TOPIC 2.A. Mathematical Biophysics

Mathematical biophysics studies biological systems by means of mathematical models. Mathematical models are equations describing the process or phenomenon which is to be investigated. Sets of differential and integral equations are used for construction of the models. Mathematical models find application on various levels of organization of biological systems: from molecular to population levels. Below, we will consider the models of medicines distribution in a cell, organ, tissue, or whole organism which is the subject of pharmacokinetics.

Exercise 2.1a. Write down definitions of the following terms:

A mathematical model is ____

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The subject of pharmacokinetics is ___________________________________

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In pharmacokinetics usually a compartment is assigned as a system unit. *Pharmacokinetic compartment* is____

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One-Compartment Pharmacokinetic Model

Assume that some medicine in the quantity of M_0 has been injected directly into patient's bloodstream. Let us consider the model of its excretion from the organism. Here patient's organism will be represented as one compartment, so that the model under consideration is one-compartment model. The quantity of administered medicine will decrease with time due to elimination processes.

Elimination is ____

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Such processes include medicine excretion by the kidneys, intestines, lungs, chemical transformations and irreversible binding.

Exercise 2.2a. Write down the names of the compartments and the pharmacokinetic constant.

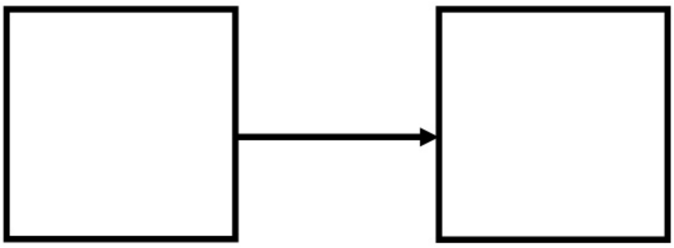

Fig. 2.1a. The scheme of one-compartment model.

The differential equation that describes the one-compartment pharmacokinetic model has the form:

$$\frac{dM}{dt} = -k_{el} M \quad ,$$

where k_{el} is elimination constant that indicated the rate of medicine elimination from the compartment. Solution of the differential equation describes the process of decreasing the introduced medicine in the quantity of M_0 after a lapse of some period of time t :

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$$M = M_0 e^{-k_{el} t} . \qquad (2.1a)$$

where M_0 ($t = 0$) is____ $[M_0]$=g

M is____ $[M]$ = g

k_{el} is ____ $[k_{el}]$ = h^{-1}

t is ____ $[t]$ = h

It is more convenient to use medicine concentration c instead of its quantity M :

$$M(t) = V \cdot c(t),$$

where V is the apparent volume of the medicine distribution. So, medicine concentration in the compartment at any time t can be found by the formula

$$C = C_0 e^{-k_{el}\, t} , \qquad (2.2a)$$

where c_0 ($t = 0$) is____ $[c_0]$ = g / L

c is____ $[c]$ = g / L

Let's derive the elimination constant from (2.2a) by applying the properties of the exponential function:

$$C = C_0 e^{-k_{el}\, t} \ ;$$

$$e^{-k_{el}\, t} = \frac{C}{C_0} \ ;$$

taking logarithm from both sides of equation

$$\ln e^{-k_{el}\, t} = \ln\frac{C}{C_0} ;$$

According to the properties of the logarithmic function $\ln e^x = x\underbrace{\ln e}_{1} = x$ we can write:

$$-k_{el}\, t \cdot \ln e = \ln\frac{C}{C_0} ;$$

$$-k_{el}\, t = \ln\frac{C}{C_0} ;$$

Exercise. 2.3a. Taking the same steps from the left derive elimination constant k_{el} from the law (2.1a).

$$M = M_0 e^{-k_{el} t}$$

$k_{el} = -\frac{1}{t}\ln\frac{C}{C_0} \quad (C_0 > C)$ (2.3a)	$k_{el} =$ $(M_0 > M)$ (2.4a)

