s test of equality of variances in more than 2 samples. Since this homogeneity of variances is one of assumptions necessary to conduct ANOVA, this will be a nice introduction for the use of R-function “aov()” using which students can conduct the formal test of equality of the

means in more than two samples. We will inspect the object produced by the function “aov()” and discuss all the output produced. In conclusion, we will demonstrate different adjustments for post ANOVA pairwise-testing (Bonferroni procedure, Fisher’s Least Significant Difference and Benjamin-Hochberg procedure).

Tutorial 7

Topic : Final project implementation

Students will use the tutorial to work on the analysis of data sets for their final project with active help and suggestions of their teaching assistant.

Tutorial 8

Topic : Final project implementation

Students will use the tutorial to work on the analysis of data sets for their final project with active help and suggestions of their teaching assistant.

Tutorial 9

Topic : Final project implementation

Students will use the tutorial to work on the analysis of data sets for their final project with active help and suggestions of their teaching assistant.

Textbooks and suggested reading materials:

1. Introductory Statistics with R, Peter Dalgaard, Springer-Verlag New York, 2008
2. What is the P-value anyway? - 34 stories to help you actually understand statistics, Andrew Vickers, Pearson, 2009
3. What is Statistics ? – Chris Wild, University of Auckland, Department of Statistics

2.3 Programing and Data Acquisition

Prepared by Asst. Prof. Emin Tahirović, PhD

Hours/credits: 60 / 6

Semester: II

Course format:

1. Method of presentation of course material: presentation, discussion, theoretical/practical classes, literature review
2. Form of assessment: quizzes, tests, assignments and small projects / student presentations

Prerequisites:

1. Basic calculus and concept of programming

Course objectives:

1. understand how measurements of various biological processes and phenomena are conducted and how data are generated from them
2. understand tools and systems for automatized measuring and data collection
3. understand the necessity of data standardization and data transformation for valid analysis
4. import data from different data generation / collection tools into a data analysis software
5. program in data analysis software / tools cleaning, transformation and formatting of raw imported data into a ready-to-analyze data set

Learning outcomes:

1. understands how data generation, data recording and data collection are done in modern data-intensive biological application
2. understands how features and specialities of the data acquisition process can determine applicable methods for data analysis later
3. can explain each step and methodological tools involved in data acquisition, collection and pre-processing
4. understands common ways for data standardization and its purpose
5. knows how to design a data collection process having the scientific question that needs to be answered in focus
6. demonstrates ability to use (pre-process, analyze, visualize) data created and / or collected by different recording or data collection tools
7. can decide when and how to apply necessary pre-processing step with respect to scientific hypothesis one wants to check
8. can program some basic data pre-processing steps (cleaning, missing data, transformation, standardization) using data scientific software tools
9. understands the importance of data privacy in the collection and subsequent phases of data analysis

Lecture 1

Topic: Course introduction and introduction to biomedical research data landscape

Students will be introduced to the syllabus, means of communicating with the instructor and the teaching assistant, times and venues for lectures and tutorials, grading criteria and weighting factors of different evaluation components. We will talk about the biomedical research landscape and where and how biomedical data is produced and circulated within the research cycle. We will talk about the data life cycle, beginning from generating data using different techniques and devices to storage and integration of the data produced during a research project. We will go into how ones data can and should be made available to the wider scientific community and ways of accessing data produced by others. We will introduce our primary programming tool R – statistical software and will give some advantages for using R for research, starting from wide availability of the cutting edge data access, data manipulation and data management functionalities. We will give a schematic visualization of the data life cycle this time with highlighted components where R- statistical software can be utilized.

Lecture 2

Topic: Data processing: The concept of a programming language and a simple example of a task executed by a computer (using R programming language)

Since the prerequisites for this course do not include any programming experience we will start with very basics of modern computer systems, their components and relationships. We will use the analogy of a computer system being an orchestra for which a programming language fulfils the purpose of a "music sheet" or more accurately signs used to produce music sheets for such an orchestra of different physical devices collected within the concept of a computer system. After introducing all components of a computer system we will demonstrate using R programming language how to steer each part of the system into an interaction that will result in completion of a task (that one could do by hand) of calculating current rate of change of world population. At this point R syntax will not be discussed in detail, and we will explain the steps done by R only at the conceptual, mechanistic level. This will serve the purpose of seeing a computer system in action and a programming language as a steering wheel. As a conclusion we will permanently save our R program that we created together so that we don't lose it, and to demonstrate the difference between working memory (RAM) and mass storage or static memory (hard drives / ROM).

Lecture 3

Topic: Basics of R and RStudio

Students will be introduced to R programming language and R environment as well as RStudio, an Integrated Development Environment (IDE) for R. We will explain the layout of R console and RStudio's Graphical User Interface (GUI). We will explain what functionalities

each window in RStudio will do for us, what an R script is, how to execute one's code or use code that someone else put at our disposal. We will first use R as a calculator and use the command line then we will move on to making our first R script. The notion of R packages will be explained through the lens of the R community and package contributors as R's great strength and advantage compared to other proprietary software. We will start getting to know R's syntax and R's semantics in order to subsequently be able to understand what R code does and how to write one's own solutions to problems using R. We will introduce basic concept of an R expression and what constitutes it. We will cover: constants, arithmetic expressions, legal variable naming conventions (symbols and assignments), structure of function calls in R and reserved keywords in R.

Lecture 4

Topic: Data processing: Data types and data structures in R

In order to know how R internally keeps single pieces of information or collections of similar information (uniform w.r.t. data type) that we manipulate during the data analysis. We will first introduce basic R data types: numeric, factor, character and logical. Then we will move on to collections of data of same data type (vectors, matrices) and collections saving data of different data types like lists and data frames. Important R base functions for creating vectors like "c()", "seq()", "rep()" in combinations with recycling rules will be introduced and explained.

Lecture 5

Topic: Data processing: More on data structures in R

After getting to know all the data types and data structures available in R, students will be familiarized with some R-internal specifics like the recycling rule, implicit type coercion, attributes, classes, date manipulation and formulas. In addition we will describe how to use a set of "interrogative" functions that R provides which reveal the structure and content of a single R object, be it a list, data frame or a vector. For this purpose we will introduce R functions: "summary()", "str()", "dim()", "length()", "head()", "tail()", "type()"and "class()". Subsetting functions in R when executed on a data structure (collection of same or different type of data) have the same result as selecting some rows and/or tables from a database. These are very similar in effect, if not identical to SQL queries sent to a DBMS system that then returns rows and columns reflecting the structure of a query. In R this is done using special (square) bracket notation. We will introduce and demonstrate different ways of subsetting data with this simple yet powerful syntactic mechanism.

Lecture 6

Topic: Data storage technologies: plain text files, binary files, spreadsheets

Students will get an overview of how data is saved and kept in modern computer systems. We will start with plain text files, explain how data is saved / coded for those and mention

advantages and disadvantages of saving data in such format. This will leads us to CSV-file format and special characters denoting line endings in plain text files. Since data in text files is stored as a series of characters, we will have to discuss how computer codes or later reads these characters based on different character *encodings*. We will then move to saving data using binary format. We will start by a small review of how computer memory works and how we save real numbers in a computer or at least what comes closest to real numbers). We will mention inevitable precision loss when we try to save real numbers in a computer. The difference between binary and plain text format will be exemplified using netCDF binary format. With this widely used and open standard binary students will understand how binary data are read using a netCDF format. The next stop within the data storage technology landscape is spreadsheets and spreadsheet software. We will talk about transportability of data using spreadsheets and problems arising from compatibility of different spreadsheet formats depending on the software used to produce the spreadsheet (MS Excel proprietary format vs. Open Document Format).

Lecture 7

Topic: Data storage technologies: extensible markup language (XML) documents and databases

From the need to save information on the structure and location of a particular data point within a file, a feature not supported by previous modes of data storage, we arrive at eXtensible Markup Language (XML) which provides a formal way to provide labelling or "markup" for data. XML is a storage format that is still based on plain text but does not suffer from many of the problems of plain text files because it adds flexibility, rigor, and standardization. We will talk about XML syntax and XML document structure. We will touch upon Document Type Definition (DTD) language as means to define one's own XML document structures. When a data set becomes very big and/or its structure very complex we cannot rely on the storage technologies covered so far. We must deploy a database (software) to keep and curate our data. We will talk about conceptual level of working with databases and let Database Management System "hide" the physical realities of saving data within a database. In particular we will talk about design of relational databases made up of *tables*, where each table is conceptually like a plain text or a spreadsheet. We will explain the concepts of a *data type, primary key, composite primary key and a foreign key in a table* and across tables of a database. Students will learn how to describe the design, or structure, of a database table—the table schema and how to use this to read and understand the structure of an unknown database. We will utilize the entity, attributes and relationship concepts to guide us through some major steps and considerations when designing a relational database. We will finish this part on databases by noting advantages and disadvantages of saving data in a database.

Lecture 8

Topic: Data processing: Data Import / Export

We will look at functions that allow us to import data permanently saved on a hard drive using different forms of data storage options that were discussed in weeks 5 and 6: plain text files, XML documents, binary files, spreadsheets, and databases. We will demonstrate the other direction too, and write a data structure from RAM to external mass storage to be permanently saved. We will start by explaining how to inspect and set the working directory "setwd()" and "getwd()". We will then turn to functions that allow us to read in simple text files lie "read.lines()" and "read.table()". Different binary file formats will be read in by using functions from the *foreign* package in R. This way we can read in data produced by different data analysis software other than R like: MS Excel, SAS, STATA, SPSS, MINITAB etc. Subsequently we will discuss how to import data saved within XML document structure using the *XML* package in R. In conclusion we will demonstrate how to access a database system and query it using R. We will run SQL queries in R using R packages *RSQLite* and *dplyr*.

Lecture 9

Topic: Data processing: Data manipulation; (Part I)

We will go into frequently used data manipulation steps and learn how to implement them in R. We will start with transformations which basically mean creating new variables from the existing ones. We will explain how to use "cut()" and "ifelse()" function to this purpose. Second frequently needed task is sorting, hence students will be introduced to the ''order()" function and how it can be used to sort data in R. Next useful and often needed task is tabulation of categorical data. For this purpose students will work with "table()"and "CrossTable()" in R. Next in line is aggregation over different groups defined by a categorical variable (factor). This is achieved using "aggregate()".

Lecture 10

Topic: Data processing: Data manipulation; (Part II)

Here we will cover the family of "apply" functions in R that offer a very powerful tool for streamlining the analysis and output by using the technical specifics of the actual data structure (lists and data frames). In addition we will show how to merge different data sets into a single one, using one or more shared columns. The opposite can be done in R too, that is to split a single data frame into several smaller ones using the function "split()" in R. In conclusion we will explain what long and wide formats for a data set are and how to do reshaping from one form into the other using R function "reshape()".

Lecture 11

Topic: Programming constructs: loops, if-then-else constructs and custom functions (Part I)

Students will find out how to write loops and conditional blocks using loops and if-then-else constructs in R. We will introduce the syntax for writing user-defined functions. The goal is for students to be able to encapsulate some of the similar, modular functionalities in their

programs and reuse often needed functionalities by calling the same function from different parts of their program. How this is done in R will be the topic of this lecture.

Lecture 12

Topic: Programming constructs: loops, if-then-else constructs and custom functions (Part II)

Students will find out how to write loops and conditional blocks using loops and if-then-else constructs in R. We will introduce the syntax for writing user-defined functions. The goal is for students to be able to encapsulate some of the similar, modular functionalities in their programs and reuse often needed functionalities by calling the same function from different parts of their program. How this is done in R will be the topic of this lecture.

Lecture 13

Topic: Overview of data acquisition methods for genomics algorithms

In this lecture we will introduce what is considered 3rd and 4th generation HTS methods. We will go into their origins and general, technically broad principles on which these methods are based on. This will be a nice segue to discuss what kind of raw data do these techniques produce. We will discuss FASTQ file format, the structure of the reads and how quality of the reads is denoted in the read and what it means. Students will learn about major databases for curating and sharing data from HTS experiments: The European Nucleotide Archive (ENA), NCBI Sequence Read Archive (SRA), and DDBJ Sequence Read Archive (DRA) all of which are gathered around the International Nucleotide Sequence Database Collaboration (INSDC). We will enumerate and describe tools for every step involved in processing raw reads: 1. Quality control (widely used software for QC of raw reads includes FastQC, FastQ Screen, NGS QC Toolkit, FASTX-Toolkit, QC-Chain, RRINSEQ, and ClinQC). We will discuss trimming based on the quality score and what this is used for. We will then discuss specialities of the DNA and RNA sequencing.

Lecture 14

Topic: Overview of data technologies for biomarker discovery

To begin we will give some basic definitions needed in biomarker discovery and validation process. Concepts like biomarker, sensitivity, specificity, positive predictive value, negative predictive value, proteomics, metabolomics, profiling will be defined. We will then discuss study design necessary for successful discovery and validation of a novel biomarker, and study execution that includes: sample collection, handling and storage conditions, sample preparation, method of analysis, number of replicates, and data analysis. Each of these steps will be analysed and discussed as well as the common errors that arise at each step of the study execution. Particular accent will be given to errors in measurement. We will conclude by giving some concluding remarks and recommendations.

Lecture 15

Topic: Student's final project discussion

Tutorial 1

Topic: Introduction to R statistical software and RStudio – integrated development environment for R

This class will be mainly about getting started with R. Students will be engaged through many code examples and comments to gain a big picture what statistical software is and how it helps us in practice to gain very quickly a big picture on the structure, components and types of data. In this first practical tutorial we will touch upon some important concepts in R programming. This includes Quick demonstration of "How to"'s concerning importing, inspecting, exporting and permanently saving the data will be given. First half (1.5 hours) of the tutorial will be reserved for introduction of some basic R functions and functionalities, while the second half will be allocated for students autonomous work under the supervision of the teaching assistant who will help, answer questions and in understanding and solving errors that the R-software produces on the way to successfully solving the exercise. Students will learn through trial and error concepts like legal naming conventions in R, reserved values (NA, NaN, NULL), arithmetic expressions, logical operators and some prominent functions like "q()", "rm()", "ls()" whose consequences are visible on the level of R environment.

Tutorial 2

Topic: Data types and data structures in R

After learning how to use legal identifiers to save values during a single R session students will have a chance to try out how R handles different types of data (variables). Students will learn how R saves numeric data compared to logical statements and values (TRUE/FALSE). In addition, we will talk about characters and character strings, and practice how to save these. Further students will get to use some applicable operations on characters. Character variables will be a nice introduction to factor variables in R, a very special memory efficient way of saving categorical (ordered or unordered) values. Students will find out and use on their own operations applicable to factor variables, and they will experience difference between factors an integers and factors and characters to convince themselves of the uniqueness that factor variables have in R. We will then introduce a very foundational data structure in R, a vector. Students will learn how to make vectors, what kind of data types can be saved in a vector data structure. Through exercises students will demonstrate for themselves what functions "c()", "seq()" and "rep()" can be used for and how they offer elegant solutions to common problems one faces, when it comes to data processing and analysis. From vectors we will transition to matrices and arrays and showcase through series of examples what and how to save data in those. We will finish with exercises involving lists and data frames that students will populate using already introduced functions rep(), seq(), c() and all their combinations.

Tutorial 3

Topic: Data processing: More on data structures in R

Students will practice recognizing implicit type coercion and recycling rules in R using vectors, matrices data frames and other data structures that they will create on their own. We will create named vectors using attributes and inspect objects to find out about their classes. Next major topic is class Date in R, where students will learn how to use, format, create, and do legal operations on dates. Students will learn what a POSix class in R is and how to subtract and add time periods using dates. Students will learn how to use composite expressions like formulas that evaluate at runtime in order to make their R scripts dynamic depending on what variables evaluate to during the runtime of their program.

Tutorial 4

Topic: Data processing: Subsetting

A very important operation involving any data analysis and manipulation will be exemplified through a series of exercises where students will use bracket notation to extract parts of vectors, data frames and lists according to logical condition given to them. This, same as all other tutorials, will be done under the supervision of TA. He / she will help students during their engagement with the problems. After a reasonable time allotted, students will have a chance to check their solutions against the correct ones given by their TA.

Tutorial 5

Topic: Data processing: Data Import / Export

Students will learn what working directory for R session means and how to change the working directory and check what is the current one. After practicing the concept of working directory students will learn how to import plain text files using read.lines() function. We will inspect what kind of an object the read.lines() function produces and how can this object further be analysed and his parts accessed. After reading in plain text files, students will practice how to use the read.table()-family of functions to read in structured text files (CSV, TSV, fixed width format), as well as the functions from R package *foreign* to read in data sets created by other common data processing software like: MS Excel, SAS, STATA, SPSS, MINITAB. We will read in different files, inspect parameters offered by these functions and evaluate their effects as reflected by the features of the resulting data set created this way within R environment.

Tutorial 6

Topic: Data processing: Data Import / Export

We will continue with exercises on importing data from different sources to R workspace (RAM). Next in line are imports from XML files and database systems. We will provide students with examples of data saved in XML file and code snippets that will allow students, through some small modifications and augmentation of the code to import the data to R from XML file. Students will get to know and learn how to use functions in the XML package to extract the desired information from the data saved in the XML file format. Exercises will be provided for some autonomous, but supervised work to practice importing data from an XML file. In this tutorial we will cover imports from database (systems) as well. Students will be provided with an example database and they will learn how to use functions in dplyr package to import different data sets with data comprised of few different tables across the database. We will inspect the resulting data sets and students will be able to try out how different SQL queries written in R and deployed to a database result in different number of rows and presence of different columns in a resulting data set.

Tutorial 7

Topic: Data processing: Data manipulation; (Part I)

Now that students have importing/exporting of the data from different sources in their toolbox, they will learn how to make new variables as transformations of existing ones or how to remove some of them completely. The function students will practice with are "cut()", and case-distinction construct/function "ifelse()". Students will get a chance to implement sorting of the data sets according to some key values or combination thereof. We will practice the use of order() and through series of exercises students will be able to implement any sorting of the data set that they need. Different tabulations will be presented through the use of table() and CrossTable() functions, and students will get a chance to practice their use and create customized tabulations according to their own interest. We will finish with exercises focussing on the correct use of *aggregate()* function with students getting to know how to use this powerful grouping strategy that often is a part of any data processing or analysis.

Tutorial 8

Topic: Data processing: Data manipulation; (Part II)

Apply-family (sapply(), lapply(), tapply(), apply()) will be extensively explained through examples and their use practices through exercises for autonomous work. This is a very versatile set of "meta-functions" that are very useful, but often also quite non-intuitive to students who haven't had any formal computing or software engineering education, and non-trivial for those who have also. For this reason we will provide extensively explained examples that students will be given to recreate identically. After that students will receive a set of exercises to practice the use and application of these functions in a realistic setting under the supervision of their TA. In addition we will first demonstrate how to use reshape() to move from long to wide data set format, and reverse. After some guided code execution students will be asked to transform data sets from long format to wide and back on their own under the supervision of the TA. We will finish with explaining and showcasing the use of

loops and conditional statements in R so that students will be able to conduct an automatized data analysis and write dynamic programs with decision blocks and repetition of some part of the computer code.

Tutorial 9

Topic : Final project implementation

Students will use the tutorial to work on their data sets for the final project with active help and suggestions of their teaching assistant.

