MEDICAL UNIVERSITY - PLEVEN
FACULTY OF MEDICINE

DEVISION OF PHYSICS AND BIOPHYSICS

PROGRAM OF STUDY

IN

BIOPHYSICS

ENGLISH MEDIUM COURSE OF TRAINING

SPECIALTY OF MEDICINE

ACADEMIC DEGREE MASTER PROFESSIONAL QUALIFICATION

DOCTOR OF MEDICINE

Developed by: Prof. M. Alexandrova, DSc	**Approved by:** Prof. A. Asparuhov, DSc	**Endorsed by:** Faculty Council	Copy № 1
1.09.2015 .... /date, signature/	.... /date, signature/	.... /date/	Valid from: 1.09.2015

According to the unified state requirements: compulsory

According to the curriculum: compulsory

Academic year I, **semester** II

Total number of hours:60 – lectures 30 and practical exercises 30

Total credits: 6

Lecturer:

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AIM AND TASKS OF EDUCATION

Modern biological sciences require the ability to recognize complex relationships, and the ability to use the laws of physics to explain processes on a molecular, cellular and organismic level. This requires interdisciplinary training that includes working with highly sensitive experimental methods to collect quantitative data and using them to construct theoretical models. The objective of training in Biophysics is to teach students how to apply the concepts and methods of physical science to biological and medical problems.

After completing the course students are expected to know physical laws underlying physiological processes, be prepared for the interdisciplinary nature of modern life sciences and capable of quantitative reasoning.

FORMS OF EDUCATION:

- Lectures
- Practical exercises

METHODS OF EDUCATION:

- Lecturing
- Practicing
- Classroom discussion
- Extracurricular activities

THEMATIC PLAN OF LECTURES

№	Topic	Ac. h
1.	Nature and subject of Biophysics. Sub-areas of Biophysics. Medical Biophysics. Brief view of the history and development of Biophysics	2
2.	Molecular structure of biological systems. Intramolecular bonds: covalent bonds, molecular orbitals, ionic bonds, coordinative bonds, metalloorganic complexes, hydrogen bonds	2
3.	Thermodynamics. Subject of thermodynamics. Basic thermodynamic terms: thermodynamic system, surrounding, homogenous and heterogeneous system, thermodynamic variables, intensive and extensive variables, variables of state, conjugate variables, equation of state, thermodynamic state, thermodynamic equilibrium, thermal, chemical and mechanical equilibrium, thermodynamic process, reversible and irreversible thermodynamic processes, dissipative structures	2
4.	Equilibrium thermodynamics. First law of thermodynamics – definitions. Mathematical formulation of the first law. Gibbs fundamental equation. Second law of thermodynamics. Entropy as a parameter of phenomenological thermodynamics. Klausius inequality. Irreversibility of real processes	2
5.	Order and probability. Thermodynamic probability and entropy. Entropy as a kind of measure of disorder. Boltzmann equation of entropy. Information and entropy. Statistical definition of entropy. Impossibility and absolute certainty. Shannon relation of information content. Negentropy. Semantic and syntactic information. Maxwell's demon. Threshold value of information, required to control the processes of living systems	2
6.	Thermodynamic potentials. Internal energy. Enthalpy. Helmholtz free energy. Gibbs free energy. Chemical and electrochemical potentials - physical meaning. Chemical, osmotic and electrical work.	2
7.	Non-equilibrium thermodynamics. Linear non-equilibrium thermodynamics. Definition and basic terms. Force and motion. Phenomenological coefficients. Conjugated fluxes. Dissipative function. Entropy and stability. Stationary state. Prigogine principle of minimum entropy production. Time hierarchy of stationary states	2
8.	Biological structures: general aspects. Dynamic and static systems. Primary, secondary, tertiary and quaternary structure of biological macromolecules. Equilibrium and non-equilibrium structures	2
9.	Cells –m chemical composition. Cell membranes – the main biological functions of plasma and organelle membranes. Chemical composition of membranes. Membrane lipids: the supporting structure. Phospholipids, glycolipids and cholesterol. Membrane proteins – categories. Protein functions. Membrane dynamics. Cholesterol effects on membrane fluidity. Ultrastructure and molecular structure of cell membranes. Lipid bilayer – unit membrane. Membrane functions. The "fluid-mosaic" model of Singer and Nicolson.	2
10.	Transport of matter across cell membranes - classification. Classification on the basis of transport mechanism, energy supply, number of transported species and direction of their translocation, trans-membrane potential changes. Passive transport. Free diffusion of non-charged and charged particles. Fick's law. Free diffusion of charged particles. Nernst-Planck molar flux equation. Simple diffusion through membranes. Permeability. Transport of water through membranes. Filtration and osmosis. Facilitated diffusion. Transport by carrier proteins. Saturability and specificity - important characteristics of	2