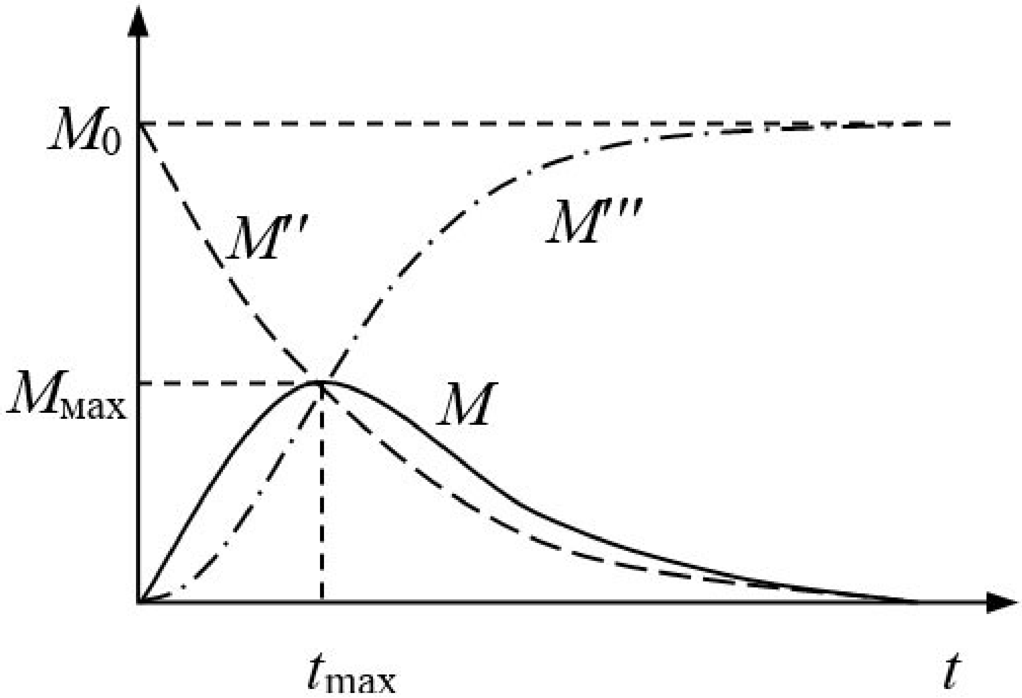

Fig. 2.2a. The dependence of quantities of medicine on time.

An important parameter of excretion process is an *elimination half-time* of a medicine $t_{1/2}$, i.e., the time interval for which the medicine concentration in the compartment halves:

$$t_{1/2} = \frac{\ln 2}{k_{el}}. \quad (2.5a)$$

Exercise. 2.4a. Fill in Table 2.1a with the parameters of mathematical biophysics, keeping in mind that only within this topic time is measured in hours, and concentration is measured in g/L.

Table 2.1a

Parameter description	Designation	Units of measurement
	k_{el}	
the amount of drug in the compartment at the initial time		
	M	
time		
	c_0	
the concentration of drug in the compartment at any time		
	$t_{½}$	

Example of problem solution.

The package leaflet of lidocaine stated that its ***elimination half-time*** is around 90 min to 120 min in most patients. Each ampoule contains lidocaine concentration of 20 mg/mL. Let's compute the elimination constant and the concentration of lidocaine in the patient's body in 5 hours after its administration to a patient intravenously.

Data:	***Solution:***
$c_0 = 20$ mg/mL $t = 5$ h $t_{1/2} = 120$ min $= 2$ h	Let's find k_{el} from formula (1.5b) $t_{1/2} = \dfrac{\ln 2}{k_{el}}$: $t_{1/2} \cdot k_{el} = \ln 2 \quad \Rightarrow \quad k_{el} = \dfrac{\ln 2}{t_{1/2}}$
$k_{el} = ?$ $c = ?$	Now substitute the numerical values: $k_{el} = \dfrac{\ln 2}{t_{1/2}} = \dfrac{0.693}{2} \approx 0.35$ (h^{-1}). Further, substituting k_{el} into the law (1.2b) $C = C_0 e^{-k_{el}\,t}$ we can compute: $c = 20 \times e^{-0.35 \times 5} = 20 \times e^{-1.75} = 20 \times 0.174 = 3.48$ (mg/mL).