Textbooks and suggested reading materials:

1. Data Wrangling with R, Bradley Boehmke, 2016, Springer – Verlag New York
2. Introduction to Data Technologies, Paul Murrel, 2017, Chapman and Hall/CRC
3. Data Acquisition and Processing in Biology and Medicine - Editorial, Yang et al., 2015
4. Curating research data: the potential roles of libraries and information professionals, Nielsen et al., Journal of Documentation Vol. 70, No.2 2014 pp. 221-240
5. Translational Bioinformatics and Clinical Research (Biomedical) Informatics, Sirintrapun et al., Surgical Pathology 8 (2015) 269–288

2.4 Engineering Mathematics

Prepared by Assist. Prof. Dr. Nima Rabiei

Hours/credits: 60

Semester: II

Course format:

- Presentation methods of course material: Theoretical lecture, tutorials, discussions.
- Form of assessment: Midterm exams and projects.

Prerequisites:

- Basic differential and integral calculus.
- Basic knowledge of matrix and determinant operations.

Course objectives:

The purpose of this course is to introduce some useful Mathematical methods and tools to engineering students that are pertinent to solving practical problems. The subjects introduced will serve as fundamental tools and methods for specialized studies in quite a few engineering fields.

The subject matter is organized into five parts as follows:

A. Ordinary Differential Equations (ODEs) - This course introduce some methods for solving differential equations and briefly look into how differential equations appear to describe or model physical phenomena in mathematical terms.

B. Numerical Solutions of Ordinary differential Equations - Finding analytic solutions to differential equations in real problems might be hard or impossible so in this course we use differential equations to construct algorithms to approximate the actual solutions.

C. Vectors, Matrices and Vector Calculus - We brush up on some familiar subjects such as dot and cross products and the theory of matrices and combine them with differential and integral calculus.

D. System of Differential Equations - This course concentrate on systems of linear first-order differential equations. We will see that the general theory of systems of linear DEs and the solution procedure is similar to that of linear higher order equations considered in

unite A.

E. Complex variable theorem – This course will introduce complex analysis and its application in engineering to students and will show quite a few interesting and surprising differences between real analysis and complex analysis.

Learning Outcomes:

After completing this course, students should be able to:

1. Classify the differential equations with respect to their order and linearity.
2. Solve first-order ordinary differential equations.
3. Find solution of higher-order linear differential equations.
4. Use power series method to find the solution of linear differential equations.
5. Use the Laplace transform in finding the solutions of linear differential equations.
6. Solve systems of linear differential equations.
7. Use numerical techniques Euler's method, Runge Kutta, Adams-Bashforth method and Adams-Moulton method to solve ordinary differential equations.
8. Understand the concepts of Multi variable functions, vector valued functions, vector field and their limits, continuity, partial derivatives and directional derivatives.
9. Calculate the gradients, curl, divergence and volume of solids.
10. Solve problems involving line integrals and surface integrals.
11. Use the Stokes' theory and Divergence's theory to simplify calculation of integral.
12. Apply change of Variables for Multiple Integrals.
13. Understand the fundamental concepts of complex analysis such as complex integration, power series, Taylor series, Laurent series and residue integration and their roles in applied contexts.

Topics covered /weekly lecture schedule:

Unite 1: Ordinary Differential equations (ODEs) (approx. 3 weeks)

- First-Order Differential Equations
- Linear Equations of Higher Order

- Power Series Methods
- Laplace Transform Methods

Upon the completion of the unit 1, Students will be presented with sets of problems in order to test their understanding of the materials. A comprehensive exam that covers all subjects in unite 1 will be given.

Unite 2: Numerical solutions of ODEs (approx. 2 weeks)

- Euler Methods
- Runge–Kutta Methods
- Multistep Methods: Adams–Bashforth–Moulton Method

Upon the completion of unite 2, Students will be grouped in order to numerically solve some ODEs using the methods taught in unite 2.

Unite 3: Vectors and Matrices (approx 2 weeks)

- Dot Product
- Cross Product
- Lines and Planes in 3-Space
- Vector Spaces
- Gram–Schmidt Orthogonalization Process
- Matrix Algebra
- Systems of Linear Algebraic Equations
- Rank of a Matrix
- Determinants
- Properties of Determinants
- Inverse of a Matrix
- The Eigenvalue Problem
- Powers of Matrices
- Orthogonal Matrices
- Approximation of Eigenvalues
- Diagonalization

Upon the completion of unite 2, Students will be presented a set of problems to test their understanding of the materials in unite 3. There is also a comprehensive exam that covers all topics in unite 3.

Unite 4: Systems of Linear Differential Equations (approx. 2 weeks)

- Theory of Linear Systems
- Homogeneous Linear Systems

- Solution by Diagonalization
- Nonhomogeneous Linear Systems
- Matrix Exponential

After completing this unit, students will be presented with a set of problems to test their understanding of the material in unite 4. Then a comprehensive exam will be given covering all subjects in unite 4.

Unite 5: Vector calculus (approx. 4 weeks)

- Vector Functions
- Motion on a Curve
- Curvature and Components of Acceleration
- Partial Derivatives
- Directional Derivative
- Tangent Planes and Normal Lines
- Curl and Divergence
- Line Integrals
- Independence of the Path
- Double Integrals
- Green's Theorem
- Surface Integrals
- Stokes' Theorem
- Triple Integrals
- Divergence Theorem
- Change of Variables in Multiple Integrals

After completing the unit 5, students will be presented with a set of problems to test their understanding of the material in unite 5. Then a comprehensive exam will be given that covers all subjects in unite 5.

Unite 6: Complex variable theorem (approx. 2 weeks)

- Functions of a Complex Variable
- Integration in the Complex Plane
- Series and Residues

After completing the unit 6, students will be presented with a set of problems to test their understanding of the material in unite 6. Then a comprehensive exam will be given covering all of the subjects in unite 6.

Upon the completion of each unite, students will be presented with sets of problems in order to test their understanding of the materials. A comprehensive exam that covers all of the subjects in the aforementioned unite will be given.

Lectures Unit 1: Ordinary Differential equations (ODEs) (approx. 3 weeks)

Unit 1 provides some important analytic methods mentioned below for solving ODEs with brief coverage of Bessel, gamma and delta functions.

- First-Order Differential Equations
- Linear Equations of Higher Order
- Power Series Methods
- Laplace Transform Methods

Lectures Unit 2: Numerical solutions of ODEs (approx. 2 weeks)

Unit 2 begins with elementary Euler methods and ends with multistep methods for numerically solving ODEs. We use basic idea introduced in unit 1 to construct algorithms to approximate the y-coordinates of the points on the actual solution curve.

Homework includes implementing the explained algorithms by Matlab or Julia and applying them to some problems.

- Euler Methods
- Runge–Kutta Methods
- Multistep Methods: Adams–Bashforth–Moulton Method

Lectures Unit 3: Vectors and Matrices (review, approx. 2 weeks)

In Unit 3 some important concepts are revised which are required for the rest of the course.

- Dot Product
- Cross Product
- Lines and Planes in 3-Space
- Vector Spaces
- Gram–Schmidt Orthogonalization Process
- Matrix Algebra
- Systems of Linear Algebraic Equations
- Rank of a Matrix
- Determinants
- Properties of Determinants
- Inverse of a Matrix
- The Eigenvalue Problem
- Powers of Matrices
- Orthogonal Matrices
- Approximation of Eigenvalues

- Diagonalization

Lectures Unit 4: Systems of Linear Differential Equations (approx. 2 weeks)

Unit 4 concentrates on the first order linear system of Differential Equations. We shall see Analogues theorems with those of linear differential equations considered in unite 1. In this unit matrix notation and matrix properties explained in unite 3 are extensively used.

- Theory of Linear Systems
- Homogeneous Linear Systems
- Solution by Diagonalization
- Nonhomogeneous Linear Systems
- Matrix Exponential

Lectures Unit 5: Vector calculus (approx. 4 weeks)

In this unit we first study functions depending upon two and more variables and the basic ideas of differential calculus and integral calculus are extended to such functions. That is the idea of definite integral is extended to double and triple integrals. We shall see that polar, spherical and cylindrical coordinates are useful to simplify computing double and triple integrals over certain solid regions in two and three dimensional spaces, respectively.
Vector valued functions are studied which is used to describe the motion of objects through space

At the end we shall study the vector field calculus. particularly line and surface integrals are defined and their relationships are given by the higher dimensional versions of fundamental Theron of calculus: Green's Theorem and stokes Theorem.

- Vector Functions
- Motion on a Curve
- Curvature and Components of Acceleration
- Partial Derivatives
- Directional Derivative
- Tangent Planes and Normal Lines
- Curl and Divergence
- Line Integrals
- Independence of the Path
- Double Integrals
- Green’s Theorem
- Surface Integrals
- Stokes’ Theorem
- Triple Integrals
- Divergence Theorem
- Change of Variables in Multiple Integrals

Unit 6: Complex variable theorem (2 weeks)

In this unit essential topics mentined below in complex analysis are coverd

- Functions of a Complex Variable
- Integration in the Complex Plane
- Series and Residues

Text books and \or References:

1. Advanced engineering mathematics, Denis G. zill (Sixth edition), (Main text book).
2. Advanced engineering mathematics, Erwin Kreyszig (Tenth edition), (supplement textbook).

2.5 Entrepreneurship and Project Management

Prepared by Asst. Prof. Benjamin Duraković and Assoc. Prof. Ramo Palić

Hours/credits: 6

Semester II

Course format:

1. Method of presentation of course material: Theoretical lectures, tutorials, demonstrations, discussions, practical Tutorial with laboratory experiments
2. Form of assessment: Midterm and final exam, project presentation

Course objectives:

1. Analyze problems and develop the marketing strategy for products/service ,
2. Equip students with,
3. Equip students with skills to write a project management plan

Learning outcomes:

1. Identify and analyze problems to develop the marketing strategy for products/service
2. Identify business opportunities and select right competitive advantage for products/service
3. Use project management's tools to apply to real-world projects
4. Apply market targeting and segmentation tool
5. Develop right strategy for a business case.
6. Use 4P concept.
7. Apply network diagrams and Gantt charts for project scheduling
8. Develop budget and resource plan.
9. Perform uncertainty analysis and project crashing
10. The student is open-minded to modern managing techniques
11. The students is able to work in a team

Lecture 1

Students are introduced to the course instructor and teacher assistant, course requirements and to the syllabus in general. The aim of this lecture is to introduce a "big picture" of the project management including Project Life Cycle, the project management elements and definitions. Some terminology, will be defined such as: program, project, task, work package etc. Here will be defined what is Project, what is management, and what is project management? How projects are distinguished from operations. "Triple constraints", which represents project objectives will be introduced. Also in general, Project Management Process Stages (Initiating, planning, executing, controlling, closing) will be introduces.

Reading: Erik Larson: Chapter 1 and Chapter 4

Lecture 2

The goal of this lecture is to define and discuss the Project Scope through the examples and theoretical aspects. Particularly, the work breakdown structure will be discussed. The work breakdown structure serves as a database that links all levels in the organization, major deliverables, and all work—right down to the tasks in a work package until work unit is identified. After this lecture, students will be able to define scope of their project and create product/work breakdown structures, which is prerequisite for network diagrams.

Reading: Erik Larson: Chapter 4

Lecture 3

The goal of this lecture is to introduce the Schedule of project with its three major elements: Milestone plan, Network diagram and Gantt Chart. Particularly, Milestone plan and estimate of Activity Times using the Beta distribution will be discussed. Expected activity time will be estimated based on optimistic, pessimistic and most likely estimates. Special attention will be paid to the design of the Network Diagrams based on Activity on Nod and Activity on Arrow. Start and finish times as well as Slack Time will be discussed through examples.

Reading: Erik Larson: Chapter 5 and Chapter 6

Lecture 4

The goal of this lecture is to estimate project resources, budget and to check uncertainty of project completion times. Here will be introduced network computation process using the forward and backward pass information. Basic of probability and statistics regarding to the normal Distribution, Project crashing will be addressed.

Reading: Erik Larson: Chapter 5 and Chapter 6

The following four (4) lectures are related to the Marketing process that is necessary through each business should go. The whole process is split-up and tackles each of the following lectures

Lecture 5

Topic: Identify and analyze problems to develop the marketing strategy for products/service:

Whether a business is startup or already established business, to start a new product or a service, it must undergo to market research to gather useful information on what is going on in the market. A critical and rigorous market analysis is necessary because if neglecting or missing some useful facts can be reflected negatively on new business. when we say a new business, it can be a whole new startup, or a new product or service in established firm. Based on gathered information, the marketing strategies are designed.

Lecture 6

Topic: Identify business opportunities and select right competitive advantage for products/service

Great ideas usually are not per se a good future business. in this regard, it is necessary to distinguish between a business idea and business opportunities. Not all ideas are regarded as good opportunities. All ideas have its primetime, place and the market. Thus, a gap, problem or disruption in the market can be identified if diligent market analysis is performed. Every business idea has its qualities and knowing that, one can easily determine whether it is right business idea for the time being. Once an opportunity is identified, marketing strategies can be designed and implemented.

Lecture 7

Topic: Apply market targeting and segmentation tool

Understanding market place, wants and demand is necessary to proceed with introducing the right products and services for targeted customers. Market segmentation and targeting is a part of the marketing strategies in general, and it is good to know different aspects of segmentation. Are we looking for needs, or wants, or demands? For any of these, different segmentation should be applied. Customized approach is recommended to successfully launch new products or services. If segmentation is properly done, we will have right customers, otherwise, the failure is most likely.

Lecture 8

Topic: Use 4P concept

Marketing tools used to deliver values to targeted customers is common, the 4Ps. This tool is the last part in performing all marketing plans based on segmentation and targeting. This comes right after the value of new products and services is identified so that targeted customers will be delighted to consume/try such products and services. It should be noted that understanding marketing needs, wants and demands is necessary to identify the unique value created by introducing new products and services. This genuine value should be communicating with the targeted customers in a most appropriate manner.

Tutorial 1-8

Topic: Presentations and Repetition of selected project topics

The student project is group-based of a case study. The outcome of the project will be a project plan in word format, which will be presented within 10-15 minuts. Students need to demonstrate critical thinking and understanding of not only their projects but also the topics presented. Students are graded on their reports but also on their active participation and ability

to engage in sound discussions during the presentations demonstrating their comprehension of the topics.

Full bibliography of textbooks, suggested readings, materials etc:

1. Project Management: The Managerial Process 8th Edition By Erik Larson and Clifford Gray ISBN10: 1260238865 ISBN13: 9781260238860
2. Marketing Management 11th Edition by Philip Kotler: ISBN-13: 978-0130336293

2.6 Heat and Mass Transfer

Prepared by Assoc. Prof. Muhamed Hadžiabdić

Hours/credits: 6

Semester: II

Course format:

1. Method of presentation of course material: Theoretical lectures, tutorials, demonstrations, discussions, practical Tutorial with laboratory experiments
2. Form of assessment: Midterm and final exam, lab report and project presentation

Prerequisites:

1. Knowledge in general physics and basic mathematics/calculus.

Course objectives:

1. Introduce concept of heat transfer and its mechanisms
2. Apply heat transfer equations on practical problems
3. Introduce numerical methods in heat transfer problems and use it for selected cases
4. Introduce basics of mass transfer

Learning outcomes:

1. Identify the mechanisms of heat transfer that occur simultaneously in nature and practice.
2. Understand the limitations of analytical solutions of conduction problems, and the need for computation-intensive numerical methods.
3. Use the non-dimensional numbers to access heat and mass transfer cases.
4. Solve one-dimensional heat conduction problems and obtain the temperature distributions within a medium.
5. Solve steady conduction problems that involve multilayer rectangular, cylindrical, or spherical geometries.
6. Analyze transient heat transfer problems and solve it when lumped system approach is applicable.
7. Calculate various characteristics of internal and external convection heat transfer problems.
8. Calculate basic problems of mass transfer.
9. Compute heat transfer problem by using numerical methods.
10. The student is open-minded to modern research techniques
11. The students is able to work in a team

Lecture 1

Topic: Introduction and basic concepts

The following topics will be discussed:

- Engineering heat transfer, heat and other form of energy, the First law of thermodynamics, heat transfer mechanisms

After this lesson student will be able to:

- Distinguish thermal energy from other forms of energy, and heat transfer from other forms of energy transfer
- Understand the basic mechanisms of heat transfer, which are conduction, convection, and radiation, and Fourier's law of heat conduction, Newton's law of cooling, and the Stefan-Boltzmann law of radiation
- Identify the mechanisms of heat transfer that occur simultaneously in practice

Reading: Chapter 1, Cengel book

Lecture 2

Topic: Heat conduction equation

The following topics will be discussed:

- General heat conduction equation

After this lesson student will be able to:

- Derive heat conduction equation from general laws of physics
- Explain physical meanings of terms in general heat conduction equation

Reading: Chapter 2, Cengel book

Lecture 3

Topic: Heat conduction equation

The following topics will be discussed:

- One-dimensional heat conduction equation
- Boundary and initial conditions

After this lesson student will be able to:

- Identify the thermal conditions on surfaces, and express them mathematically as boundary and initial conditions.
- Solve one-dimensional heat conduction problems and obtain the temperature distributions within a medium and the heat flux.
- Analyze one-dimensional heat conduction in solids that involve heat generation.

Reading: Chapter 2, Cengel book

Lecture 4

Topic: Steady heat conduction equation

The following topics will be discussed:

- Introduction of thermal resistance concepts in an analogous manner to electrical circuit problems.
- Solution of steady 1-D heat conduction problems
- Heat generation in solids

After this lesson student will be able to:

- Solve steady conduction problems that involve multilayer rectangular cylindrical, or spherical geometries

Reading: Chapter 3, Cengel book

Lecture 5

Topic: Steady heat conduction equation

The following topics will be discussed:

- Heat generation in solids
- Contact resistance

After this lesson student will be able to:

- Solve steady conduction problems that involve multilayer rectangular, cylindrical, or spherical geometries with heat generation in solids
- Estimate thermal contact resistance and assess circumstances under which it may be significant
- Identify applications in which insulation may actually increase heat transfer

Reading: Chapter 3, Cengel book

Lecture 6

Topic: Transient heat conduction

The following topics will be discussed:

- analysis of lumped systems

After this lesson student will be able to:

- Analyze transient heat transfer problems
- Solve transient heat transfer problem when lumped system approach is applicable

Reading: Chapter 4, Cengel book

Lecture 7

Topic: Transient heat conduction

The following topics will be discussed:

- variation of temperature with time as well as position for one-dimensional heat conduction problems

After this lesson student will be able to:

- Solve one-dimensional heat conduction problems such as those associated with a large plane wall, a long cylinder, a sphere, and a semi-infinite medium using transient temperature charts and analytical solutions

Reading: Chapter 4, Cengel book

Lecture 8

Topic: Numerical methods in heat conduction

The following topics will be discussed:

- Numerical methods
- Finite difference, finite element and finite volume method
- Boundary and initial conditions

After this lesson student will be able to:

- Discretize heat transfer equation by using some of numerical methods
- Solve numerically some basic simple heat transfer problems
- Solve more complex heat transfer problems by using SolidWorks software

Reading: Chapter 5, Cengel book

Lecture 9

Topic: Fundamentals of convection

The following topics will be discussed:

- Physical Mechanism on Convection
- Classification of Fluid Flows
- Heat and Momentum Transfer in Turbulent Flow

After this lesson student will be able to:

- Describe the mechanism of convection
- Define and estimate main non-dimensional flow parameters relevant for convection
- Estimate thermal boundary layer properties for flow over flat plate

Reading: Chapter 6, Cengel book

Lecture 10

Topic: External forced convection

The following topics will be discussed:

- overview of external flow
- parallel flow over flat plates
- cross flow over cylinders and spheres

After this lesson student will be able to:

- Calculate heat transfer rate from flat plate with parallel flow over it
- Calculate heat transfer rate for cylinder in cross flow
- Calculate heat transfer rate for sphere in cross flow

Reading: Chapter 7, Cengel book

Lecture 11

Topic: Internal forced convection

The following topics will be discussed:

- physical description of internal flow
- mean velocity and mean temperature
- hydrodynamic and thermal entry lengths,
- developing flow and fully developed flow

After this lesson student will be able to:

- Calculate heat transfer rate in different internal configurations

Reading: Chapter 8, Cengel book

Lecture 12

Topic: Heat exchanger

The following topics will be discussed:

- Types of Heat Exchangers
- The Overall Heat Transfer Coefficient
- Analysis of Heat Exchangers

After this lesson student will be able to:

- Define and describe basic types of heat exchangers
- Calculate overall heat transfer coefficient

Reading: Chapter 13, Cengel book

Lecture 13

Topic: Mass transfer

The following topics will be discussed:

- Fick's law of diffusion
- Mass diffusion

After this lesson student will be able to:

- Calculate basic problems of mass transport by using analytical solutions

Reading: Chapter 14, Cengel book

Lecture 14

Topic: Mass transfer

The following topics will be discussed:

- Steady mass diffusion through a wall

After this lesson student will be able to:

- Calculate basic problems of mass transport by using analytical solutions

Reading: Chapter 14, Cengel book

Lecture 15

Topic: Review of topics

The following topics will be discussed:

- Review of the course topics

Tutorial 1

Topic: Introduction and basic concepts

Homework is given with exercises envisaged to refresh knowledge in physics about heat transfer and some basic math skills.