№	Topic	Ac. h
	the membrane transport systems. Transport by channels and pores. Three examples of pores important for cellular physiology. Ionophores	
11.	Primary active transport. Sodium-potassium ATP-ase. Putative structure of sodium-potassium pump. Calcium ATP-ase. Putative structure of calcium pump. Basic steps of ion transport processes. Secondary (ion gradient-driven) active transport. Lactose permease requires a proton gradient. Putative mechanism of lactose transport in E. coli.	2
12.	Model potentials. Diffusion potential. Generation of diffusion potential. The Henderson equation. Time dependence of diffusion potential. Membrane (equilibrium) potential. Generation of membrane potential. The Nernst equation. Donnan potential. The Gibbs-Donnan equilibrium. Approach to electrical and chemical equilibrium. Gibbs-Donnan equation. Osmotic consequences of the Gibbs-Donnan equilibrium	2
13.	Generation of resting membrane potential. The Goldman and Thomas equations. Factors contributing to the resting potential	2
14.	Generation of action potential. Voltage-gated channels. Saltatory conduction	2
15.	Free radical processes. Sources of free radical generation in human body. Lipid peroxidation. Basic stages. Mechanism of lipid peroxidation. Antioxidant defence system. Enzymic and nonenzymic antioxidants. Lipid peroxidation and toxicology. Oxidative stress contribution to atherosclerosis and nervous system injury	2
	Total	30

LECTURES - THESES

1. Nature and Subject of Biophysics

1.1. Subject of Biophysics
1.2. Subdivision of Biophysics
1.3. Relationships between Biophysics and other sciences
1.4. Brief view of the history and development of BIophysics

2. Molecular structure of biological systems

2.1. Quantum-mechanical approaches to the explanation of molecular bonds. "Microphysical" and "macrophysical" processes. Effective parameters
2.2. Intramolecular bonds
2.2.1. Some properties of atomic orbitals
2.2.2. Covalent bonds, molecular orbitals
2.2.3. Ionic Bonds
2.2.4. Coordinative Bonds, Metallo-Organic Complexes
2.2.5. Hydrogen bond