Answer: in 5 hours after administration of 20 mg/mL of lidocaine the concentration of it will decrease to 3.48 mg/mL.

Problem 2.5b. Find the elimination constant k_{el} for luminal if its elimination half-time is $t_{1/2} = 3$ days. The elimination process is described by one-compartment model.

Data:	***Solution:***

Answer: ____

Problem 2.6a. A patient has been administered $M_0 = 250$ μg of a medicine intravenously. Calculate the amount of the medicine in the blood in $t = 2$ hours after administration. The elimination constant of this medicine is $k_{el} = 0.23$ h^{-1}. The elimination process is described by the one-compartment model.

Data: | ***Solution:***

Answer: ______________________________

Problem 2.7a. In what time t will the concentration of a medicine in the blood decrease 4 times if it is known that the elimination half-time is $t_{1/2} = 6$ h. The elimination process is described by the one-compartment model.

Data: | ***Solution:***

Answer: ______________________________

The Pharmacokinetic Model with Sub-Compartment

Drugs are often administered not directly into blood, but into other tissues. In this case, the concentration of medicine in blood reaches maximum value not at once but in some time. For such processes in addition to the main compartment, modelling the blood and other tissues to which the medicine penetrates, a *sub-compartment* is introduced. It simulates the tissue which is the place of medicine administration. In this case, the rate of medicine infusion from the sub-compartment (tissue) into the main compartment (blood) is represented by k_{in}, infusion constant.

Exercise 2.8a. Write down the names of the compartments and the pharmacokinetic constants.

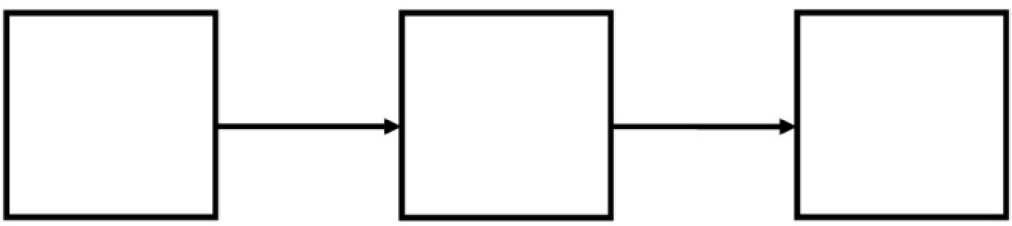

Fig. 2.3a. The scheme of the model with sub-compartment.

Within sub-compartment model the law which describes the change of medicine amount with a lapse of time in the main compartment (blood) has the following form:

$$M(t) = \frac{M_0 k_{in}}{(k_{in} - k_{el})}\left(e^{-k_{el}\,t} - e^{-k_{in}\,t}\right). \qquad (2.6a)$$

Exercise 2.9a. Since $M = C \cdot V \;\Rightarrow\; C = \frac{M}{V}$, please write down the dependence of medicine concentration on time:

$$C(t) = \qquad (2.7a)$$

You can see now that knowing the parameters k_{in}, k_{el}, V and M_0, we can compute the concentration of the medicine at any instant of time.

t_{max} is time during which the medicine concentration in the main compartment attains its maximum value :

$$t_{max} = \frac{\ln\left(\frac{k_{in}}{k_{el}}\right)}{(k_{in} - k_{el})}. \qquad (2.8a)$$

The velocity of medicine excretion from blood is equal to the first derivative of concentration with respect to time t:

$$\upsilon = \frac{dC}{dt} = \frac{M_0 k_{in}}{V(k_{in} - k_{el})}\left(-k_{el} e^{-k_{el}\,t} + k_{in} e^{-k_{in}\,t}\right) \qquad (2.9a)$$

Units of measurement for the velocity of medicine excretion from blood is [υ] = g / (L·h). Note that the value of the velocity should be negative, since the amount of drug in the compartment decreases.