Tutorial 2

Topic: Heat conduction equation

Tutorials go through topics of week 1 and include written exercises. Students are expected to get familiar with basic formulas and constants introduced in lectures.
Homework is given with exercises aiming to refresh knowledge in physics such as First Law of Thermodynamics – energy conservation principle, the main heat transfer mechanisms, thermal properties of matter. Math skills in ordinary differential equations are posed to enable students to calculate basic problems of heat conduction.

Tutorial 3

Topic: Heat conduction equation

Tutorials go through topics of week 2 and include written exercises. Apart from exercises, students will start to learn how to use commercial software SolidWorks.
Homework is given with exercises that include topics from week 2.

Tutorial 4

Topic: Steady heat conduction equation

Tutorials include written exercises on solving heat conduction equation for simplified geometries under different boundary conditions.

Homework will include computing some basic problems by using SolidWorks.

Tutorial 5

Topic: Steady heat conduction equation

Tutorials include written exercises on solving heat conduction equation with heat generation for simplified geometries under different boundary conditions.
Homework is based on the topics of week 4. Homework will include computing some basic problems by using SolidWorks.

Tutorial 6

Topic: Transient heat conduction

Tutorials include written exercises on solving transient heat conduction equation problems based on the lumped system approach.
Homework is based on the topics of week 5. Homework will include computing some basic problems by using SolidWorks.

Tutorial 7

Topic: Transient heat conduction

Tutorials include written exercises on solving transient heat conduction equation problems based on the transient coefficient diagrams.
Homework is based on the topics of week 6. Homework will include computing some basic problems by using SolidWorks.

Tutorial 8

Topic: Numerical methods in heat conduction

Tutorials: Basic equations of heat transfer will be numerically discretized and solved for a limited number of computational points.
Homework is based on the topics of week 7. Homework will include computing some basic problems by using SolidWorks.

Tutorial 9

Topic: Fundamentals of convection

Tutorials in week 9 include discussions on convection heat transfer mechanism, heat transfer coefficient and type of fluid flows.
Homework is based on the topics of week 7. Homework will include computing some basic problems by using SolidWorks.

Tutorial 10-12

Topic: Project work

The students are divided in groups of two to three and offered a range of project ideas – they are expected to conduct a short non-trivial research project using SolidWork software. Students need to write a plan for the numerical experiments, including a hypothesis, methodology and simulation details.
Every project demands a deeper dive in theory covered during the semester, and subsequent practical work and implementation of the planned experiment. Additional research and problem formulation is conducted by students, and practical problem solving is exercised.
At the end of the three-week period, groups submit their reports stating the aims and motivation of the conducted experiments, describe the methodology, explain and analyze the results of the computations, outline main conclusions and finally list references and background literature. Detailed records of the work must also be in their project books. Team work is exercised, but every member's contribution to the report is clearly marked.
Homework is not given in this period; students work in laboratories and have consultation hours with the lecturer. At the end of the three-week period all groups deliver their reports to the course instructor.

Tutorial 13-14

Topic: Presentations and Repetition of selected topics

All groups prepare a 15 minute presentation for other groups as well as the course instructor and possible other academic staff or students, where they in a conference-like atmosphere explain their experiments and findings in the given time-frame. Other groups ask questions during the 20 minute question session. Students need to demonstrate critical thinking and understanding of not only their projects but also the topics presented. Students are graded on their reports but also on their active participation and ability to engage in sound discussions during the presentations demonstrating their comprehension of the topics.
No laboratory work or tutorials is envisaged the last week. Besides the presentations, a session where students ask for clarifications of specific topics, exercises etc take place. Examples of exercises typical for final exams are worked out step by step if demanded by students.

Full bibliography of textbooks, suggested readings, materials etc:

1. Heat and Mass Transfer: Fundamentals and Applications, By Yunus Cengel
2. Ashim K. Datta, Heat and Mass Transfer: A Biological Context

2.7 Machine learning in medicine and health

Prepared by Asst. Prof. Dr. Kanita Karađuzović-Hadžiabdić

Hours/credits: 6

Semester: II

Course format:

1. Method of presentation of course material: Theoretical lectures, tutorials, demonstrations, discussions, practical tutorial with laboratory experiments
2. Form of assessment: Midterm, final exam, and project.

Prerequisites:

1. Knowledge in basic mathematics (introductory statistics and basic linear algebra). Computer fundamentals and programming experience are useful but not required.

Course objectives:

1. Introduce/understand the basic principles of machine learning
2. Understand and manage the data
3. Select and apply machine learning methods in medicine and healthcare
4. Performance evaluation of machine learning models applied to (bio)medical data
5. Critically read relevant research articles on machine learning in (bio)medical data

Learning outcomes:

1. Understand the basic concepts and the potentials of artificial intelligence in medicine (with emphasis in machine learning).
2. Understand, analyze and apply machine learning methods in medical settings.
3. Data pre-processing and feature engineering.
4. Application of supervised and unsupervised machine learning methods to medical datasets.
5. Performance evaluation of machine learning methods as applied to medical problems.
6. Effecively disseminate knowledge of a performed research in the form of a research paper.
7. The student is open-minded to modern research techniques
8. The students is able to work in a team

Lecture 1

Topic: Introduction to the course, getting started with Machine Learning and programming language for application of machine learning tasks such as R or Python.

The following topics will be discussed:

- Basics concepts of machine learning

- Getting started with a programming language such as R or Python

After this lesson student will be able to:

- Understand the basics of machine learning
- Write a simple code in R or Python

Reading: Chapter 1, Introduction to Data Mining book; Chapter 1 ML in R

Lecture 2

Topic: Understanding and preparing the data

The following topics will be discussed:

- Understanding the data
- Data pre-processing:
    - data cleaning,
    - data formatting,
    - transformation,
    - outliers
    - handling missing values,
- feature selection (basics) and dimensionality reduction
- principal component analysis

After this lesson student will be able to:

- Understand and analyze the underlying data
- Perform basic statistics on the data (e.g. mean, median, variance, standard deviation, explore the relationship between variables, etc.)
- Visualize the data
- Apply feature selection and dimensionality reduction on the data
- Prepare the data for input into machine learning methods

Reading: Chapter 2, Introduction to Data Mining book; Chapter 2, Machine Learning in R book

Lecture 3

Topic: Classification

The following topics will be discussed:

- Basic concepts
- Holdout and cross validation methods
- Bias and variance
- K-nearest neighbour (k-nn) algorithm
- Naive Bayes algorithm
- Model evaluation (basics)
- Hyper-parameter tuning

After this lesson student will be able to:

- Understand the general framework for classification
- Apply k-nn and Naive Bayes classification methods on a dataset
- Evaluate the performance of a applied model

Reading: Chapter 3 (Sections: 3.1, 3.2, 3.4, 3.6, 3.7, 6.3, 6.4), Introduction to Data Mining book; Chapter 3, 4, Machine Learning in R book

Lecture 4

Topic: Decision trees and rule-based classifier

The following topics will be discussed:

- Decision trees
- Rule based classifier

After this lesson student will be able to:

- Understand and apply decision tree classifier on a dataset
- Understand and apply rule-based classifier on a dataset
- Evaluate the performance of applied models

Reading: Chapter 3 (Section 3.3, 6.2), Introduction to Data Mining book; Chapter 5, Machine Learning in R book

Lecture5

Topic*:* Performance evaluation; Class imbalance problem

The following topics will be discussed:

- Performance evaluation, a closer look
- Handling class imbalance

After this lesson student will be able to:

- Understand the confusion matrix
- Measure the performance of a classifier using confusion matrix
- Apply appropriate method to handle class imbalance

Reading: Chapter 6 (Section 6.11), Introduction to Data Mining book; Chapter 10, Machine Learning in R book

Lecture 6

Topic: Ensemble methods

The following topics will be discussed:

- Understanding ensembles
- Bagging
- Boosting
- Random forest algorithm

After this lesson student will be able to:

- Apply ensemble methods on a dataset
- Evaluate ensemble methods

Reading: Chapter (Section 6.10), Introduction to Data Mining book; Chapter 11, Machine Learning in R book

Lecture 7

Topic: Regression

The following topics will be discussed:

- Linear regression
- Logistic regression
- Performance evaluation of regression methods

After this lesson student will be able to:

- Understand and apply linear regression method
- Apply logistic regression method on a dataset
- Evaluate the performance a regression model

Reading: Chapter (Section 6.6), Introduction to Data Mining book; Chapter 6, Machine Learning in R book

Lecture 8

Topic: Artificial neural networks (ANNs), support vector machines (SVM)

The following topics will be discussed:

- Artificial neural networks
- Support vector machines
- Performance evaluation of ANNs and SVMs

After this lesson student will be able to:

- Understand and apply artificial neural networks
- Understand and support vector machine algorithm
- Evaluate the performance of artificial neural network and support vector machine models

Reading: Chapter (Section 6.7, 6.9), Introduction to Data Mining book; Chapter 7, Machine Learning in R book

Lecture 9

Topic: Association analysis

The following topics will be discussed:

- Basic concepts of association analysis and finding patterns in data
- Association analysis algorithms (e.g. apriori algorithm)
- Apply association rule algorithm on a dataset
- Evaluation of association patterns

After this lesson student will be able to:

- Understand and apply data analysis using association rules

Reading: Chapter 4, Introduction to Data Mining book; Chapter 8, Machine Learning in R book

Lecture 10

Topic: Clustering

The following topics will be discussed:

- Basic concepts
- Clustering algorithms (k-means, hierarchical clustering algorithm)
- Evaluating model performance

After this lesson student will be able to:

- Understand and apply clustering algorithms
- Evaluate model performance

Reading: Chapter 5, Introduction to Data Mining book; Chapter 9, Machine Learning in R book

Tutorial 1

Topic: Introduction to the course, getting started with Machine Learning and a programming language that will be used for application of machine learning tasks such as R or Python.

Homework

Since the course will involve a term based project, from day one, students will be informed to start thinking about the topic of their project. The project will be done in groups of two to three students. The topic of the project needs to be related to a biomedical task where students will apply machine learning algorithms to real-world tasks (students will also be offered a number of project ideas such as application of machine learning methods in diagnosis of a specific disease, prediction of mortality rate of cardiovascular patients, epidemic outbreak prediction, etc.). At the end of the semester the students will need to present their projects and write a detailed project report (see details in the outlines of weeks/Tutorial 11-12 and 13 below)

Tutorial 2

Topic: Understanding and preparing the data

Perform basic statistics on a sample dataset, data visualisation and data pre-processing using programming language such as R or Python. **Note:** *during all tutorials/labs, student exercises are intended to be done using a programming language such as R or Python.*

Homework

The students will need to write a project proposal due next week were they will clearly outline the problem that they would like to work on. The project topic will need to be approved by the instructor. 2) Students will also need to perform basic statistics either on the selected dataset associated with the project or on a sample dataset.

Tutorial 3

Topic: Classification

Application of k-nn and Naive Bayes methods an on a sample dataset (including splitting of the dataset into training - (validation) – test subsets, model evaluation and hyper-parameter tuning). Discussions and consultations on the selected project. Homework is given so that the students apply k-nn and Naive Bayes methods on a dataset as explained during class and

demonstrated during the lab session. Students also need to start reading research papers related to their project topic.

Tutorial 4

Topic: Decision trees and rule-based classifier

Application of decision trees and rule-based classifiers on a sample dataset.

Homework is given so that the students apply decision trees and rule-based classifier on a dataset as explained during class and demonstrated during the lab session.

Tutorial 5

Topic: Performance evaluation; Class imbalance problem

Tutorials include a deeper look into performance evaluation of one of the previously covered machine learning models. Discussions and consultations on the selected project.

In the given homework students will be asked to use the performance evaluation techniques covered in class and lab to a sample dataset.

Tutorial 6

Topic: Ensemble methods

Application of ensemble methods on a sample dataset.

Homework is given so that the students apply ensemble classifiers on a dataset as explained during class and demonstrated during the lab session.

Tutorial 7

Topic: Regression

Application of regression methods on a sample dataset.

Homework is given so that the students apply regression classifiers on a dataset as explained during class and demonstrated during the lab session.

Tutorial 8

Topic: Artificial neural networks (ANNs), support vector machines (SVMs)

Application of artificial neural networks and support vector machine algorithms on a sample dataset.

Homework is given so that the students apply ANN and SVM classifiers on a dataset as explained during class and demonstrated during the lab session.

Tutorial 9

Topic: Association analysis

Finding patterns in data using association analysis.

Homework is given so that the students apply association analysis for finding patterns in data.

Tutorial 10

Topic: Clustering

Tutorials Finding clusters/groups of data using clustering algorithms such as k-means clustering algorithm.

Homework is given so that the students apply clustering algorithms to find clusters in data.

Tutorial 11-12

Topic: Project consultations and work on the project.

Homework Students need to prepare and submit a report of their project which needs to be done using the academic paper writing style (i.e. the report must include abstract, introduction, related work, methodology, results and discussion and conclusion.)

Tutorial 13

Topic: Presentations and revision for the final exam.

All students will need to prepare a 20 minute project presentation that will be attended by their course mates, instructor and other academic staff or students, where the students will present their projects. 15 minute question session is planned as a follow up of each presentation. Students need to demonstrate critical thinking and understanding of not only their projects but also the topics presented. Students are graded on their reports but also on their active participation and ability to engage in sound discussions during the presentations, demonstrating their comprehension of the topics. Both team work and individual contribution will be considered during the overall marking of the project. No laboratory work or tutorials is envisaged the last week. Revision for the final exam.

2.8 Biophotonics

Prepared by Assoc. Prof. Emir Karamehmedović

Hours/credits: 6

Semester: II

Course format:

1. Method of presentation of course material: Theoretical lectures, tutorials, demonstrations, discussions, practical Tutorial with laboratory experiments
2. Form of assessment: Midterm and final exam, lab report and project presentation

Prerequisites:

1. Knowledge in general physics and basic mathematics/calculus.
2. Basic knowledge of any mathematical modelling software.

Course objectives:

1. To introduce the concepts of generation of monochromatic and polychromatic light, light propagation and general optics and passive components
2. To study light-matter interaction with focus on light-tissue interaction, propagation, scattering
3. To understand and use basic methods and instruments used in biological systems, in particular spectroscopic and imaging techniques
4. To understand recent literature in the field of bio-photonics
5. To bring together students with engineering or natural sciences background in multidisciplinary teamwork

Learning outcomes:

1. The students understand the basic principles and specificities of different light sources used in biomedical applications, including lasers and various polychromatic sources
2. The student explains different light-tissue interactions including thermal, ablative, and photochemical interaction, and is able to relate the interactions to the specific characteristics of the light source
3. The student discusses optical properties, including absorption and scattering of tissues, and understands the wavelength dependency of these processes
4. The student describes different imaging or diagnostic techniques such as fluorescence, OCT, Raman spectroscopy, and understands limitations of different techniques or methods
5. The student applies bio-photonic techniques such as OCT, ITP spectroscopy for sample imaging and diagnostics
6. The student operates basic optical laboratory equipment
7. The student chooses appropriate literature to support analyses the final product

8. The student reports obtained experimental results, analyses and draws conclusions and interpretations
9. The student is open-minded to modern research techniques
10. The students is able to work in a team
11. The student proceeds according to good practice regulations in the production of pharmaceutical substances and applies H&S procedures

Lecture 1

Topic: An Introduction to the course mechanics, light and matter

Students are introduced to the course instructor and teacher assistant, course requirements and to the syllabus in general. "What do you take home from the course".
Light-matter interactions are listed with a special focus on types of light-tissue interactions. This underlines the importance of biophotonics as a modern discipline. Light as the essential tool in techniques for imaging and diagnostics is discussed. Light propagation through lossy and scattering medium, such as most tissues, is described using Beer-Lamberts' law. Absorption and elastic scattering in tissue are quantized.
Elastic and inelastic processes and their respective importance and roles are explained.
The concepts of light power, intensity, energy and penetration depth are introduced, all with examples demonstrated during the lectures.
Different light sources and their differences as well as light detectors are listed.
It is assumed that students are familiar with fluorescence, but basic properties and physical background for this process is stated.
In-class demonstration of Beer-Lamberts' law include shining a red or a green laser through a number of identical dielectric tissue-like media where the beam traverses different paths, and measurement of the light power before and after the passage. Absorption coefficient is calculated for the media and for water for comparison with literature data.

Reading: Keiser: Chapter 1: 1.1 – 1.7 (20)

Lecture 2

Topic: Light sources: black-body radiation, Stefan Boltzmanns' law, Wiens' displacement law, principles of lasers

Light sources and their very specific characteristics are essential in correct use or design of experiments involved in biophotonics. Black-body radiation with pertaining laws - Stefan Boltzmanns' law, Wiens' displacement law, is explained together with practical examples where and how these laws are used – e.g. thermal camera or contactless thermometers. Discussion of relevant characteristics of light as the wavelength, coherence, polarization are backed by in-lecture demonstrations using polarizers, lasers, light emitting diodes and other types of light. Relevance of these characteristics for imaging techniques is emphasized.

The in-lecture demonstrations include:

- overlapping two linear polarizers to block/unblock passage of white light,
- rotating a polarizer in the path of a laser to demonstrate the light be polarized,

- monitoring stress in plastic using a polarizer and analyzer,
- coherence of a laser demonstrated by passage through a slit,
- incoherence of LED or flashlight demonstrated by passage through a slit.