3. Thermodynamics

3.1. Subject of thermodynamics
3.2. Basic thermodynamic terms
3.2.1. Thermodynamic system
3.2.2. Thermodynamic variables
3.2.3.Thermodynamic state
3.2.4. Thermodynamic equilibrium
3.2.5.Thermodynamic process
3.1. Equilibrium thermodynamics.
3.1.1. First law of thermodynamics
3.1.1.1. Definitions of the 1st law of thermodynamics
3.1.1.2. Mathematical formulation of the 1st law
3.1.1.3. Limitations of the first law
3.1.2. Second law of thermodynamics
3.1.2.1. Phenomenological definition of entropy
3.1.2.2. Thermodynamic Probability and Entropy. Boltzmann equation of entropy
3.1.2.3. Information and entropy. Mathematical probability. Statistical definition of entropy. Shannon relation of information content. Maxwell's demon
3.1.3. Thermodynamic potentials
3.1.3.1. Internal energy
3.1.3.2. Enthalpy
3.1.3.3. Helmholtz free energy
3.1.3.4. Gibbs free energy
3.1.3.5.Chemical and electrochemical potentials
3.2. Non-equilibrium thermodynamics.
3.2.1. Linear nonequilibrium thermodynamics
3.2.1.1. Force and motion
3.2.1.2. Conjugated fluxes. Coupling coefficients or Onsager coefficients. Onsager's law on the reciprocal relation
3.2.1.3. Dissipative function. Entropy production. Entropy and stability.
3.2.1.4. Stationary state. Time hierarchy of stationary states
3.3. Biological structures: general aspects
3.3.1. What is a structure?
3.3.2.Dynamic and static systems
3.3.3. Primary, secondary, tertiary and quaternary structure of biological macromolecules
3.3.4. Equilibrium and non-equilibrium structures

4. Cells

4.1. General Features of Cells
4.2. Chemical Composition of Cells
4.3. Functions, Composition and Structure of Cell Membranes
4.4. The Main Membrane Functions
4.5. Chemical Composition of Membranes
4.6. Structure of Membranes

5. Transport of Matter across Biological Membranes

5.1. Transmembrane transport in general
5.2 Classification of transport processes
5.3 Passive Transport
5.3.1. Free diffusion

5.3.1.1. Free diffusion of non-charged and charged particles. Free diffusion of non-charged particles. Fick's law

5.3.1.2. Free diffusion of charged particles. Nernst-Planck molar flux equation

5.3.2. Diffusion through membranes. Permeability

5.3.2.1. Transport of water through membranes. Filtration and osmosis

5.3.2.2. Facilitated diffusion. Ionophores

5.3.2.2.1. Transport by carrier proteins. Saturability and specificity - important characteristics of the membrane transport systems

5.3.2.2.2. Transport by channels and pores. Three examples of pores important for cellular physiology

5.4. Primary active transport

5.4.1. Sodium-potassium ATP-ase. Putative structure of sodium-potassium pump. Basic steps of ion transport process.

5.4.2. Calcium ATP-ase. Putative structure of calcium pump. Basic steps of ion transport process

5.5. Secondary (ion gradient-driven) active transport

5.5.1. Lactose permease requires a proton gradient

5.5.2. Putative mechanism of lactose transport in E. coli

6. Bioelectrical potentials

6.1. Model potentials

6.1.1. Diffusion potential

6.1.1.1. Generation of diffusion potential

6.1.1.2. The Henderson equation

6.1.1.3. Time dependence of diffusion potential

6.1.2. Membrane (equilibrium) potential

6.1.2.1. Generation of membrane potential

6.1.2.2. The Nernst equation

6.1.3. Donnan potential. The Gibbs-Donnan equilibrium

6.1.3.1. Effect of selectively permeable and impermeable ions

6.1.3.2. Effect of the electroneutrality principle

6.1.3.3. Approach to electrical and chemical equilibrium

6.1.3.4. Electrical consequences of the Gibbs-Donnan equilibrium

6.1.3.5. Osmotic consequences of the Gibbs-Donnan equilibrium

6.2. Generation of resting membrane potential

6.2.1. The Goldman and Thomas equations.

6.2.2. Factors contributing to the resting potential

6.3. Generation of action membrane potential

6.3.1. Graded potentials

6.3.2. Threshold potential and threshold stimulus

6.3.3. Voltage-gated channels

6.3.4. Hodgkin-cycle

6.3.5. Refractoriness and Inactivation

6.3.5.1. Absolute refractory period

6.3.5.2. Relative refractory period

6.3.5.3. Nerves Transmit Information as Action Potentials

7. Free-radical processes

7.1. Free radical biology – basic terms
7.2. Free radical generation in human body
7.3. Lipid peroxidation
7.3.1. Initiation of lipid peroxidation
7.3.2. Metal ions and the peroxidation process
7.4. Singlet oxygen
7.5. Consequences of free-radical processes
7.6. Antioxidant defense
7.7. Lipid peroxidation and toxicology
7.8. Free radicals and human diseases
7.8.1. Atherosclerosis
7.8.2. Central nervous system injury