Problem 2.10a. A patient was intramuscularly administered M_0 = 100 µg of medicine. Calculate the amount of medicine in the blood in 5 hours after administration, infusion constant k_{in} = 2 h $^{-1}$ and elimination constant k_{el} = 0.6 h $^{-1}$

Data:	***Solution:***

Answer: ______________________________

Problem 2.11a. 290 mg of medicine were administered to the patient by intramuscular injection. Calculate maximal concentration of medicine in blood if apparent blood volume V = 5.25 liters; $k_{in} = 1.7\ h^{-1}$ and $k_{el} = 1.3\ h^{-1}$.

Data:	***Solution:***

Answer: ____

Problem 2.12a. 175 mg of medicine were administered to the patient by intramuscular injection. Calculate velocity of medicine excretion from blood in 2 hours after administration. V = 5.3 L; $k_{in} = 2.56\ h^{-1}$ and $k_{el} = 1\ h^{-1}$.

Data:	***Solution:***

Answer: ____

Control questions

1. What does the mathematical biophysics study?
2. What is a model?
3. What is the method of mathematical modeling?
4. What is the pharmacokinetic model?
5. What pharmacokinetic model does describe the elimination process of the medicine from an organism if the medicine was injected directly into the patient's blood?
6. What does indicate such a parameter as the elimination half-time of a medicine?
7. What pharmacokinetic model does describe the elimination process of the medicine from an organism if the medicine was injected to the patient by intramuscular injection?

Individual assignments

1. Calculate the elimination half-time of medicine if its elimination constant equals to 0.34 h^{-1}. The elimination process is described by one-compartment model.
2. Find the elimination constant k_{el} for luminal if its elimination half-time is *two* days. The elimination process is described by one-compartment model.
3. The patient was administered 100 mg of medicine intravenously. Calculate medicine amount in blood in 1.5 hours after administration if k_{el} = 0.35 h^{-1}. The elimination process is described by one-compartment model.
4. Calculate the elimination half-time $t_{1/2}$ of a medicine if for the time interval $t = 3$ h of supervision of the patient the concentration of this medicine in the blood has decreased from $c_0 = 100$ μg L^{-1} to $c = 30$ μg L^{-1}. The elimination process is described by the one-compartment model.
5. Find the initial concentration c_0 of a medicine in the blood if in time $t = 7$ h after intravenous introduction its concentration has become $c = 25$ μg L^{-1}. The elimination half-time of the given medicine is $t_{1/2} = 3$ h. The elimination process is described by the one-compartment model.
6. In what time t after introduction will the concentration of a medicine in the blood decrease by 30 %. The elimination half-time is $t_{1/2} = 8$ h. The elimination process is described by the one-compartment model.
7. $M_0 = 130$ μg of a medicine was introduced to a patient intramuscularly. Calculate the concentration c of the medicine in blood in $t = 2.5$ h after introduction if $k_{in} = 2$ h^{-1} and $k_{el} = 0.5$ h^{-1} ; $V = 4.5$ L. The elimination process is described by the sub-compartment model.
8. $M_0 = 115$ mg of a medicine was introduced to a patient intramuscularly. Calculate velocity of medicine excretion from blood v in $t = 3$ h after introduction if $k_{in} = 1.2$ h^{-1} and $k_{el} = 0.3$ h^{-1} ; $V = 5.3$ L. The elimination process is described by the sub-compartment model.
9. $M_0 = 210$ μg of a medicine was introduced to a patient intramuscularly. Calculate the maximum concentration c_{max} of the medicine in blood if $k_{in} = 2$ h^{-1} and $k_{el} = 1.45$ h^{-1} ; $V = 5$ L. The elimination process is described by the sub-compartment model.
10. $M_0 = 50$ mg of a medicine was introduced to a patient intramuscularly. Calculate the maximum velocity v_{max} of excretion of the medicine from blood if $k_{in} = 2.2$ h^{-1} and $k_{el} = 1.15$ h^{-1} ; $V = 4.7$ L. The elimination process is described by the sub-compartment model.