Reading: Keiser: Chapter 2: 2.1 – 2.3 (12)

Lecture 3

Topic: Xe lamp, white light sources, laser, coherence, spectral properties, light measurement units

Spectral properties of broadband light sources like Xe-lamp and some more modern white light sources used in bio-imaging are presented. Units for source and detector light measurement are introduced. Notion for spatial and temporal coherence are explained with some examples of typical light sources. A special emphasis is made on laser as a coherent monochromatic light source and its application in interferometry. A review of how Michelson interferometer works is given. This is related to e.g. optical coherence tomography where light coherence is also essential for the method. Calculations of photon energy, Planck's constant, pulse energy, energy integration etc. Dosimetry is introduced.

Reading: Keiser: Chapter 4: 4.1 – 4.4.2 (20)

Lecture 4

Topic: Absorption, refraction, diffraction, reflection, transmission, scattering

Refractive index and Snell's law are refreshed. Total internal reflection and Brewster's angle of no reflection are stated. Absorption and elastic scattering in tissue are repeated. Ray optics is introduced. Wave optics is mentioned and limitations of ray optics are listed. Airy disc, point spread function and spatial resolution of an optical system are defined. Scattering as a function of particle size compared to wavelength, and refractive index is explained and Rayleigh scattering as well as Mie scattering are introduced. Speckle formation is demonstrated in class.

A computer program based on Monte Carlo simulations is demonstrated – a model of light propagation through a tissue-like medium. Reference to use of the simulation in quantitative clinical diagnostics.

How a lens works is explained, chromatic and spherical aberrations are introduced. Image formation in thin lens system is explained.

Reading: Keiser: Chapter 2: 2.4 – 2.6 (9), Chapter 6: 6.1 – 6.4 (23)

Lecture 5

Topic: Diffraction grating spectrometer

Main component in this class that is introduced is a diffraction grating. Transmission and reflection gratings are described with various types – ruled and blazed gratings. The diffraction grating equation for normal incidence is derived, together with the grating constant and its importance for functioning of a diffraction grating spectrometer (DGS). Setup of a

simple DGS is analyzed and design parameters are discussed in the class. A note on design of DGS is reviewed. Importance of DGS in medical imaging and diagnostics is emphasized with examples of equipment using DSG internally.
Optical detectors including 1D and 2D arrays are discussed. Spectral sensitivity of Si based components and sources of noise are also mentioned. Operation of UV extended range detectors is explained, and spectrometers in other than visible and near infrared regions are presented. In particular, possibilities for spectrometry and medical diagnostics applications in the mid-infrared region are emphasized.

Reading: Note on diffraction grating spectrometer design "Spectrometer design guide" by Ibsen photonics

Lecture 6

Topic: Photobiology

Introduction to the term "Photobiology", what it covers and a brief history on the topic. Fundamental equations and governing factors for the three primary mechanisms of laser-light action: photochemical (photobiomodulation), photothermal, and photomechanical are discussed. Light-tissue interactions are covered in more detail together with calculations of dosimetry in biological tissues. Energy transfer induced by laser light with concepts and mechanisms. FRET and its applications, photodynamic therapy and how it is applied in medical applications. Photoreactivity and phototoxicity of drugs and drugs as photosensitizers are discussed. UV-induced DNA damage is discussed with reference to UV light sources and exposure. Influencing circadian rhythms by lighting is mentioned.

Reading: Keiser: Chapter 6: 6.5 (18)

Lecture 7

Topic: Bioimaging: optical microscope, fluorescence microscopy, upconversion

The concept of contrast in imaging is explained. Microscope, with its main components, is reviewed, as well as calculation of field of view and magnification. Diffraction limit is repeated defining the resolution. Physics behind fluorescence, luminescence or chemoluminescence is introduced. Notions as fluorescence lifetime and autofluorescence are explained. Different fluorophores are listed and their typical applications. Optical filters are listed. Electron microscopy as SEM and TEM and AFM are mentioned as methods for subwavelength imaging.

Fluorescence microscopy and confocal microscopy as methods are explained.

Process of spontaneous and stimulated Raman scattering is explained. Applications of Raman scattering, its efficiency and requirements for light-source are listed.
Different analytical methods are described and their applications listed:

- Absorption spectroscopy,
- Raman spectroscopy and
- Fluorescence spectroscopy.

The emerging imaging methods using upconversion are discussed. Advantages in terms of noise and resolution of the various methods are listed. Super resolution imaging STED is mentioned.

Reading: Keiser: Chapter 6: 6.6-6.7 (2), Chapter 8: 8.1 – 8.4, 8.6 (19)

Lecture 8

Topic: Optical coherence tomography, principles and applications

OCT is an established clinical imaging technique for screening and diagnosis of several diseases within primarily ophthalmology, but also cardiology or dermatology/oncology. A typical OCT setup with its main components is presented. A review of theoretical formulation for signal extraction is given, and examples of primitive OCT signal traces are shown. OCT image characteristics are listed with artefacts, speckle, other distortions etc. Theories behind Michelson interferometer and spectrometer are recapitulated which are highly relevant for this method. Implementations of time-domain and frequency-domain, swept source, spectrometric and polarization sensitive OCT are compared and discussed. An accent is on applications and limitations of OCT. Optical coherence elastography is also mentioned and compared with OCT but also other methods in elastography.

Reading: Keiser: Chapter 10: 10.1 (12), Chapter 7: 7.5.2 (1)

Lecture 9

Topic: Bio-imaging and diagnostics applications

Approaches in imaging can be based on fluorescence, bioluminescence, absorption or reflectance to generate contrast, while diagnostics can be based on analysis of optical signals as sample response to some excitation. In particular, the possible techniques that are discussed can be

- isotachophoresis or another electrophoretic method.
- Fluorescence lifetime imaging
- Bioluminescence imaging

A number of modern bio-imaging and diagnostics applications are presented. Setup construction of the specific application is presented while a discussion with students is engaged about possibilities and choices made in the design from optical point of view – choice of light sources, what influences resolution, sensitivity, what may be a range of applications etc. Students are encouraged to review recent research results and find applications of bio-imaging in the field of interest.

Reading: Keiser: Chapter 9: 9.1-9.6 (20)

Lecture 10

Topic: Project work

The students are divided in groups of two to three and offered a range of project ideas – they are expected to conduct a short non-trivial research project using equipment that is available in the laboratories. Tutorials are not held and Homework is not given in this period; students work in laboratories and have consultation hours with the lecturer. At the end of the three-week period all groups deliver their reports to the course instructor.

Reading: Keiser: Chapter 11: 11.1-11.5 (12)

Lecture 11

Topic: Presentations and Repetition of selected topics

All groups prepare a 15 minute presentation for other groups as well as the course instructor and possible other academic staff or students, where they in a conference-like atmosphere explain their experiments and findings in the given time-frame. Other groups ask questions during the 20 minute question session. Students need to demonstrate critical thinking and understanding of not only their projects but also the topics presented. Students are graded on their reports but also on their active participation and ability to engage in sound discussions during the presentations demonstrating their comprehension of the topics.
No laboratory work or tutorials is envisaged the last week. Besides the presentations, a session where students ask for clarifications of specific topics, exercises etc take place. Examples of exercises typical for final exams are worked out step by step if demanded by students.

Tutorial 1

Topic: An Introduction to the course mechanics, light and matter

Homework is given with exercises envisaged to refresh knowledge in physics about light refraction, and math skills in exponential functions. The homework demands also plotting graphs in a computer simulation program such as MATLAB.

Tutorials start second week of the course.

Tutorial 2

Topic: Light sources: black-body radiation, Stefan Boltzmanns' law, Wiens' displacement law, principles of lasers

Tutorials go through topics of week 1 and include written exercises. Students are expected to get familiar with basic formulas and constants introduced in lectures.
Homework is given with exercises aiming to refresh knowledge in physics about basic light properties – wavelength, intensity/power and polarization, together with light diffraction. Math skills in trigonometric functions are posed to enable students to calculate light path at different angles.

Tutorial 3

Topic: Xe lamp, white light sources, laser, coherence, spectral properties, light measurement units

Tutorials go through topics of week 2 and include written exercises. Apart from exercises, students learn how to operate an optical power meter and are introduced to conduct specific for optics laboratory. Laser safety with possible laser damage on ocular tissue is emphasized. An interferometer is prepared in the laboratory to demonstrate the ability of an optical instrument to measure in nanometer range taking advantage of coherence. Tutorials include demonstration of various light sources and measurement of their spectra, power and estimation of energy.
Homework is given with exercises that include topics from week 2 and focus on applications of the introduced physical principles on biophotonics applications. Math skills in integration are refreshed.

Tutorial 4

Topic: Absorption, refraction, diffraction, reflection, transmission, scattering

Tutorials include written exercises on calculations of reflection angles, refraction, absorption, power reaching a point in an optical system. Exercises demonstrating dependence of maximum spatial resolution (compared to e.g. biological material) on wavelength.
Homework is to download the simulation program from the course web page, for propagation of light in turbid medium and discover which factors influence on penetration depth, resolution, and dwell on the conclusions.

Tutorial 5

Topic: Diffraction grating spectrometer

Tutorials include an analysis of a DGS instrument built by IUS students. The instrument is shown from a close range to give opportunity to students to see and dismantle it to simple components.
Homework involves designs of DGS where requirements are possible to meet and analysis of a DGS that may have suboptimal components with task of students to identify and replace them.

Tutorial 6

Topic: Photobiology

Tutorials include exercises within dosimetry, development or use of a MATLAB script (depending on students proficiency) that calculates dosage for pulsed laser with varying repetition rate, pulse shape and power.
Homework includes FRET related problems that help clarify and understand the effect.

Tutorial 7

Topic: Bioimaging: optical microscope, fluorescence microscopy, upconversion

Tutorials include hands-on work on fluorescent microscope and getting experience with use of the optical microscope and pertaining software available in the GBE laboratory.
Homework includes finding of numerical aperture of various objectives and implications on working distance. Choice of objectives/magnifications for various purposes.

Tutorial 8

Topic: Optical coherence tomography, principles and applications

OCT is a useful imaging technique for a wide range of biological, medical and research applications. It is one of the topics that students can choose as a short research project at the end of the semester. For that reason, apparatus in the laboratories that may be used in an OCT setup is shown and handling is explained.
Homework includes reading a journal paper on OCT and finding a commercial version of OCT apparatus listing its main characteristics (type, resolution, application).

Tutorial 9

Topic: Bio-imaging and diagnostics applications

Tutorials in week 9 include discussions on OCT method and various derivatives of the method.

Homework is to read a journal paper describing a specific imaging or diagnostics method.

Tutorial 10-12

Topic: Project work

The students are divided in groups of two to three and offered a range of project ideas – they are expected to conduct a short non-trivial research project using equipment that is available in the laboratories. It can be pathogen detection using isotachophoresis setup, performing fluorescence imaging of a specific cell culture, building an interferometer for bio-related analysis etc. Students need to write a plan for experiments, including a hypothesis, methodology and list of equipment.
Every project demands a deeper dive in theory covered during the semester, and subsequent practical work and implementation of the planned experiment. Additional research and problem formulation is conducted by students, and practical problem solving is exercised.
At the end of the three-week period, groups submit their lab reports stating the aims and motivation of the conducted experiments, describe the methodology, explain and analyze the results of the measurements, outline main conclusions and finally list references and background literature. Detailed records of lab work must also be in their lab books. Team work is exercised, but every member's contribution to the report is clearly marked.

Homework is not given in this period; students work in laboratories and have consultation hours with the lecturer. At the end of the three-week period all groups deliver their reports to the course instructor.

Tutorial 13

Topic: Presentations and Repetition of selected topics

All groups prepare a 15 minute presentation for other groups as well as the course instructor and possible other academic staff or students, where they in a conference-like atmosphere explain their experiments and findings in the given time-frame. Other groups ask questions during the 20 minute question session. Students need to demonstrate critical thinking and understanding of not only their projects but also the topics presented. Students are graded on their reports but also on their active participation and ability to engage in sound discussions during the presentations demonstrating their comprehension of the topics.
No laboratory work or tutorials is envisaged the last week. Besides the presentations, a session where students ask for clarifications of specific topics, exercises etc take place. Examples of exercises typical for final exams are worked out step by step if demanded by students.

Full bibliography of textbooks, suggested readings, materials etc:

1. Gerd Keiser: Biophotonics: Concepts to Applications, Springer (2016)
2. Paras N. Prasad: Introduction to Biophotonics, John Wiley & Sons, Hoboken, New Jersey (2003)
3. Notes on spectrometer design “Spectrometer design guide” by Ibsen photonics
4. Notebook, permanent markers, MATLAB simulations

2.9 Intellectual Property Law for Scientists

Prepared by Assoc. Prof. Emir Karamehmedović

Hours/credits: 6

Semester: II

Course format:

1. Method of presentation of course material: lectures, tutorials, classes, discussion, seminar
2. Form of assessment: homework assignments, project work, midterm and final exam

Course objectives:

1. To reach an understanding of what constitutes Intellectual Property, its classification, features and coverage
2. To understand the significance of IP portfolio of an organization, principles of licensing, and basic strategies for market protection
3. To analyze and generate intellectual property
4. To develop intellectual property that can be protected on various levels

Learning outcomes:

1. The student describes the process of patent application, types of intellectual property (IP) and use of IP in business.
2. The student evaluates the type, coverage, applicability, novelty, and validity of IP.
3. The student possesses knowledge concerning developments in IP and its history, newest trends of IP relevant for specific industry.
4. The student analyzes existing intellectual property, applies knowledge in search of data bases and extracts essential data on specific IP
5. The student uses available databases to assess applicability of IP
6. The student generates possible IP by writing a sample application and pertinent documentation
7. The student reports on results obtained in investigation, analyses and draws conclusions and interpretations.
8. The student is open-minded to modern research techniques
9. The students is able to work in a team
10. The student proceeds according to good practice regulations in the production of pharmaceutical substances and applies H&S procedures

Lecture 1

Topic: An Introduction to the course mechanics and basics of Intellectual Property

Students are introduced to the course instructor and teacher assistant, course requirements and to the syllabus in general.
Some history of intellectual property is presented, from ancient Rome to modern times. Influence, both positive and negative, of IP on technological advances is discussed.

Understanding of the notion of idea is examined as well as societal impact of ideas, knowledge, environment encouraging free thinking and innovation. Objectives of enforcement of IP rights are also discussed, listing some difficulties and problems of appropriation. IP rights as human rights are explained. Value of intangible assets is discussed.
Morality, in particular in the specific case of pharmaceutical patents, is brought to discussion with some examples justifying the need for balanced IP laws. Examples of misuse of IP are shown in e.g. tax payment manoeuvres. A discussion on values in the era of internet and immediate access to information and abundance of physical resources is encouraged and expectations of students with respect to their careers are examined.
Finally, a very important part of the course is learning and understanding the language used in context of intellectual property. A list of useful words and phrases is given, followed by a short discussion in the auditorium about their meaning and roots.
No tutorials and no homework are scheduled for this week.

Reading: Rockman, Chapter 1

Lecture 2

Topic: Overview and types of Intellectual Property and its classification

There are different recognized types of intellectual property, namely, patents, trademarks, trade secrets and copyrights. Examples of what is, and what is not considered intellectual property is summarized and some cases of every type of IP are presented. The course will focus mainly on patents and process of patenting an idea, method or device. Some patented products, methods or "composition of matter" in biotechnology are mentioned, such as insulin, anti-cancer drugs, pasteurisation. "Utility patents" are introduced. A discussion with students on what is patentable is stimulated.
Trademarks are second most important subject treated in the course. Most drugs are marketed using a registered and protected name – a trademark. This does not prevent other companies producing and selling the same compound on the same market. Branding is, however, getting more attention and importance, stimulating larger companies to protect their marketing investments.
Trade secret covers design, process, formula or similar that is not common knowledge and is held to a great extent secret, unlike a patent. Trade secrets, just like patents can constitute a significant fraction of a company's value. Protection of trade secrets through e.g. non-disclosure agreements is discussed. Also, on one side the duration of a trade secret and on the other marketability and valuation are compared to that of a patent. Legal and illegal ways to find out the trade secrets are discussed.
Copyrights are defined and usual use of copyrights presented. Copyrights are less relevant in biotechnology, they relate primarily to artistic works.

Reading: Rockman, Chapters 4, 5

Lecture 3

Topic: Copyright, trademark, related rights

A short history and function of trademark is presented. Types of trademark, duration and renewal of a trademark protection and some examples of trademarks are shown and studied. Visually perceptible and other kinds of trademarks are explained – requirements for registering a trademark are listed – absolute and relative grounds. It is also mentioned what is not a trademark and cannot be protected by the trademark law. Possibility of licensing of a trademark is shown by a few examples, and obligation to use a trademark is discussed. International conventions that protect trademarks are introduced together with the Office for the Harmonization of the Internal Market (OHIM) in the EU. Differences between trademark and trade name are noted. Goods or services covered by a trademark, infringing an existing trademark, defensive trademark and registering a trademark in "bad faith" are explained. Trademark cancellation and invalidation are distinguished. The concept of "likelihood of confusion" is introduced.
Protection for geographical indications (different from territoriality of IP) is presented with some examples.

Reading: Rockman, Chapters 5, 25, 26

Lecture 4

Topic: Geographical specificities

Different geographical or political regions have somewhat different rules within protection of intellectual property. The two most relevant jurisdictions at the moment are American and EU, with rapidly growing Chinese. Differences can be significant in terms of level of originality of the subject IP. The patent cooperation treaty (PCT) is introduced. The body coordinating PCT applications, the so-called "the world intellectual property organization (WIPO)" is also mentioned. Rules of patenting in different regions are discussed together with the most typical patenting strategies and deadlines.
Emphasis on significance of IP protection and globalization in pharmaceuticals and drugs is made through examples of how costly it can be to introduce a new product into a market. Awareness of the need for generating, obtaining, protecting, and managing the IP is underlined. IP due diligence is explained.

Reading: Rockman, Chapter 4

Lecture 5

Topic: Industrial design, applicability, novelty

In this lecture, the process of national and international patenting is presented. The specific requirements for patentability of an invention are presented. The notions of uniqueness, "innovative step" and industrial applicability are introduced while "person skilled in the art" and "state-of-the-art" are explained. The "best mode" description, that is not required in EU, is discussed. The priority date and "first to invent" system (valid in the US) are considered. Examples of "search report" or "novelty report" are presented.

Exclusions specific for biotechnology or medical industry related inventions are listed, such as new species of plants and animals, human body and non-separated parts, medical, surgical, therapeutic and diagnostic methods. However, there are IP rights for plant varieties or products, compounds, substances used in e.g. surgical methods that may be patented.

Reading: Rockman, Chapters 6, 7

Lecture 6

Topic: Patent application and grant

The chain of events and actions taken, from IP creation to enforcement is described. The lecture proposes the choice of countries where the patent is to be valid, and what is covered once the patent is granted. The importance of obtaining professional assistance in this process is underlined. Mandatory elements of a patent application are listed with a few examples. Claims (independent and dependent), claim language and patent families are reviewed. Purpose of patent application, its publication and content with respect to scope and disclosure are given. The significance of technology transfer offices (TTOs) is explained and rights of the authors and the applicant are given. Time to grant a patent from the application is shown for various fields and territories together with novelty-breaking publications by the inventor. The role of patent examiner is explained and correspondence with the examiner.
Retroactive rights on intellectual property – an overview of what rights does the author or assignee have in case of an infringement. The term litigation is explained together with why this may not be preferred way of settling disputes.