THEMATIC PLAN OF PRACTICAL EXERSICES

№	T o p i c	Ac. h.
1.	Model membranes: preparation of hemosomes	2
2.	Thin-layer chromatography: qualitative analysis of membrane lipids	2
3.	Molecular (size exclusion) chromatography: determination of molecular masses	2
4.	Biophysics of hemodialysis: transport of urea across a semipermeable membrane	2
5.	Transport across membranes: osmosis	2
6.	A kinetic study of acid-catalysed sucrose hydrolysis	2
7.	Test – part I	2
8.	Diffusion of electrolytes: measuring diffusion potential	2
9.	Microelectrophoresis: determination of electrokinetic (zeta) potential	2
10.	Paper electrophoresis: separation of proteins	2
11.	Absorption spectrophotometry: determination of concentration of solutions. Absorption spectrophotometry: studying acid haemolysis of erythrocytes	2
12.	Copper-induced superoxide production in erythrocytes	2
13.	Lipid peroxidation: measuring malonedialdehyde concentration	2
14.	Test – part II	2
15.	Seminar	2

PRACTICAL EXERSICES – THESES

1. Model membranes: preparation of hemosomes. To explain differences among plane and spherical artificial membranes, to know how to entrap different substances into liposomes, to state model membrane applications.

2. Thin-layer chromatography: qualitative analysis of membrane lipids. To describe the molecular structure of phospholipids and sphingolipids, to know the principle of the method of thin-layer chromatographty, to define R_f value and to know how to find it, to explain the procedure of thin layer chromatography.

3. Molecular (size exclusion) chromatography: determination of molecular masses. To know the principle of separation of substances by gel-chromatography, to explain the main components of a gel chromatography system, to explain how to determine the molecular weights of separated fractions.

4. Biophysics of hemodialysis: transport of urea across a semipermeable membrane To know factors the velocity of hemodialysis depend on, to know the meaning of the time constant $t_{0.5}$, to know how to find the value of the constant experimentally

5. Transport across membranes: osmosis. To define osmosis, to know factors the osmotic pressure depend on, to define oncotic pressure and explain the role of osmosis for supporting water exchange between blood and lymph.

6. A kinetic study of acid-catalysed sucrose hydrolysis. To know how to determine the angle of rotation of an optically active substance by a polarimeter of Loran, to can express the rate constant of reaction of hydrolysis of sucrose by the angle of rotation, to explain usage of polarimetry for studying structural conformation of biomolecules

7. Test - part I It includes experiment performance, theory test and interview.

8. Diffusion of electrolytes: measuring diffusion potential. To define diffusion potential, to explain the change in diffusion potential with time, to derive Henderson’s equation, to know how to measure diffusion potential.

9. Microelectrophoresis: determination of electrokinetic (zeta) potential. To know the processes participating in the formation of surface electrical charge, to define “potential-forming” ions, to define double electric layer, sliding plane, thickness of double electric layer and ς-potential.

10. Paper electrophoresis: separation of proteins. To define electrophoresis and electrophoretic mobility, to explain how to evaluate quantitatively the electrophoregram, to know what is the diagnostic significance of the method of electrophoretic division of proteins.

11. Absorption spectrophotometry: determination of concentration of solutions. To state the law of Lambert-Bouguer; to know the meaning of extinction, to can describe the block-diagram of one and two-beam spectrophotometers, to know how to determine the unknown concentration of solutions. **Studying acid haemolysis of erythrocytes.** To draw acid erythrogram of human erythrocytes.