Licensing a patent is described with types of licenses - exclusive and non-exclusive and voluntary and non-voluntary licences. Standard essential patents are mentioned.

Reading: Rockman, Chapters 8, 9, 10, 11

Lecture 7

Topic: Unfair competition

The definition of unfair competition is given with some examples from the real world. Creating confusion, issuing false allegations or misleading the public in a way that influences financials of a company are discussed. Other illegal actions in the scope of IP are mentioned. Rules and mechanisms for market control are listed and some case studies are analyzed, where students need to give a qualified opinion on who has legally advantage.
A short discussion on open access publishing of research at a university is also conducted.
A review of topics covered in the course is given, and some selected topics are repeated before the midterm exam.

Reading: Rockman, Chapter 12

Lecture 8

Topic: Enforcement of IP

An explanation of the need for maintenance and protection of IP is given together with the fact that it is the owner of the IP rights who take actions and enforces the protection. Sometimes it may be difficult to present evidence of infringement making it more appropriate to protect IP as a trade secret.
Cases where use of arbitrary IP is allowed, such as in experimental use, private use or, what is most relevant, tests and trials on medicinal products in the process of obtaining market authorisation for a pharmaceutical product is listed with some examples. Competent court in EU countries is stated. Exploitation of patent rights is typically through selling the patent rights or licensing. These modalities are discussed with the term "royalties". A brief summary of indicators (such as industry turnover, coverage, citations, remaining time of life, claim structure etc.) for the patent value are given. It is noted that there are companies in the IP eco-system that do evidence collection, IP valuation and propose settlement modalities and transactions. Agreements signed between parties have obligatory content noting that some clauses are not permitted in the EU. Risks of the licensor and the licensee are discussed in the class.

Reading: Rockman, Chapter 18, 19

Lecture 9

Topic: IP in biotechnology

Every segment of IP protection has its particularities, be it microelectronics, mechanical devices or medical and biotech products and methods. This class treats special cases and principles that apply in biotech and medical IP niches. Definition of "biological material" is made. A list of patentable inventions and exclusions in the area of biotech are listed.
The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS agreement) and the Convention on Biodiversity are presented, and how TRIPS members provide protection for pharmaceutical products without discrimination to the field of technology, provided that patentability requirements are met. Patenting living organisms and IP in agriculture with geographical indications is reviewed. The International Treaty on Plant Genetic Resources for Food and Agriculture (CGIAR) is also briefly presented.
A discussion on morality in biotech related IP and e.g. compulsory licensing of essential medicines in developing countries is initiated and again the role of IP is discussed in the classroom. Discussion can include ethical and possible religious concerns about patenting life forms.

Reading: Rockman, Chapter 15

Lecture 10

Topic: Project work

In the project part of the course there are no lectures, Tutorial only. Homework is not given and there are no tutorials in this period; student groups work independently and have

consultation hours with the lecturer, who acts as an external advisor to the inventors. At the end of the three-week period, all groups deliver their reports to the course instructor.

Reading: Rockman, Chapter 17

Lecture 11

Topic: Presentations and Repetition of selected topics

All groups prepare a 20 minute presentation for other groups as well as the course instructor and possible other academic staff or students, and explain their proposal and findings in the given time-frame. Other groups ask questions during a 10 minute question session. Students need to demonstrate critical thinking and understanding of not only their projects but also the topics presented. Students are graded mostly on their reports but also on their active participation in discussions during the presentations.
No tutorials are envisaged for the last week. Besides the presentations, a session where students ask for clarifications of specific topics, exercises etc take place. A session where questions typical for the final exam are presented, with their solutions. A survey on student satisfaction with the course is conducted.

Textbooks and suggested reading materials:

1. Intellectual Property Law for Engineers and Scientists, Hoboken, New Jersey: Wiley – IEEE Press (2004), Howard Rockman
2. Intellectual Property: Inventors, Entrepreneurs, Creators
3. The Intangible Advantage: Understanding Intellectual Property in the New Economy

2.10 Scientific Writing

Prepared by Asst. Prof. Dr. Mirza Suljagić

Hours/credits: 60

Semester: II

Lectures

1. Method of presentation of course material: presentation, discussion, theoretical/practical classes, literature review

2. Form of assessment: quizzes, tests, assignments and small projects/student presentations

Tutorials

1. Writing sessions and homework

Prerequisites:

1. English languange B2 level, MS Word

Course objectives:

1. To explain the process and teach the fundamentals of effective scientific writing.
2. To teach how to write effectively, concisely, and clearly.
3. To prepare students to write an actual scientific manuscript or grant application.

Learning outcomes:

1. The students will gain knowledge in writing in both, active and passive voice.
2. The students will be able to analyze and dissect scientific news electronic articles as well as the original research articles and reviews.
3. To describe methodology of scientific writing and classify research articles
4. To write a research proposal and to develop a manuscript of their choice.
5. To apply methodology used in scientific writing.
6. To plan the process of organization of a research manuscript and to examines and analyze research publications.
7. To prepare an overview of scientific research literature.
8. The students will learn to systematically and critically analyze published scientific articles.
9. To design the structure of scientific article and independence in decision making and carrying out the tasks entrusted.
10. To design the structure of scientific article and independence in decision making and carrying out the tasks entrusted.

Lecture 1

Topic: Introduction, What makes good writing? Are there "good writers" and "bad writers"?

The students will be introduced with the syllabus and whole semester plan as well as get information about grading criteria, Tutorial and importance of attendance. The lecture will be introduction in Words, word choice, the basic elements of sentences and sentence structure. Writing in the active voice.

Homework:
- Read chapters 1-4 *Sin and Syntax* (pp. 1-87)
- Read Chapter 6 of *Successful Scientific Writing*

Lecture 2

Topic: Dissecting the news article

News-writing is the art of maximizing information and minimizing words; it's the barest-bones form of writing. The fundamentals of good writing can be learned by dissecting news articles.

In-Class Exercise: Sorting through news articles

Homework:
- Exercise: pick a lengthy feature article (3000+ words) from a popular magazine, on any subject (have fun with it!) and rewrite it as a bare-bones news article (500 words maximum for 3-unit students).
- Read chapters 5-8 of *Sin and Syntax* (pp. 88-128)

Lecture 3

Topic: Writing Basics I: Punctuation and Parallelism.

The students will be introduced with tricks for clarity, brevity, and finesse. In-Class Exercise: Peer interviews and write-up mini-profiles

Homework:
- Read chapters 9-10 of *Sin and Syntax* (pp. 129-168)
- Read Chapter 7 of *Successful Scientific Writing*
- Revise news article based on our edits
- Exercise: more sentence re-writing exercises

Lecture 4

Topic: Writing Basics II : Paragraphs, logic, and organization. Organizational strategies.

In-Class Exercise: Peer interviews and write-up mini-profiles (swap)

Homework :
- Read chapters 11-12 of *Sin and Syntax* (pp. 169-195)
- Exercise: paragraph re-writing practice
- Choose an article for the "Letter to the Editor" assignment

Lecture 5

Topic: Writing Basics III: "Putting it all together…"

In-class exercise: group rewrites of hard-to-read scientific snippets

Homework:

- Read chapters 13-16 of *Sin and Syntax* (pp. 197-finish)
- Read Chapter 5 of *Successful Scientific Writing*
- Work on your chosen manuscript, paper, thesis, or grant proposal in preparation for the 2nd half of the course.
- Write "Letter to the Editor"

Lecture 6

Topic: The Scientific Manuscript: Methods and Results Sections

The students will be exposed to examples of how to present data effectively. How to write prose that complements a table or figure.

In-class exercise: Discuss a variety of journal articles that present data in different ways; rewrite a results paragraph.

Homework:

- Read chapter 3-4 of *Successful Scientific Writing*
- Edit a peer's "Letter to the Editor"

Lecture 7

Topic: The Scientific Manuscript: The Abstract, Introduction, and Discussion

Getting to the main point and summarizing effectively. How to conduct literature reviews. Writing an effective discussion.

Homework:

Read chapter 2 of *Successful Scientific Writing*

DUE: tables, figures, results, and methods sections (as your data permit)

DUE for the following week: Write the introduction or background section for your ongoing manuscript/grant and email it to the instructor

Lecture 8

Topic: Wrap-up scientific manuscripts plus Overview of grant writing

I. Submission and authorship for scientific manuscripts.

II. Overview of the NIH grant writing process.

Homework:

- Review chapter 2 of Successful Scientific Writing
- Complete final revisions on your Letter to the Editor
- DUE TODAY: the introduction or background section of your ongoing manuscript/grant/thesis/paper
- **Conference: Sign up for a time to meet with the instructor for 30-minute individual copy-editing session. Following these sessions, revise your tables, figures, results, methods, and introduction/background.
- DUE NEXT WEEK: Write the discussion section for your ongoing manuscript/grant and email it to the instructor

Lecture 9

Topic: Wrap-up scientific manuscripts

Lectures: Submission and authorship for scientific manuscripts.

Homework:

- Review chapter 2 of Successful Scientific Writing
- Complete final revisions on your Letter to the Editor
- DUE: the introduction or background section of your ongoing manuscript/grant/thesis/paper
- **Conference: Sign up for a time to meet with the instructor for 30-minute individual copy-editing session. Following these sessions, revise your tables, figures, results, methods, and introduction/background.

Lecture 10

Topic: Overview of grant writing

Overview of the NIH grant writing process. This lecture students will be exposed to writing the section for your ongoing manuscript/grant and email it to the instructor.

Lecture 11

Topic: Cohesion and fluency

Cohesion and fluency are crucial in this section. One of the malpractices resulting in disrupted fluency is switching from passive voice to active and vice versa within the same paragraph. To improve the coherence and fluency of written paragraphs, one should be consistent in choosing the point of view: first person “we” or passive voice.

HOMEWORK: Read “How to Write Your First Research Paper”

Lecture 12

Topic: Guidelines on how to initiate the writing process and draft each section of a research manuscript I

The students will be exposed to discussion of seven rules that allow the writer to prepare a well-structured and comprehensive manuscript for a publication submission. in addition, they will learn of different strategies for successful revision. Each of those strategies represents a step in the revision process and should help the writer improve the quality of the manuscript.

Lecture 13

Topic: Guidelines on how to initiate the writing process and draft each section of a research manuscript II

The focus of this lecture will be on the best approaches to start a scientific paper, tips for writing each section, and the best revision strategies.

Lecture 14

Topic: Course Overview

Tutorial 1

Topic: Writing Basics : Paragraphs, logic, and organization

- In this class, students will get to know Exercise: paragraph re-writing practice
- Students will conduct peer interviews and write-up mini-profiles

Tutorial 2

Topic: Writing Basics I: Punctuation and Parallelism.

The students will be introduced with tricks for clarity, brevity, and finesse. Example from research articles will be demonstrated. At this class, students will need to recognize "good" and "bad" examples of clarity, brevity, and finesse.

Tutorial 3

Topic: The Scientific Manuscript: Materials and Methods and Results Sections

In this class, students will practice to write parts of scientific manuscript

The students will be introduced with the background on proper writing techniques in Methods and Results section of a scientific manuscript.

Tutorial 4

Topic: The Scientific Manuscript: Discussion and Introduction Sections

In this class, students will practice to write parts of scientific manuscript

The students will be introduced with the background on proper writing techniques in Discussion and Introduction section of a scientific manuscript.

Tutorial 5

Topic: Exercise: Write "Letter to the Editor"

Based on data and input provided in Lectures, students will practice at this exercise writing skills for a sound presentation of their manuscript in the form of "Letter to Editor".

Tutorial 6

Topic: Exercise: Edit a peer's "Letter to the Editor"

Students will analyze and make comments of peer's "Letter to the Editor".

Full bibliography of textbooks, suggested readings, materials etc:

1. Sin and Syntax, Constance Hale, Three Rivers Press, 2013, Constance Hale
2. Successful Scientific Writing: A step-by-step guide for biomedical scientists, Cambridge University Press, 2014, Janice R. Matthews
3. Provided examples and material on Science news, original research manuscripts, scientific review, grant applications

2.11 Pharmaceutical Biotechnology

Prepared by Asst. Prof. Dr. Altijana Hromić-Jahjefendić

Hours/credits: 60

Semester: III

Course format:

1. Method of presentation of course material: practical classes
2. Form of assessment: lab reports, observation, test of practical skills

Prerequisites:

1. Knowledge in biochemistry, basic biotechnology and bioprocess technologies, enzymology and microbiology

Course objectives:

1. To facilitate an understanding of major concepts of pharmaceutical biotechnology including preclinical and clinical drug development
2. To understand significance of use of microbial synthesis of biological molecules
3. To identify the regulatory issues related to the biopharmaceutical approval process
4. To understand the ethical and social implications of modern biotechnology
5. To facilitate an understanding of major concepts of pharmaceutical biotechnology in the evaluation of novel drug targets

Learning outcomes:

1. The students describe technologies used in industry and evaluate the dependence of efficiency of the obtained bioproduct regarding the applied method.
2. The student evaluates the type and characteristics of microorganisms useful for bioprocess technologies, synthesis of biological molecules and identifies microbiological contaminations occurring in fermentation industry
3. The student possesses knowledge concerning developments in industrial production of biomolecules as well as regulatory issues behind those processes.
4. The student explains the mechanisms leading to the overproduction of economically important metabolites.
5. The student knows the ethics and social implications of biomolecules production.
6. The student applies mibrobiological techniques preparing inoculum for microbial cultures.
7. The student operates basic laboratory equipment.
8. The student chooses respective culture conditions and culture method as well as analyses the final product.
9. The student reports obtained experimental results, analyses and draws conclusions and interpretations.
10. The student is aware of the value of modern research techniques.
11. The student is taking care of laboratory equipment.

12. The student proceeds according to good practice regulations in the production of pharmaceutical substances and acts in accordance with the principles of occupational health and safety.

Lecture 1

Topic: Introduction to pharmaceutical biotechnology

The students will be introduced with the syllabus and whole semester plan as well as get information about grading criteria, Tutorial and importance of attendance. The lecture will be introduction to pharmaceutical biotechnology where students will get to know definitions, historical background about development, importance in the past and present as well as application possibilities. Moreover, the introduction lecture will be more interactive where students will be asked for their opinions, understanding and thinking.

Lecture 2

Topic: Review of the major techniques used to detect specific proteins or determine protein structure/amount

Detection of proteins represents nowadays a major aspect in many life science areas. The students will be introduced with major techniques for protein purification (chromatography approaches) and detection methods (spectroscopy, spectrophotometric methods, blotting, electrophoresis etc.). Moreover, the students will get to know the way from protein expression until structure determination. The determination of protein structure part will include X-ray crystallography, NMR and cryo-EM methods explained in to the detail. Additionally, biochemical and biophysical methods will be introduced (ITC, CD, SAXS) which can help in getting broader picture about stability of proteins as well as oligomerisation state (in solution).

Lecture 3

Topic: Production of biotech compounds - major principles and procedures

This lecture has the purpose to introduce students the term biotechnology and what are biotech compounds that we use in everyday life. Modern biotechnology is the result of the following two core techniques: genetic and chemical engineering. The students will have the opportunity to learn the differences and how to apply both concepts in the large scale productions. The concepts of both methods will be extensively discussed. In genetic engineering recombinant DNA technology (plasmids, restriction enzymes etc.), gene transfer and gene cloning will be explained while in chemical engineering maintenance of microbial contamination free (sterile) atmosphere with an objective to initiate the large growth of desired eukaryotic or microbe cell in order to manufacture biotechnological products like enzymes, vaccines and antibiotics will be introduced.

Lecture 4

Topic: Formulation of biotech products, including their delivery strategies

Formulation is the process by which the active drug(s) is converted into a safe, efficient and convenient form to be administrated by patient through its (their) combination with other chemical additives. It involves the collaboration among the research chemists, analytical chemists, biologists and clinicians. The process consists of two main stages: Pre-formulation stage and the formulation stage itself. In the pre-formulation stage when a group of compounds have been identified as efficient candidate drugs, their initial characteristics are assessed by the development scientists. Certain pre-formulation studies are performed to evaluate the structural properties, degradability, biophysical and physicochemical properties of the macromolecules. The formulation stage starts after complete characterization of the properties of different substances supposed to be used as biopharmaceutical drugs with understanding their possible inactivation mechanisms during the pre-nomination stage along with the needs of both the clinician and patient. It involves the designing of suitable formulation scheme for certain drug products with certain safety, convenience and efficacy levels. This can be achieved with choosing the most suitable types of excipients, final forms and technologies that suite the administration route, the nature and whether the drug delivery is for intracellular or extracellular effects. The students will have the opportunity to learn about the stages on various examples from the literature.

Lecture 5

Topic: General concepts in pharmacology, including pharmacokinetics and pharmacodynamics of therapeutic proteins

The rational use of drugs and the design of effective dosage regimens are facilitated by the appreciation of the central paradigm of clinical pharmacology that there is a defined relationship between the administered dose of a drug, the resulting drug concentrations in various body fluids and tissues, and the intensity of pharmacologic effects caused by these concentrations. This dose-exposure-response relationship and thus the dose of a drug required to achieve a certain effect are determined by the drug's pharmacokinetic and pharmacodynamic properties. The understanding of the dose-concentration-effect relationship is crucial to any drug—including peptides and proteins—as it lays the foundation for dosing regimen design and rational clinical application. General pharmacokinetic and pharmacodynamic principles are to a large extent equally applicable to protein and peptide drugs as they are to traditional small molecule-based therapeutics. Deviations from some of these principles and additional challenges with regard to the characterization of the pharmacokinetics and pharmacodynamics of therapeutic peptides and proteins, however, arise from some of their specific properties. This chapter will highlight some of the major pharmacokinetic properties and processes relevant for the majority of therapeutic peptides and proteins and will provide examples of well-characterized pharmacodynamic relationships for protein drugs. The students will be introduced with the differences and basic concepts following the last achievements in the literature.

Lecture 6

Topic: Importance of genomics and other `Omics` technologies in biomarkers development

Genomics as interdisciplinary field of biology has the focus on the structure, function, evolution, mapping, and editing of genomes. In contrast to genetics, genomics aims at the collective characterization and quantification of all of an organism's genes, their interrelations and influence on the organism. The branches of science known informally as omics are various disciplines in biology whose names end in the suffix -omics, such as genomics, proteomics, metabolomics, and glycomics. Omics aims at the collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism or organisms. Those technologies will be introduced to the students where they need to know basic definitions and concepts and to know where to apply each of those technologies. Moreover, the focus will be on application of omics in biomarker development. Biomarkers are playing an increasingly important role in drug discovery and development and can be applied for many purposes, including disease mechanism study, diagnosis, prognosis, staging, and treatment selection. Advances in high-throughput "omics" technologies, including genomics, transcriptomics, proteomics and metabolomics, significantly accelerate the pace of biomarker discovery. Comprehensive molecular profiling using these "omics" technology has become a field of intensive research aiming at identifying biomarkers relevant for improved diagnostics and therapeutics. Although each "omics" technology plays important roles in biomarker research, different "omics" platforms have different strengths and limitations.

Lecture 7

Topic: Pharmacogenomics and personalized therapy

Pharmacogenetics and pharmacogenomics have been widely recognized as fundamental steps toward personalized medicine. They deal with genetically determined variants in how individuals respond to drugs, and hold the promise to revolutionize drug therapy by tailoring it according to individual genotypes. The goal of personalized medicine is to provide individualized treatment and to predict the clinical outcome of different treatments in different patients. Pharmacogenomics is one of the core elements in personalized medicine. The basic concept is that interindividual variability in drug response is a consequence of multiple factors, including genomics, epigenomics, the environment and a patient's characteristics, such as gender, age and/or concomitant medication. The students will get to know the application procedures in various examples of personalized therapy. Moreover, this lecture will be covered with recent advances in medicine published in scientific journals where each student has to choose one publication and briefly introduce others about the topic and conducted research.

Lecture 8

Topic: Major applications and issues associated with gene therapy

Gene therapy holds promise for treating a wide range of diseases, such as cancer, cystic fibrosis, heart disease, diabetes, hemophilia and AIDS. Gene therapy can be used to correct or replace the defective genes responsible. Gene therapy has been especially successful in the

treatment of combined immunodeficiency syndromes, showing lasting and remarkable therapeutic benefit. There are two general approaches for introducing genes into a cell: viral and nonviral. Viral vectors have been used in ~70% of the clinical trials to date. Viral vectors are extremely efficient at transferring genes but can create some safety risks. Gene transfer mediated by viral vectors is referred to as transduction. Nonviral vectors are considered to be much safer than viral vectors, but at present, they are fairly inefficient at transferring genes. Gene transfer mediated by nonviral vectors is referred to as transfection. The concepts will be discussed in the class among the students and examples of concepts will be covered using recent achievements in the science and medicine. However, not only applications but health and ethical issues using the methods will be discussed among the students.

Lecture 9

Topic: Principles of gene silencing and its potential therapeutic applications

During recent decades there have been remarkable advances in biology, in which one of the most important discoveries is RNA interference (RNAi). RNAi is a specific post-transcriptional regulatory pathway that can result in silencing gene functions. Efforts have been done to translate this new discovery into clinical applications for disease treatment. However, technical difficulties restrict the development of RNAi, including stability, off-target effects, immunostimulation and delivery problems. The major principles which every student should already know from the molecular biology and genetics lecture will be repeated with the impact on application of this method in therapeutic approach. Again, it will be covered by reading and understanding of recent literature since gene silencing techniques have been widely used by researchers to study genes associated with disorders. These disorders include cancer, infectious diseases, respiratory diseases, and neurodegenerative disorders. Gene silencing is also currently being used in drug discovery efforts, such as synthetic lethality, high-throughput screening, and miniaturized RNAi screens.

Lecture 10

Topic: The major application of cell therapy in pharmaceutical biotechnology

Cell therapies offer the promise of treating and altering the course of diseases which cannot be addressed adequately by existing pharmaceuticals. Cell therapies are a diverse group across cell types and therapeutic indications and have been an active area of research for many years but are now strongly emerging through translation and towards successful commercial development and patient access. Cell therapies can be classified by the therapeutic indication they aim to address, e.g. neurological, cardiovascular, ophthalmological; by whether they comprise cells taken from and administered to the same individual (autologous) or derived from a donor (allogeneic); or most commonly by the cell types, often using the EU regulatory classification. The EU regulatory classification of cell-based therapies discriminates between minimally manipulated cells for homologous use (transplants or transfusions) and those regulated as medicines which are required to demonstrate quality, safety and efficacy standards to obtain a marketing authorization before becoming commercially available

(referred to as Advanced Therapy Medicinal Products; ATMPs) which are further subdivided into somatic cell, gene therapy and tissue engineered products. The application of cell therapy (e.g.stem cells) offer great potential in tissue engineering procedures that are designed to generate three-dimensional structures characteristic of specific tissues for use in the fields of organ transplantation and wound treatment which represents the part of pharmaceutical biotechnology. These applications and methods will be introduced to the students where they need to understand the definitions, concepts as well as regulations associated with the application of cell therapy mainly prescribed by EU.

Lecture 11

Topic: Significance of industrial microbiology in modern pharmaceutical biotechnology

Industrial microbiology is a branch of biotechnology that applies microbial sciences to create industrial products in mass quantities, often using microbial cell factories. There are multiple ways to manipulate a microorganism in order to increase maximum product yields. Introduction of mutations into an organism may be accomplished by introducing them to mutagens. Another way to increase production is by gene amplification, this is done by the use of plasmids, and vectors. The plasmids and/ or vectors are used to incorporate multiple copies of a specific gene that would allow more enzymes to be produced that eventually cause more product yield.[1] The manipulation of organisms in order to yield a specific product has many applications to the real world like the production of some antibiotics, vitamins, enzymes, amino acids, solvents, alcohol and daily products. Microorganisms play a big role in the industry, with multiple ways to be used. Medicinally, microbes can be used for creating antibiotics in order to treat antibiotics. Microbes can also be used for the food industry as well. Microbes are very useful in creating some of the products that are consumed by people in everyday life. The chemical industry also uses microorganisms in order to synthesis amino acids and organic solvents. Microbes can also be used in an agricultural application for use as a biopesticide instead of using dangerous chemicals and or inoculants to help plant proliferation. The applications and full potential in pharmaceutical biotechnology will be introduced to the students and major concepts about the application procedures will be discussed.

Lecture 12

Topic: Biotech products: Insulin/Vaccines

This lecture is basically continuation of Lecture 11 since microorganisms are used for insulin and vaccine development/production. The basic concepts of microbiology covered in undergraduate studies are expected to be known as well as varieties of vaccines and its development.

The lecture will focus more on application of microorganisms from pharmaceutical biotechnology point of view where various types of vaccines and their way of production will be introduced to the students. Moreover, production of insulin using variety of microorganisms will be covered. Here the students will have the opportunity to get to know

production procedures, development until FDA approval and potential for modifications and improvement.

Lecture 13

Topic: Bioethical and regulatory issues related to applications of pharmaceutical biotechnology

Ethical issues that arise from modern biotechnologies include the availability and use of privileged information, potential for ecological harm, access to new drugs and treatments, and the idea of interfering with nature. Applications include agriculture, health care but also pharmaceutical biotechnology. Biotechnology comprises on various techniques that exploit the application of biological organisms, systems or processes for the benefit of human being. It has helped the medical science by developing new diagnostic tools and kits to diagnose the diseases. Industrially it has created a thriving business in enzymes, antibody and promises newer and less expensive products. Biotechnology has improved the agricultural production, by developing varieties having resistance against biotech and abiotech stresses. Production of diseases free plants with improved nutritional value has proven the role of biotechnology in agriculture sector. Theses biotechnological techniques also have been criticized by various religious scholars, scientist and economists. This lecture will focus on main ethical issues where students will have the opportunity to express their own opinion in class discussion what would be the major ethical concern regarding applications of pharmaceutical biotechnology and its main products.

Lecture 14

Topic: Selected topics in pharmaceutical biotechnology

This lecture will enable students to look in the literature for most recent advances in pharmaceutical biotechnology. They will choose a topic and briefly introduce it to other colleagues in the class. The main focus will be in applications and successes covered previously in the lectures (cell therapy, gene therapy, vaccine development, ethical issues etc.). This kind of lecture will have open class discussion and the active contribution of other students will be noted for their grading.

Lecture 15

Topic: Review of lectures and preparations for final exam

This last lecture in semester will be used to go through all lectures covered in the semester and to focus on main topics and parts which every student must know after completing this course. Moreover, it will be discussed about final exam and the form of final exam. The students will be prepared for various types of questions during the final exam. Also, if someone needs additional explanations regarding any of covered topics, they will have opportunity to ask during this last lecture.

Tutorial 1

Topic: Lactic acid bacteria – structure, characteristics, lactic acid fermentation

Lactic acid bacteria (LAB) are capable of converting carbohydrate substrates into organic acids (mainly lactic acid) and producing a wide range of metabolites. Due to their interesting beneficial properties, LAB are widely used as starter cultures, as probiotics, and as microbial cell factories.

In this class, students will get to know the structure of LAB, main characteristics regarding growth condition and benefit for human health and perform lactic acid fermentation in lab.

Experiment performed in the lab would include application of MRS medium for the growth of LAB. Also HHD agar will be used for separation and enumeration of bacteria based on the fermentation process. This medium is based on the colour change of the medium due to the pH change. To be more precise, bromcresol green in the medium reacts in the change of the pH that is caused by the fermentation process of the LAB. If the bacteria is a heterofermentative type, the colour of the medium will not change and it will remain blue. If the bacteria is homofermentative, the colour will change to green because of the drop of the pH. If the pH drops bellow 3.8 the colour will change, while if it remains in the pH 5.4 pH range the colour of the medium remains blue.

Tutorial 2

Topic: Yeast (Baker's, winery, distillery) - structure, characteristics, alcoholic fermentation

In this class, students will get to know various types of yeasts used for the production of bread and alcoholic beverages. Those various kinds of yeasts have different structure as well as different characteristics regarding growth conditions. Ethanol fermentation, also called alcoholic fermentation, is a biological process which converts sugars such as glucose, fructose, and sucrose into cellular energy, producing ethanol and carbon dioxide as by-products. Because yeasts perform this conversion in the absence of oxygen, alcoholic fermentation is considered an anaerobic process. The overall chemical formula for alcoholic fermentation is: $C_6H_{12}O_6 \rightarrow 2\ C_2H_5OH + 2\ CO_2$

The students will be introduced with the background of fermentation formula. One way to test for alcoholic fermentation in yeast cells is to evaluate whether CO2 is produced by yeast cells in water with sugar vs. water without sugar. CO2 can be produced by a simple chemical reaction without any living cells or enzymes and without producing ATP (e.g., baking soda and vinegar react to produce CO2). This raises the possibility that dead yeast cells in sugar water produce CO2 as a result of a simple chemical reaction without carrying out alcoholic fermentation. To evaluate this possibility, test for CO2 production by dead yeast cells will be introduced. In this experiment the students will test for CO2 production by living yeast cells in plain water, by living yeast cells in sugar water and by dead yeast cells in sugar water using standard protocols.

Tutorial 3

Topic: Production of vitamins by microorganisms, biosynthesis of glucose oxidase

This lab class will be used to introduce the students with main concepts of vitamin production using various kinds of microorganisms. For this part, video material will be provided and

students will write a short observation report about it. Second part of class is biosynthesis of glucose oxidase. Glucose oxidase (beta-D-glucose:oxygen 1-oxidoreductase; EC 1.1.2.3.4) catalyzes the oxidation of beta-D-glucose to gluconic acid, by utilizing molecular oxygen as an electron acceptor with simultaneous production of hydrogen peroxide. Microbial glucose oxidase is currently receiving much attention due to its wide applications in chemical, pharmaceutical, food, beverage, clinical chemistry, biotechnology and other industries. Novel applications of glucose oxidase in biosensors have increased the demand in recent years. The experiment that will be performed in this class includes Glucose Oxidase Assay Kit provides a convenient tool for very sensitive and convenient detection of glucose oxidase in a variety of samples. With D-glucose as a specific substrate, the absorbance (λ = 570 nm) or fluorescence (Ex/Em = 535/585 nm) signal is proportional to the activity of GOx in the sample. The protocol will be provided with the kit and allow students to follow every step of the experiment in the correct way.

Bibliography of textbooks, suggested readings materials:

1. Crommelin, Daan J. A., Sindelar, Robert, Meibohm, Bernd: Pharmaceutical Biotechnology: Fundamentals and Applications, Springer (2019); Gary Walsh: Pharmaceutical Biotechnology: Concepts and Applications, Wiley (2013)
2. https://www.ncbi.nlm.nih.gov/books/NBK234703
3. https://bmcmicrobiol.biomedcentral.com/articles/10.1186/s12866-018-1356-8
4. https://www.nature.com/scitable/topicpage/yeast-fermentation-and-the-making-of-beer-14372813/
5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4993173/

2.12 Applied Immunotechnologies

Prepared by Dr. Daria Ler

Hours/credits: 60

Semester: III

Course format:

1. Method of presentation of course material:
   presentation, theoretical and practical classes, literature review and discussions
2. Form of assessment:
   Quizzes/Tests, assignments and projects and student presentations

Prerequisites:

Principles of Molecular Biology, Biochemistry, Immunology and Molecular Biology Techniques

Course objectives:

- Identify the fundamentals of immunologic science for the management of human disease and its clinical relevance.
- Identify key immunologic and molecular processes with comprehensive and consistent design program.
- Become proficient with the experimental observations and techniques required to perform the most commonly used protocols at the molecular, cellular, and whole-organism levels.
- Identify the components of well-controlled analysis.
- Use critical thinking skills to troubleshoot problems as they occur and determine possible causes.

Learning outcomes:

1. Investigate fundamental principles of molecular immunological methods and their implications in human diseases and treatment.
2. The students will explore the principles of methodology, quality assurance and the application of immuno-technologies to the research and clinical laboratory.
3. The students are exposed to aspects of statistics, quality control, regulatory issues and applications of immunological methods to the diagnosis and prognosis of the disease.
4. The student follows and apply related protocols and tools in basic and clinical research.
5. The student comprehends current laboratory approaches through applying immuno-biochemical and molecular biology principles.

6. Correlating tools used in research with biochemical and immunological applications on cellular level.
7. To recognize the importance of strong work ethics, persistence and intellectual integrity.
8. Understands gradually the important role of good laboratory and clinical practice.
9. Successfully develop protocols and implement them.
10. Works as a team member, be responsible, confident, independent and able to actively participate in discussions and tasks.

Lecture 1

Topic: Properties and overview of immune responses; types of immunity, cellular components.

Students will be introduced to historical perspective of immunology, early vaccination studies, vaccination as an ongoing, worldwide enterprise. Additionaly, it will be described how immunity involves both, humoral and cellular components and how foreign substances are being recognized by the immune system. Important concepts for understanding the mammalian immune response will be also discussed, as well as pathogen recognition molecules which can be encoded as genes or generated by DNA rearrangement.

Lecture 2

Topic: Innate immunity, stimulation and mechanisms of limitations.

In this part the students will learn about anatomical barriers to infection, epithelial barriers which prevent pathogen entry into the body's interior. It will be presented how antimicrobial proteins and peptides can act as *kill would-be* invaders, and how cellular innate response receptors and signaling work at the molecular level.

Lecture 3

Topic: Antibodies and antigens: structure, synthesis, assembly and expression.

Antibodies and antibody-derived macromolecules have established themselves as the mainstay in protein-based therapeutic molecules (biologics). Mammals make five Tutorial of antibodies, each of which mediates a characteristic biological response following antigen binding Our knowledge of the structure, synthesis and function relationships of antibodies provides a platform for protein engineering that has been exploited to generate a wide range of biologics for a host of therapeutic indications. In this section, students will learn basic understanding of the antibody structure along with how that knowledge has leveraged the engineering of antibody and antibody-related therapeutics having the appropriate antigen affinity, effector function, and biophysical properties. The platforms examined include the development of antibodies, antibody fragments, bispecific antibody, and antibody fusion products, whose efficacy and how manufacturability can be improved via humanization, affinity modulation, and stability enhancement. We will also review the design and selection

of binding arms, and avidity modulation. Different strategies of preparing bispecific and multispecific molecules for an array of therapeutic applications are included.

Lecture 4

Topic: The complement system.

The major pathways of complement activation and the classical pathway, initiated by antibody binding to antigens, will be described. Topics will cover also how complement receptors connect complement-tagged pathogens to effector cells, complement enhancement of host defense against infection, regulation of complement activity and how complement acts at the interface between innate and adaptive immunities, microbial complement evasion strategies, and the evolutionary of the complement system.

Lecture 5

Topic: Immune receptors and signal transduction: immune receptor family, T-cell receptor, B-lymphocyte antigen receptor complex.

This section will cover B-Cell Receptor expression, editing of potentially autoreactive receptors, mRNA Splicing which regulates the expression of membrane-bound versus secreted Ig, T-Cell Receptor Genes and their expression, understanding the Protein Structure of the TCR, Recombination of TCR gene segments, and allelic exclusion.

Lecture 6

Topic: Lymphocyte development and antigen receptor gene rearrangement.

The student will be introduced with the organization and expression of lymphocyte receptor genes and the puzzle of Ig gene structure. Two early theoretical models of antibody genetics and breakthrough experiments will be shown. Multigene organization of Ig genes, i.e. κ Light-Chain Genes (V, J, and C Segments), λ Light-Chain Genes (Paired J and C Segments), Heavy-Chain Gene Organization (VH, D, JH, and CH Segments) will be explained, along with the Mechanism of V(D)J Recombination.

Lecture 7

Topic: Differentiation and functions of CD4+ and CD8+ effector T cells.

$CD4^+$ and $CD8^+$ T lymphocytes have been shown to produce pro-inflammatory cytokines and exert cytotoxicity especially in disease conditions. Investigators have suggested that $CD4^+/CD8^+$ T lymphocytes are highly activated cells exhibiting an effector memory phenotype. Here we will explore the what is the function, role and the difference between these two T cell subsets. A greater understanding of these factors has the potential to aid the design of more effective vaccines and to improve regulation of pathologic CD4/CD8 T cells, such as in the context of autoimmunity and allergy.

Lecture 8

Topic: B-cell activation and Antibody production.

Vertebrates inevitably die of infection if they are unable to make antibodies. Antibodies defend us against infection by binding to viruses and microbial toxins, thereby inactivating them. The binding of antibodies to invading pathogens also recruits various types of white blood cells and a system of blood proteins, collectively called *complement* (discussed in Lecture 4). Synthesized exclusively by B cells, antibodies are produced in billions of forms, each with a different amino acid sequence and a different antigen-binding site. In this section, we will discuss the structure and function of antibodies and how they interact with antigen.

Lecture 9

Topic: Mechanism of humoral immunity: neutralization, opsonisation and phagocytosis.

Humoral immunity is the type of host defense mediated by secreted antibodies that is necessary for protection against extracellular microbes and their toxins. Antibodies prevent infections by blocking microbes from binding to and entering host cells. Antibodies also bind to microbial toxins and prevent them from damaging host cells. In addition, antibodies function to eliminate microbes, toxins, and infected cells from the body. Although antibodies are a major mechanism of adaptive immunity against extracellular microbes, they cannot reach microbes that live inside cells. However, humoral immunity is vital even for defense against microbes that live inside cells, such as viruses, because antibodies can bind to these microbes before they enter host cells or during passage from infected to uninfected cells, thus preventing spread of infection. Defects in antibody production are associated with increased susceptibility to infections by many bacteria, viruses, and parasites. All the vaccines that are currently in use work by stimulating the production of antibodies.

This chapter describes how antibodies provide defense against infections, addressing the following questions:

1. What are the mechanisms used by secreted antibodies to combat different types of infectious agents and their toxins?
2. How do antibodies combat microbes that enter through the gastrointestinal and respiratory tracts?
3. How do antibodies protect the fetus and newborn from infections?

Lecture 10

Topic: Immunologic tolerance and mechanism of autoimmunity.

Immunological tolerance is a complex series of mechanisms that impair the immune system to mount responses against self antigens. Central tolerance occurs when immature lymphocytes encounter self antigens in the primary lymphoid organs, and consequently they die or become unreactive. Peripheral tolerance occurs when mature lymphocytes, escaped from negative selection during ontogeny, encounter self antigens in secondary lymphoid organs and undergo anergy, deletion or suppression. Here it will be shown and discussed how

failure or breakdown of immunological tolerance results in autoimmunity and autoimmune diseases, and how such events are related to both, genetic and environmental factors.