12. Copper-induced superoxide production in erythrocytes. To demonstrate the generation of superoxide during copper ions-erythrocyte membranes interaction, to describe the method for measuring superoxide, to know the mechanism of copper ions toxicity.

13. Lipid peroxidation: measuring malonedialdehyde concentration.
To explain the process of initiation of lipid peroxidation, to know the main stages of lipid peroxidation, to know what is MDA, to describe the method for quantitative evaluation of MDA.

14. Test –II part. It includes experiment performance, theory test and interview.

15. Seminar

CONTROL AND EVALUATION OF STUDENTS' KNOWLEDGE:

Grades are awarded to students based on the level of performance they have achieved:
- in the lab topics tests
- in the colloquium
- in the lecture tests
- in the term exam

THE ATTENDANCE TO LECTURES AND PRACTICAL EXERSICES IS MANDATOTORY. THE OMITTED EXPERIMENTAL TOPICS HAVE TO BE REDONE. DURING THE LAB EXERCISES STUDENTS' KNOWLEDGE IS EVALUATED ON THE BASIS OF THE TESTS FOR THE RESPECTIVE TOPIC.

At the end of the semester total students' performance is evaluated. If the mark obtained is higher than very good (4.50), the student is exempt from some topics in sections Thermodynamics and Free radicals in the examination synopsis.

The final (term) exam is given during the exam session according to the schedule approved by the Dean.

The final exam consists of a written and oral part and is composed of 3 levels:

1st level: Conversion of units of measure from one form to another;

2nd level: Solving a test on the study material of the type True or false, Fill in the blanks, etc.

3rd level: oral exam according to the synopsis.

In case of poor results on the 1st and/or 2nd levels, the student is not allowed to sit for the oral exam. Only after passing successfully both the first and second levels, the student is required to answer the questions from the synopsis.

THE POSITION OF THE DISCIPLE IN THE TOTAL EDUCATION IN MEDICINE:

The discipline Biophysics is in the list of compulsory subjects in the Medicine curriculum. It is studied in the second semester of the first year and ends with a semestral exam. One of the main objectives of medical biophysics is the identification of physical and physicochemical parameters for the purposes of objective diagnosing an organism's functional state. Violation of life processes can be primarily judged by changes in these parameters. Characteristic properties of living cells are the presence of biopotentials, the ability to maintain ionic gradients and carry electric currents, the capability to produce chemiluminescence, etc. The objective of training in Biophysics is to teach students how to apply the concepts and methods of physical science to biological and medical problems.

EXPECTED RESULTS:

After completing the Biophysics Program students are expected to know physical laws underlying physiological processes. The program has a strong emphasis on Biothermodynamics, Cellular Biophysics and Free Radical Generation and Oxidative Stress.

EXAMINATION SYNOPSIS IN BIOPHYSICS

Academic Year 2015/2016

1. Nature and subject of biophysics.
2. Molecular structure of biological systems. Intramolecular bonds, covalent bond, molecular orbitals, ionic bonds, coordinative bonds, metalloorganic complexes, hydrogen bonds.
3. Thermodynamics. Subject of thermodynamics, basic thermodynamic terms: thermodynamic system, thermodynamic variables, thermodynamic state, thermodynamic equilibrium, thermodynamic process.
4. Equilibrium thermodynamics. First law of thermodynamics. Mathematical formulation of the first law. Limitations of the first law.
5. Equilibrium thermodynamics. Second law of thermodynamics. Second law of thermodynamics. Phenomenological definition of entropy.
6. Order and probability. Thermodynamic probability and entropy. Boltzmann equation of entropy.
7. Information and entropy. Statistical definition of entropy. Shannon relation of information content. Maxwell’s demon.
8. Thermodynamic potentials. Internal energy. Enthalpy. Helmholtz free energy. Gibbs free energy. Chemical and electrochemical potentials.
9. Non-equilibrium thermodynamics. Linear non-equilibrium thermodynamics Definition and basic terms. Force and motion. Phenomenological coefficients. Conjugated fluxes.
10. Non-equilibrium thermodynamics. Stationary state. Dissipative function. Entropy and stability. Stationary state.
11. Biological structures: general aspects.
12. Bioenergetics. Energy. Metabolism. Stages to catabolism/anabolism. Oxidation as a source of metabolic energy. ATP and energy transduction. Mechanism of coupling the oxidative – phosphorylation reactions.
13. Molecular separation procedures: size exclusion and thin-layer chromatography.
14. Cell membranes. Plasma membrane. Internal membranes. Lipid bilayer – unit membrane. Membrane functions.