Lecture 11

Topic: Immunity to microbes; vaccine development.

Vaccines are the most effective means available for preventing infectious diseases. However, vaccine-induced immune responses are highly variable between individuals and between populations in different regions of the world. Understanding the basis of this variation is of fundamental importance to humanhealth. Although the factors that are associated with intra- and inter-population variation in vaccine responses are manifold, emerging evidence points to a key role for the gut microbiome in controlling immuneresponses to vaccination. Much of this evidence comes from studies in mice. In this section the studies on vaccination in subjects treated with broad-spectrum antibiotics will be desribed and disscussed. These studies have provided causal evidence and mechanistic insights into how the microbiota controls immune responses in humans.

Lecture 12

Topic: Transplantation immunology.

Historically the focus of transplant immunology has mainly relied on targeting the mechanisms of specific (adaptive) immunity. However, there are emerging data that both, rejection and tolerance are influenced by both nonspecific (innate) and adaptive immune responses. These data will be shown and expolred in this part of lectures.

Lecture 13

Topic: Tumor immunity: tumor antigens, immune response, immunotherapy.

Cancer is a major health problem worldwide and one of the most important causes of morbidity and mortality in children and adults. The lethality of malignant tumors is due to their uncontrolled growth within normal tissues, causing damage and functional impairment. The malignant phenotype of cancers reflects defects in regulation of cell proliferation, resistance of the tumor cells to apoptotic death, ability of the tumor cells to invade host tissues and metastasize to distant sites, and tumor evasion of host immune defense mechanisms. The existence of immune surveillance has been demonstrated by the increased incidence of some types of tumors in immunocompromised experimental animals and humans. It is now clear that the innate and adaptive immune systems do react against many tumors, and exploiting these reactions to specifically destroy tumors remains an important goal of tumor immunologists. In this section an overview of several characteristics of tumor antigens and immune responses to tumors will be desribed and it presented how are they fundamental to an understanding of tumor immunity and for the development of strategies for cancer immunotherapy.

Lecture 14

Topic: Hypersensitivity: mechanisms and classification, therapeutic approaches.

Hypersensitivity reactions occur when the normally protective immune system responds abnormally, potentially harming the body. Various autoimmune disorders as well as allergies fall under the umbrella of hypersensitivity reactions. A symptomatic reaction only occurs in sensitized individuals, i.e., they must have had at least one prior asymptomatic contact with the offending antigen. In this particular section the students will get familiar with the classification types and the examples of hypersensitivity reactions which occurs when the normally protective immune system responds abnormally, potentially harming the body. Hypersensitivity reactions are commonly classified into four types. Type I hypersensitivity reactions are immediate allergic reactions (e.g., food and pollen allergies, asthma, anaphylaxis), type II hypersensitivity reactions are referred to as cytotoxic, as they involve antibodies that are specific to particular tissues within the body and cause destruction of cells in these tissues (e.g., autoimmune hemolytic anemia, Goodpasture syndrome), type III hypersensitivity reactions are immune complex-mediated, with tissue damage caused by antigen-antibody complex deposition (e.g., many vasculitides and glomerulonephritides), and type IV hypersensitivity reactions (e.g., TB skin tests, contact dermatitis) are delayed and cell-mediated and are the only hypersensitivity reaction that involves sensitized T lymphocytes rather than antibodies.

Lecture15

Topic: Allergy: IgE production and allergic reactions, genetic susceptibility, pathogenesis and therapy.

Allergic disease can be viewed as an early manifestation of immune dysregulation. Environmental exposures including maternal inflammation, diet, nutrient balance, microbial colonization and toxin exposures can directly and indirectly influence immune programming in both pregnancy and the postnatal period. Targeting aspects of the modern environment that promote aberrant patterns of immune response is logical for interventions aimed at primary prevention of allergic disease. Defining the mechanisms that underpin both, natural and therapeutic acquisition of immunological tolerance in childhood will provide insights into the drivers of persistent immune dysregulation. In this overview, we will summarize evidence that allergy is a consequence of intrauterine and early life immune dysregulation, with specific focus on contributing environmental risk factors. We will explore the immunological mechanisms which underpin tolerance and persistence of allergic disease during childhood.

Tutorial 1

Topic: HLA genotyping

HLA typing is a kind of genetic test used to identify certain individual variations in a person's immune system. The process is critical for identifying which people can safely donate bone

marrow, cord blood, or an organ to a person who needs a transplant. HLA stands for human leukocyte antigen, but it is almost always referred to as HLA. It includes testing for Abs targeted to specific HLA proteins. If a person already has an antibody against an HLA protein (i.e., if it already is primed to attack a certain color string), it may attack that protein if it is transplanted. It will be demonstrated how Lymphocyte crossmatching is performed to see if the recipient has an antibody against a protein on the donor's lymphocytes.The entire data sets and controls are composed by molecular typing for both HLA class I and II genes. The PCR sequence-specific primer method and/or the reverse PCR sequence specific oligonucleotide hybridization method is planned to be demonstrated.

Tutorial 2

Topic:qRT-PCR detection of genetically based autoimmune disesasses

The students willwhich include all diseases caused by an extreme reaction of the immune system against the body's own tissue. Quantitative PCR (qPCR) is used to detect, characterize and quantify nucleic acids for numerous applications. Commonly, in RT-qPCR, RNA transcripts are quantified by reverse transcribing them into cDNA first, as described above and then qPCR is subsequently carried out. As in standard PCR, DNA is amplified by 3 repeating steps: denaturation, annealing and elongation. However, in qPCR, fluorescent labeling enables the collection of data as PCR progresses. This technique has many benefits due to a range of methods and chemistries available. In dye-based qPCR (typically green), fluorescent labeling allows the quantification of the amplified DNA molecules by employing the use of a dsDNA binding dye. During each cycle, the fluorescence is measured. The fluorescence signal increases proportionally to the amount of replicated DNA and hence the DNA is quantified in "real time".Students will work practical on identifying different genetically based autoimmune disesasses amplifying various sequences on DNA and RNA level include multiple sclerosis, diabetes type I, rheumatoid arthritis and Crohn's disease and identifying gene mutation and hetero- homozygosity.

Tutorial 3

Topic:Enzyme-linked immunosorbent assay (ELISA)

ELISA is a plate-based assay technique designed for detecting and quantifying soluble substances such as peptides, proteins, antibodies, and hormones. Other names, such as enzyme immunoassay (EIA), are also used to describe the same technology. In an ELISA, the antigen (target macromolecule) is immobilized on a solid surface (microplate) and then complexed with an antibody that is linked to a reporter enzyme. Detection is accomplished by measuring the activity of the reporter enzyme via incubation with the appropriate substrate to produce a measurable product. The most crucial element of an ELISA is a highly specific antibody-antigen interaction. In this pratical section, student will work on detection of antibody indexes of various microorganisms, autoimmune diseases etc. Following antibodies and/ antigens will be performed: antibodies against Rubella, Toxoplasma, HSV i and II

viruses, Citomegalo virus (CMV), Epstein Barr Virus (EBV), ENA 6-profiles, Antids DNA, ANA-screen, Helibacter pylorii, anti-Gliadine and anti-Tranglutamine etc.

Tutorial 4

Topic: Immunoblolotting techniques- detection of specific Immunoglobulins (IgG, IgA, IgM, IgE).

Based upon the observation that allergic responses typically affect the skin, gut, and respiratory tract, the major sites of parasitic invasion, it is thought that IgE evolved as a defense mechanism against parasitic infestation. Helminths stimulate a vigorous IgE production, including parasite-specific IgE antibody. However, another hypothesis for the beneficial function of IgE antibodies is that they play a key role in very early recognition of foreign material ("gate keeper function") or a general potentiation of the immune system response by improved antigen presentation. Actually, allergy triggered by IgE may provide a beneficial function to the host; the typical allergic reactions of mucus secretion, sneezing, itching, coughing, bronchoconstriction, tear production, inflammation, vomiting and diarrhoea are all mechanisms that expel allergenic proteins from the body.The measurement of allergen specific IgE antibodies in serum is of similar diagnostic value to that of skin tests but has a much higher reproducibility and is not influenced by ongoing symptoms or treatment, eg, antihistamines or anti-inflammatory therapy. In some instances, especially in food allergic individuals where, in rare cases, even skin prick testing with minute amounts of allergen might cause an anaphylactic reaction, in-vitro tests using blood samples is a safe method to determine levels of specific IgE antibodies. In-vitro tests are also preferred for individuals who have widespread eczema, which precludes skin prick testing. For the purpose of detectin levels of IgE, students will perform different alergen panels such as nutritive (20 alergens), inhalatory (20 alergens), antibiotics and milk-gluten detection.

Textbooks and suggested reading materials:

1. Abbas, Abul K.; Lichtman, Andrew H.; Pillai, Shiv.: Cellular and molecular immunology 9th ed, Elsevier Science Health Science (2017)
2. Jenni Punt, Sharon Stranford, Patricia Jones, Judy Owen: Kuby Immunology, W. H. Freeman; Eighth edition (2018)
3. The World of the Cell by Hardin, Bertoni, Kleinsmith (PEARSON) (2012)

2.13 Cell Signalling Networks

Prepared by Asst. Prof. Dr. Mirza Suljagić

Hours/credits: 60

Semester: III

Lectures

1. Method of presentation of course material: presentation, discussion, theoretical/practical classes, literature review

2. Form of assessment: quizzes, tests, assignments and small projects/student presentations

Tutorials

1. Original research paper analysis and homework

Prerequisites:

1. Principles of Molecular Biology, Biochemistry, Genetics, Molecular Biology Techniques

Course objectives:

1. To explain the basic principles of intracellular signalling networks.
2. To identify the important parameters in intracellular signal transduction system.
3. To recognize main signal transduction pathways and explain their biological outcome.
4. To explain pato-physiological conditions as a result of deregulated cell signaling networks.

Learning outcomes:

1. To explore the fundamental principles of molecular methods and their implications in intracellular molecular signalling, as well as disease occurrence.
2. To learn the fundamental principles, methodology, and the application of molecular methods in intracellular protein networks.
3. To discuss cell cycle control mechanisms and cancer occurrence
4. To utilize tools used in clinical research with biomedical applications on different level of genetic information
5. To demonstrate principles of protein / vesicular trafficking and control.
6. To to work as a team member, be responsible, confident, independent and able to actively participate in all discussions and tasks.
7. To prepare an overview of scientific research literature.

Lecture 1

Topic: Presentation of the Syllabus - Introduction of the Course

Students will be introduced with the course syllabus, course goals and learning outcomes. The assments metodology will be explained and overview of the whole couse will be presented. Discussion on critical course points will be facilitated.

Lecture 2

Topic: Organelles of the Eukaryotic cell

Organelles contain a unique group of proteins that are essential for the organelle to carry out its unique functions. In addition, students will see how certain chimeric proteins-consisting of a protein of interest covalently linked to a naturally fluorescent protein-enable biologists to image movements of individual proteins in live cells.

Homework: Explore the first part of Chapter 9

Lecture 3

Topic: Visualizing, Fractionating and Culturing Cells ; Light microscopy, Electron microscopy, Purification of Organelles, Isolation and culturing the cells

Developments in both light and electron microscopes together with those techniques for generating monoclonal antibodies, have enabled modern cell biologists to detect specific proteins in fixed cells' thus providing a static image of their location within cells. Students will learn how Cultured cells have several advantages over intact organisms for cell biology research. Cells of a single specific type can be grown in culture, experimental conditions can be better controlled, and in many cases a single cell can be readily grown into a colony of many identical cells.

Homework: Explore the end of Chapter 9

Lecture 4

Topic: Biomembrane structure: Lipid composition, structural organization, protein components

To fully understand the nature of cellular signaling, students will be exposed to presentations on conversion of extracellular signal through transmembrane receptors. Cellular membranes participate in many aspects of cell structure and function. The plasma membrane defines the cell and separates the inside from the outside. In eukaryotes, membranes also define the intracellular organelles such as the nucleus and lysosome. These biomembranes all have the same basic architecture-a phospholipid bilayer but they are not static; their function is not to prevent all exchange across a border. Each cellular membrane has its own set of proteins that allow it to carry out its multitude of specific functions.

Homework: Explore Chapter 10

Lecture 5

Topic: Moving proteins into Membranes and Organelles

In this lecture students will learn about the delivery of newly synthesized proteins to their proper cellular destinations, usually referred as Protein targeting or Protein sorting. First process involves targeting of the protein to the membrane of intracellular organelle, during translation or after the protein sythesis. A second general sorting process is known as the Secretory pathway. It begins in the ER and include not only soluble and membrane proteins that reside in the ER itself, but also proteins that are secreted from the cell, resident proteins in the Golgi complex and lysosomes, and integral proteins in the membrane, transmembrane receptors. These concepts are essential for students understanding of the material demonstrated later during the course.

Homework: Explore Chapter 13

Lecture 6

Topic: Molecular mechanisms of vesicular trafficking and endocytosis

In this lecture we will discuss the related processes of endocytosis and autophagy, which deliver proteinsand small molecules from either outside the cell or from the cytoplasm to the interior of the lysosome for degradation. Soluble secreted proteins follow the same pathway to the cell surface as plasma membrane proteins, but instead of remaining embedded in the membrane, secreted proteins are released into the aqueous extracellular environment in soluble form. Examples of secreted proteins are digestive enzymes, peptide hormones, serum proteins, and collagen. In contrast to the secretory pathway, which is generally used to deliver newly synthesized membrane proteins to their correct address the endocytic pathway is used to take up substances from the cell surface into the interior of the cell.

Homework: Explore Chapter 14

Lecture 7

Topic: Signal transduction and cellular responses: Cell surface receptors and components of intracellular signal transduction pathways

We will discuss how many extracellular signaling molecules are synthesized and released by signaling cells within the organism. In all cases signaling molecules produce a specific response only in target cells that have receptors for the signaling molecules. Many types of chemicals are used as signals: small molecules (e.g., amino acid or lipid derivatives, acetylcholine) peptides(e.g', ACTH and vasopressin), soluble proteins (e.g., insulin and growth hormone) and many proteins tethered to the surface of a cell or bound to the extracellular matrix. Some small signaling molecules are hydrophilic and are transported by membrane proteins into the cell cytoplasm in order to influence cell behavior. Most signaling molecules, however, are too large and too hydrophilic to penetrate through the plasma membrane. These bind to cell-surface receptors that are integral proteins.

Homework: Explore Chapter 15

Lecture 8

Topic: G protein-coupled receptors, cAMP and PKA, second messangers

Main focus of the course is to understand molecular mechanism of intracellular signaling neworks that are deciding the fate of the cell, including, division, migration, autophagy, differentiation and apoptosis. In this lecture we explore the main molecular players that are facilitating these proccesses. The cytosolic concentrations of second messengers such as Ca2* and cAMP, increase or occasionally decrease in response to binding of ligand to cell-surface receptors. Here we consider the general features of

GPCR signal transduction and then discuss each of the membrane- bound components in turn: the receptor, the trimeric G protein, and the effector proteins.

Homework: Explore Chapter 15

Lecture 9

Topic: Pathways that control gene activity: Receptor tyrosine kinases, Ras/MAP pathway, PI3/Akt pathway, NF-kB activity

Extracellular signals that induce long-term responses affect many aspects of cell function: division, differentiation, and even communication with other cells. Alterations in these signaling pathways cause many human diseases, including cancer, diabetes, and immune defects. In addition to the crucial roles external signals play in development, signals are essential in enabling differentiated cells to respond to their environment by changing their shape, metabolism, or movement. For example, one type of transcription factor (NF-kB) ultimately impacts expression of more than 150 genes involved in the immune response to infection; NF-kB is activated by many protein hormones that act on immune system cells.

Homework: Explore Chapter 16

Lecture 10

Topic: Regulating the Eukaryotic Cell Cycle: CDKs and cell-cycle control

Whithin this topic students will leasrn about molecular mechnism of the control of cell division that is vital to all organisms. In unicellular organisms, cell division must be balanced with cell growth so that cell size is properly maintained. If several divisions occur before parental cells have reached the proper size, daughter cells eventually become too small to be viable. If cells grow too large before cell division, the cells function improperly and the number of cells increases slowly. In developing multicellular organisms, the replication of each cell must be precisely controlled and timed to faithfully and reproducibly complete the developmental program in every individual. The term cell cycle refers to the ordered series of macromolecular events that lead to cell division and the production of two daughter cells, each containing chromosomes identical with those of the parental cell. Two main molecular processes that take place during the cell cycle will be thoroughly discussed within this lecture.

Homework: Explore Chapter 20

Lecture 11

Topic: Regulating the Eukaryotic Cell Cycle: Checkpoints in Cell cycle regulation

In this lecture students will learn about mechanisms controling the cell cycle. During cell cycle molecular mechanisms that control the process with resting intervals in between: during the S phase of the cycle, the parental chromosomes are duplicated; in mitosis (M phase), the resulting daughter chromosomes are distributed to each daughter cell. High accuracy and fidelity are required to assure that each daughter cell inherits the correct number of each chromosome. Chromosomal abnormalities are prevented by multiple layers of control mechanisms that regulate the eukaryotic cell cycle.

Homework: Explore Chapter 20

Lecture 12

Topic: Cell Birth, Lineage and Death: Stem cells and differentiation

Students will learn about the formation of working tissues and organs during development of multicellular organisms depends in part on specific patterns of mitotic cell division. A series of such cell divisions akin to a family tree is called a cell lineage. A cell lineage traces the birth order of cells, the progressive restriction of their developmental potential, and their differentiation into specialized cell types. A cell lineage begins with stem cells, unspecialized cells that can potentially reproduce themselves and generate more-specialized cells indefinitely. Once a new precursor cell type is created, it often produces transcription factors characteristic of its fate. These transcription factors coordinately activate, or repress genes that direct the differentiation process.

Homework: Explore Chapter 21

Lecture 13

Topic: Cell Birth, Lineage and Death: Cell Death and its regulation

Typically we think of cell fates in terms of the differentiated cell types that are formed. A quite different cell fate, programmed cell death, also is absolutely crucial in the formation and maintenance of many tissues. A precise genetic regulatory system, with checks and balances, controls cell death just as other genetic programs control cell differentiation.
In this lecture, we consider the life cycle of cells patterns of division (lineage), and regulation of cell death. These aspects of cell biology converge with developmental biology and are among the most important processes regulated by the signaling pathways.

Homework: Explore Chapter 21

Lecture 14

Topic: Cancer: Tumor cells and Genetic basis of cancer

Cancer occurrence mechanism will be discussed within this lecture. Cancer occurs when the mechanism that maintains normal growth rates malfunction and cause excess cell division. The losses of cellular regulation that give rise to most cases of cancer are due to genetic damage that is often accompanied by influences of tumor promoting chemicals, hormones, and sometimes viruses. It will also be discussed how mutations of two Tutorial of genes are implicated in the onset of cancer: proto-oncogenes and tumor-suppressor genes.

Homework: Explore Chapter 25

Tutorial 1

Interpretation, analysis, critical thinking and presentation of original research articles by students in teams. Papers will be delivered and announced one week in advance. Selection of research articles is made by professor.

Tutorial 2

Interpretation, analysis, critical thinking and presentation of original research articles by students in teams. Papers will be delivered and announced one week in advance. Selection of research articles is made by professor.

Tutorial 3

Interpretation, analysis, critical thinking and presentation of original research articles by students in teams. Papers will be delivered and announced one week in advance. Selection of research articles is made by professor.

Tutorial 4

Interpretation, analysis, critical thinking and presentation of original research articles by students in teams. Papers will be delivered and announced one week in advance. Selection of research articles is made by professor.

Tutorial 5

Interpretation, analysis, critical thinking and presentation of original research articles by students in teams. Papers will be delivered and announced one week in advance. Selection of research articles is made by professor.

Tutorial 6

Interpretation, analysis, critical thinking and presentation of original research articles by students in teams. Papers will be delivered and announced one week in advance. Selection of research articles is made by professor.

Full bibliography of textbooks, suggested readings, materials etc:

1. Lodish, Berk, Kaiser, Krieger, Scott, Bretscher. Ploegh and Darnell. (2008) Molecular Cell Biology, 6th Edition by W. H. Freeman and Company, New York, USA
2. Cellular Signal Processing: An Introduction to the Molecular Mechanisms of Signal Transduction 2nd ed
3. The World of the Cell by Hardin, Bertoni, Kleinsmith (PEARSON) (2012)

2.14 Bioinformatics

Prepared by Asst. Prof. Dr. Džejla Međedović

Hours/credits: 60 / 6

Semester: III

Course format:

1. Method of presentation of course material: presentation, discussion, theoretical/practical classes, literature review
2. Form of assessment: quizzes, tests, assignments and small projects/student presentations

Course objectives:

1. Understanding how biology problems can be solved using algorithms and computational approach
2. Integrate the algorithmic, data mining and cloud knowledge in a bioinformatics application
3. Recognize opportunities for technological innovation in the biology field

Learning outcomes:

1. The student understands how structures and processes in genomics and bio-molecular research offer themselves for computer and algorithmic solutions
2. The student understands the purpose and the structure of online biological databases and repositories
3. The student understands how and when different computational algorithms can be applied to solve specific biological questions and to check hypothesis about biological phenomena
4. The student is able to translate a biological problem into a computational one
5. The student understands the multisiciplinary context of bioinformatics successfully integrating algorithmic, data mining and cloud knowledge in a bioinformatics application
6. The student understands the choices and different algorithmic paradigms to choose from when efficiently solving biology problems
7. The student is able to write code to efficiently solve biology problems
8. The student is able to use genomic and biology databases
9. The student is able to work in a multidisciplinary team

10. The student is able to present their results and methods in a form of a talk/presentation

Lecture 1

Topic: Replication Origins/Idea of an algorithm, simple string searching
We will focus on basics of DNA replication and hidden messages in DNA. We will write simple programs to understand how to find simple patterns within DNA. Before starting to write programs, we will understand a basic idea of an algorithm. Then we will use the example of finding orii in bacterial genomes. To do this, we will first need to understand what kind of information a program needs in order to solve a problem such as this one, primarily understanding the notion of input and output of a program. We will review basic ways to do DNA replication as well as asymmetry present in replication. This lesson will introduce students to basic string-searching algorithms and finding occurrences of particular patterns in much bigger strings (genomes.) To find orii in E.coli, we will need to learn how to count occurrences of most frequent words and k-mers in a genome.

Lecture 2

Topic: Motif Identification/Exhaustive search, Randomized algorithms
We will continue to look for patterns in strings, however we will focus on finding (k,d)-motifs, k-mers that can have up to d characters of mutation from its original description. The key application that will drive our quest will be looking for genes that control circadian rhythm, i.e., answering the question: What DNA patterns play the role of molecular clocks. We will use the example of plants, for whom knowing what time it is is the matter of life and death. Algorithmically, it is not as trivial to find the motifs, considering that our earlier Frequent words algorithm will not work. We can perform what is called exhaustive search, exploring all the possibilities in which one k-mer can have up to d characters of change --- this kind of approach is one way to learn about the limits of computers if we do not use a clever algorithm. In the end, we will resort to the randomized approach to solving this problem.

Lecture 3

Topic: Genome assembly/Graph algorithms
In this lesson, we will learn about the algorithms that enable genome assembly. Modern PCR machines can obtain small pieces of DNA, but what is the algorithm underneath that combines all the pieces together? An appropriate analogy would be having a newspaper cut into small fragments of words, where some fragments are altogether lost, and our task is to put the newspaper back together, a problem we formally call A String Reconstruction Problem. Perhaps surprisingly, even though we are dealing with strings (i.e., words), graph algorithms, a particular type of combinatorial algorithms help us tackle string reconstruction problems. A graph is a combinatorial structure with nodes (entities) and edges (connections between entities), and as such has enormous importance in modeling many real-world problems, including many problems in biology. Assembling a genome can, in a particularly

modeled graph called De Bruijn graph, be equivalent to the ability to do a particular type of walk through the graph. In this lesson, we will dive into graph concepts such as De Bruijn graphs, Eulerian paths/cycles, and the famous Konigsberg problem to learn more about how to assemble a genome. We will also mention some of the other applications of graph algorithms in bioinformatics.

Lecture 4

Topic: Antibiotic Sequencing/Brute force algorithms, branch-and-bound algorithms
In this class, we first review the discovery of antibiotics and how bacteria make antibiotics. In order to sequence antibiotics, we need a mass spectrometer that shatters molecules into pieces and then weighs the remaining fragments. It is from these masses that we will work to reconstruct the cyclopeptides. We will first learn about the brute force algorithm that solves this problem. There are many potential combinations of individual masses and many cyclopeptides to which some of these combinations would correspond. For the brute force algorithm, we will again find that its runtime is prohibitive when run on a real dataset, because the number of potential options to explore is exponential. In this lesson, we will also learn how to find approximate solutions to such problems, by cleverly cutting down on the number of options using a method called branch-and-bound.

Lecture 5

Topic: Sequence Alignment/Dynamic programming

In this lecture, we will be concerned with effective algorithms to align sequences. First, we will acquaint ourselves with different measures of distance and similarity between two or more sequences (e.g., Hamming distance) and many applications of this important problem. In this class, we will introduce an important class of optimization algorithms for this and many other problems in biology called dynamic programming. Dynamic programming works by solving smaller versions of the original problem, and using the small instances to build up solutions to larger instances, and finally to our original problem. We start with a simple example of Manhattan distance problem to introduce the idea of dynamic programming, and then we pose the central problem of edit distance, that as an output gives the distance between two sequences as the total number of character inserts, deletes and substitutes that need to be performed to transform one sequence into another. We also show how this solution can be improved to cost less than quadratic space.

Lecture 6

Topic: Mid-term Review

In this class, we will review both practical and theoretical underpinnings of the algorithms learned thus far, review the coding exercises implementing such algorithms on real data, and also review how to solve examples on paper. The key parameter to measure how well students

are ready is their ability to differentiate between different algorithmic paradigms and learning to differentiate when is which one appropriate to use.

Lecture 7

Topic: Mid-term

The mid-term will have a problem-solving format: it will expect students to think and to recognize situations in which to use a particular algorithm, and not only know how the algorithm works and showing how it works on an example. The students will be expected to know, for each of the problems studied in the first half of the semester, the appropriate algorithm to solve it.

Lecture 8

Topic: Genome re-arrangements/ Greedy algorithms

In this class, we will review different biological mechanisms in which genomes often tend to re-arrange themselves and change. Then we will formulate this as a computer science problem. Namely, a common way for a genome to change is with reversals. To that end, we will learn about the algorithm Sorting by Reversals, which is a method to transform a genome into another genome using a sequence of reversal operations, where the length of the part of the string to be reversed can be chosen. The idea of breakpoints is introduced, where genome items are out of order, but also out of the opposite order, which makes a particular location a good candidate to make it the breakpoint of a reversal. By knowing a number of breakpoints in the permutation, we can design an algorithm Sorting by reversal is an example of a greedy paradigm of algorithms, where the optimal solution is obtained by choosing locally optimal step. During this lecture, we will also explore other examples of greedy algorithms such as certain scheduling problems, and graph problems such as minimum spanning tree.

Lecture 9

Topic: Evolutionary trees/Phylogeny trees

How did SARS, one of the greatest recent pandemics (or COVID, for that matter) cross the barrier to humans? How did the first human get infected? Once it spread to humans, who infected whom, and how did the pandemic spread throughout the planet? All these questions are in one way or the other related to the problem of constructing evolutionary trees (i.e., phylogenies). Scientists perform alignments between different genomes, but with viruses this is difficult due to frequent mutations. After having performed a multiple alignment from n species, scientists form what is known as distance matrix. Distance matrices, and again, graphs, are used to build phylogenies, specifically using an algorithm called distance-based phylogeny reconstruction. We will introduce the idea of a parsimony score, and we will formulate an algorithmic problem of finding the most parsimonious labeling of the nodes of

the tree (small parsimony problem) and given a number of strings, finding a tree with a minimum parsimony score (large parsimony problem.)

Lecture 10

Topic: Gene expression/ClusteringIn this lecture we will learn to identify groups of genes with similar expressions using the algorithm called clustering. For the purposes of the clustering algorithm, gene expression can be modeled as a point in m-dimensional space. The goal of clustering is to divide a set of points into natural-looking groups, where each pair of elements within a group (i.e., cluster) are closer to each other than to any other point in another cluster. Clustering is an optimization problem that we will learn has a large number of important practical applications in biology and other disciplines. The algorithm k-means clustering will be an algorithm that iterates to find a better solution in each new iteration, and at the end will have k clusters as the output. In this lecture, we will see many examples of how the algorithm works, some interesting implementations, and also limitations of this approach.

Lecture 11

Topic: Locating disease-causing mutations/String matching algorithms

Figuring out the differences between two genomes is a topic we already encountered in this course. However, here are looking for small changes between two or more genomes, that might indicate a potential condition, for example. To that end, constructing De Bruijn graph and all the other methods we have seen to match two genomes seems like an overkill. In this lecture, we will find a more space and time efficient solution to this specific problem, by attempting to match reads to reference genome as much as possible. To do that, we will learn about the naive matching algorithm, about suffix trees, suffix arrays, and tries. These are the data structures for processing strings and are heavily used in bioinformatics applications.

Lecture 12

Topic: Bioinformatics and entrepreneurship

In this lecture, we will survey different directions in bioinformatics startup and state-of-the-art of innovation in bioinformatics. This lecture is intended to provide students with the overview of current technology transfer ideas, and what it takes to turn a positive scientific result into a marketable product. This lecture is meant, more than anything, to open up avenues for students to think about potential innovation and startup ideas.

Lecture 13

Topic: Bioinformatics startups/Guest lecture: Prof.Aida Hajdarpasic

This guest lecture is a continuation to our entrepreneurship theme from the previous lecture. Our guest speaker is a professor, entrepreneur, educator and a researcher. She has helped start

multiple bioinformatics startups and is currently working for a startup that aims to commercialize microbiom data by offering personalized analysis to its clients. Our guest speaker will spend some time talking about the science behind the startup, technology that they are offering, what are the greatest challenges in starting a bioinformatics company, what equipment is necessary and her advice on how to promote the company and locate funding for a project. The talk is meant to inspire curiosity and a conversation about potential new ideas, and also address the pros and cons of starting a company with foreign investors in Bosnia-Herzegovina.

Lecture 14

Topic: Project presentations

In this lecture, every team of 2 will present their final project. The project needs to have a computer science as well as biological component. The students need to write a piece of code that solves a particular biological problem that will be given to them to solve, and with a number of variations. The programming skills obtained during the semester should be sufficient to implement a project of this complexity.

Lecture 15

Topic: Final Review

We will use this class to review all algorithmic paradigms and related biology problems in preparation for the final exam. The plan is to practice problem-solving skills by solving examples from greedy algorithms, brute-force algorithms, dynamic programming, branch-and-bound, etc.

Tutorial 1

Topic: Introduction to Programming in Python
This week we will acquaint ourselves with the idea of writing programs, notionf of input and output, compilation process and execution of a simple program. We will also acquaint ourselves with the idea of programming languages, and focus on Python, in which we will be doing most of the coding. The idea of variables will be introduced and some simple programs will be written and shown how they execute.

Tutorial 2

Topic: Variables, conditional statements, loops
This week, we will work with variables, writing simple programs, and introduction the conditional statements. We will practice conditional statements using the example of the simple string searching algorithm from the first week of lectures. Students will be encourages to download genomes of their choice and experiment with real inputs and outputs. The

particular exercise will be locating a substring inside a given genome and counting the number of its occurrences.

Tutorial 3

Topic: Creating graphs in Python, testing them for basic properties/De Bruijn graph I
This week, we will learn how to model graphs in Python. The basic idea of how to create vertices and edges, and work to find out the basic properties of a graph will be practiced. In particular, the exercises will include testing the graph for a) connectedness, b) directedness, c) whether it has an eulerian cycle, d) whether it is a tree. Students will look at and try to implement their own De Bruijn graph in order to assemble a genome. In this lab, we will see the first part of this. This exercise will also take up a part of the next tutorial.

Tutorial 4

Topic: De Bruijn graph II, Sequence alignment I/Dynamic Programming
In this tutorial, we will finish constructing De Bruijn graph on a given set of reads to assemble a genome. We will introduce the topic of dynamic programming, give examples of where it is used, do some hands-on and on-board simple examples, and then write code to implement those examples. The sample examples include: Fibonacci numbers, Walking the Manhattan, Making change. This tutorial is an introduction to the next part of dynamic programming, where we will treat a particular topic of sequence alignment.

Tutorial 5

Topic: Sequence Alignment II/Dynamic programming
Given a set of reads, our task in this tutorial is to assemble a genome out of them, or at least analyze the edit distance between each pair of reads and discuss how we would use that information to assemble the complete genome. The edit distance exercise will involve making a matrix on the board, and then figuring out the recursive formulation to implement in the edit distance program. Then we will write that program in Python, and use some sample reads to see what the distance is. The second part of the tutorial will be figuring out how to retrace the actual path of transforming one read into another, i.e., not just knowing how many minimum substitutions/deletions/insertions we need, but also in which places we need to apply which operation to transform a read into another read.

Tutorial 6

Topic: Greedy algorithms/ Sorting by Reversals
In this tutorial, we will take 2 sample genomes and sort one by reversals to obtain another one. In other to do that, we will first do a number of small examples on the board, to get the intuition about the algorithm. Then, we will try to implement the greedy algorithm for sorting by reversals, in Python. We will test and analyze the efficiency of the algorithm, and try it on

a number of different examples, and see how the algorithm solves the ties. We will discuss a number of potential improvements to the algorithm.

Tutorial 7

Topic: String-matching (the advanced version) I
We will analyze more sophisticated string-matching algorithms and try to get intuition about their efficiency by running them on strings and patterns of different length. Considering that this is not a classical computer science audience, we will not formally analyze the runtime of these algorithms, but we will run examples on the board, then implement the algorithm in Python, and run it on many different instances. The main algorithms involved will be KMP and Rabin-Karp.

Tutorial 8

Topic: String matching (the advanced version) II
In this tutorial, we will continue to implement KMP and Rabin-Karp algorithms. We will compare the efficiency of these algorithms to the basic string searching algorithm we learned about in the tutorials at the beginning of the semester. We will run a mini experiment on real biological data (big data) to demonstrate the differences in the efficiency between different algorithms. Note: For some students of biology, implementing some of the more sophisticated algorithms will not be easy. This is why we will first take a look at the implemented algorithm, run it, and then try to implement it on our own. For student projects, students are advised to ask for help from the instructor, and are also encouraged to use the code samples from the internet and textbooks, as long as they eventually understand what the code is about.

Tutorial 9

Topic: Final exam review
Final exam will contain some of the programming and problem-solving questions, and this session will present some sample types of questions for the exam.

Full bibliography of textbooks, suggested readings, materials etc:

1. Bioinformatics Algorithms: An Active-Learning Approach (3rd Edition), Philip Compeau and Pavel PEvzner, Active Learning Publishers, 3rd edition (2018). [Online version of the book available for free, along with lecture videos at: https://www.bioinformaticsalgorithms.org/]
2. Bioinformatics and Functional Genomics, Jonathan Pevzner, 2006. Wiley-Blackwell.
3. Introduction to Bioinformatics, Arthur Lesk, 2014. Oxford University Press
4. https://ehmatthes.github.io/pcc/

5. https://www.academia.edu/39951012/Eric_Matthes_Python_Crash_Course_A_Hands_On_Project_Based_Introduction_to_Programming_No_Starch_Press_2019_
6. https://www.amazon.com/Python-Cookbook-Third-David-Beazley/dp/1449340377
7. https://www.manning.com/books/the-quick-python-book-third-edition

Bioanalytical Technologies Study Program at International University of Sarajevo

The work of multiple authors, titled *Study Program, Bioanalytical Technologies* most certainly represents an innovation in the Bosnian-Herzegovinian educational landscape. Namely, no other existing study program locally does the work of uniting three different yet complementary domains that need to be integrated to produce versatile and practically capable graduates in the domain of bioanalytical tools and methods.

The goal of this program is to create an all-rounded graduate that is at the same time able to use existing immunological therapies, develop new ones, while also being able to cogently communicate their ideas in recognized scientific journals. To do that, three key and complementary skills need to be developed:

1) Detailed knowledge of fundamental theoretical tenets common to all projects that developed new bioanalytical methods
2) Awareness of the basic postulates of a valid study design, data collection, and data preprocessing and processing
3) Clear and complete communication of the results produced by using the former two skills to the narrow scientific and general public audience.

My opinion is that the study program designed and described in the manuscript titled *Study Program Bioanalytical Technologies*, achieves all three aforementioned goals and does so with a detailed and structured description of the intricacies of the study program. As an example of this nuanced approach, I would in particular point out the manner in which the integration of the courses concerned, the collection, preprocessing, presentation and communication of data from in vitro and in vivo studies and the technical courses that introduce the laboratory methods needed for a successful technical execution of these experiments is conducted. Moreover, the interdisciplinary profile of the group of authors of the manuscript is apparent in the design of the document, and the fact that they are all part of one faculty, the Faculty of Engineering and Natural Sciences (FENS) at International University of Sarajevo, has resulted in the synergy of education about the laboratory methods on one side, and the principles of data generation, storage, preprocessing and presenting data on the other. Courses such as „Programming and Data Collection“, „Biostatistics“, „Bioinformatics“ and „Machine Learning“ expose students to the entire process that occurs after the work done in the laboratory, and they get acquainted with the standards such as standardization, normalization, and various scales of measurements that later enable a much more widespread use of the results in the lab.

Finally, I consider the manuscript *Study program, Bioanalytical technologies* published by IUS an excellent blueprint for the institutions of higher education in Bosnia-Herzegovina that are planning on embarking on the design of a similar interdisciplinary program, or modifying an existing one. Authors have made sure to encompass and connect all key aspects relevant for producing high-quality graduates equipped with sophisticated and modern theoretical skills, as well as practically well-rounded graduates.

Dr. Mohamed E. Yahia

Master studies in Bioanalitical technologies – Instructions for lecturers are useful, detailed descriptions of the courses and activities planned as a part of educational process in Master study in Bioanalitical technologies at International university of Sarajevo. The courses' activities are described for both lectures and tutorials accompanied by the bibliography and resource references. The publication is important part of the quality assurance system of the master study program.

Assist. Prof. Tariq Namas

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