15. Biological Membranes. Membrane lipids: the supporting structure. Phospholipids, glycolipids and cholesterol. Membrane proteins – categories. Protein functions. Membrane dynamics. Cholesterol effects on membrane fluidity.
16. Model membranes: preparation of hemosomes.
17. Paper electrophoresis: separation of proteins.
18. Transport of matter across cell membranes - classification. Classification on the basis of transport mechanism, energy supply, number of transported species and direction of their translocation, trans-membrane potential changes.
19. Passive transport. Free diffusion of non-charged and charged particles. Free diffusion of non-charged particles. Fick's law. Free diffusion of charged particles. Nernst-Planck molar flux equation.
20. Simple diffusion through membranes. Permeability. Transport of water through membranes. Filtration and osmosis.
21. Biophysics of hemodialysis: transport of urea across a semipermeable membrane.
22. Facilitated diffusion. Transport by carrier proteins. Saturability and specificity - important characteristics of the membrane transport systems. Transport by channels and pores. Three examples of pores important for cellular physiology. Ionophores.
23. Primary active transport. Sodium-potassium ATP-ase. Putative structure of sodium-potassium pump. Basic steps of ion transport process.
24. Primary active transport. Calcium ATP-ase. Putative structure of calcium pump. Basic steps of ion transport process.
25. Secondary (ion gradient-driven) active transport. Lactose permease requires a proton gradient. Putative mechanism of lactose transport in E. coli.
26. Microelectrophoresis: determination of electrokinetic (zeta) potential.
27. Diffusion potential. The Henderson equation. Time dependence of diffusion potential
28. Membrane (equilibrium) potential. The Nernst equation.
29. Donnan potential. Approach to electrical and chemical equilibrium. Gibbs-Donnan equation. Osmotic consequences of the Gibbs-Donnan equilibrium.
30. Generation of resting membrane potential. The Goldman and Thomas equations. Factors contributing to the resting potential.
31. Generation of action potential. Voltage-gated channels. Saltatory conduction.
32. Free radical biology – basic terms. Free radical reactions. Classification. Chemical reactivity of free radicals.
33. Sources of free radical generation in human body.
34. Lipid peroxidation. Basic stages. Initiation and Propagation of lipid peroxidation.
35. Lipid peroxidation. Decomposition stage Metal ions and the peroxidation processes.
36. Copper-induced superoxide production in erythrocytes.
37. Lipid peroxidation: measuring malonedialdehyde concentration.
38. Singlet oxygen – generation and role in living systems.

39. Consequences of free-radical processes in living systems.
40. Antioxidant defense system. Enzymatic antioxidants.
41. Antioxidant defense system. Non enzymatic antioxidants.
42. Lipid peroxidation and toxicology. Contribution of oxidative stress to atherosclerosis.
43. Lipid peroxidation and toxicology. The importance of oxidative stress in the development of nervous system injury.

REFERENCES

- Alexandrova M, Lecture course, MU-Pleven
- Glaser R, Biophysics. Springer Science & Business Media, 2001 - Science - 361 pages
- Davidovits P. Physics in Biology and Medicine. 3rd Edition, © 2008, Elsevier Inc.
- An Introduction to Biophysics with Medical Orientation, ed. G. Ronto and I. Tarjan, Budapest, 1994