TOPIC 2.B. Biophysics Of Muscle Contraction

The muscle cell differs from other excitable cells with such a specific property as *contraction*, that is, the ability to generate mechanical stress and contract. All vital functions of humans and animals are associated with muscular activity. The propagation of the action potential over the muscle fiber activates its contractile apparatus. Depending on the conditions under which the contraction occurs, two types are distinguished: isotonic and isometric contraction modes.

Exercise 2.1b. Define the following terms and write the answer to the question:

Sarcolemma is____

____

Muscle contraction process ____

____

What kinds of muscles are divided on the structure?_____________________________

____

In the process of *Isotonic Contraction* the muscle produces________________________

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In the process of *Isometric Contraction* the muscle produces_______________________

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The important characteristics of muscle operation are ***force*** and ***speed*** of contraction. Hill's equation is connecting these characteristics and has the following form:

$$(P+a)(v+b)=(P_0+a)b=a(v_{\max}+b) \tag{2.1b}$$

or

$$(P+a)(v+b)=(P_0+a)b \tag{2.2b}$$

$$(P_0+a)b=a(v_{\max}+b) \tag{2.3b}$$

Exercise 2.2b. Write down the parameter definitions and their units of measurement from Hill's equation:

P is ____ [P] = ______

υ is ____ [υ] = ______

*P_0 is*____ [P_0] = ______

*υ_{max} is*____ [υ_{max}] = ______

a is ____ [*a*] = ______

b is ____ [*b*] = ______

Exercise 2.3b. Through algebraic transformations express

constant b from equation (2.2b):	the maximal speed of muscle contraction υ_{max} from equation (2.3b):
$(P+a)(v+b)=(P_0+a)b.$ open the brackets: $Pv+Pb+av+ab=P_0b+ab.$ both sides of the equation contain ab, cancelling: $Pv+Pb+av=P_0b.$ moving Pb to the right side of the equation: $Pv+av=P_0b-Pb.$ Take out of the brackets υ and b as common factors: $v(\quad + \quad) = b(\quad - \quad)$	
then $b =$ ____________ (2.4b)	$\upsilon_{max} =$ ________ (2.5b)

Example of problem solution. A muscle is contracted with a speed of v =30 mm s^{-1} at a load of P = 0.5 N. It is known that the load during isometric contraction P_0 is equal to 1.5 N; the constant a is equal to 0.3 N. Calculate the maximal speed $v_{\max}$ of contraction.

Data:	***Solution:***
P = 0.5 H υ = 30 mm·s^{-1} P_0 = 1.5 H a = 0.3 H	Using (2.4b) and (2.5b), which we have derived from the Hill's equation: $b=\dfrac{\upsilon(P+a)}{P_0-P}=\dfrac{30\times10^{-3}\times(0.5+0.3)}{1.5-0.5}=24\times10^{-3}\left(m\cdot s^{-1}\right);$
υ_{max}-?	$\upsilon_{\max}=\dfrac{b}{a}P_0=\dfrac{24\times10^{-3}}{0.3}\times0.5=40\times10^{-3}\left(m\cdot s^{-1}\right)$

Answer. Maximal speed of muscle contraction under given conditions is 40 mm per second.

Power characteristics of muscle operation are ***work*** and ***power*** of contractions. The work W done by the muscle during time t is equal to

$$W_{useful} = P\cdot\upsilon\cdot t\,. \tag{2.6b}$$

Work is measured in *Joules* (J). The *total power* N_{total} developed by the muscle is described by the formula:

$$N_{\text{total}} = (P+a)v = b(P_0 - P)\,. \tag{2.7b}$$

The *useful power* N_{useful} developed by the muscle is described by the formula:

$$N_{useful} = P\cdot\upsilon\ . \tag{2.8b}$$

Power is measured in *Watts* (W). The *efficiency of muscle* η can be written down in the form:

$$\eta=\frac{W_{useful}}{W_{useful}+Q}, \tag{2.9b}$$

where Q is muscle` *heat production*, i.e. heat quantity, which is liberated during the process of muscle contraction. Efficiency of muscle can be calculated by another formula:

$$\eta = \frac{Pv}{N_{total}} = \frac{N_{useful}}{N_{total}} \tag{2.10b}$$

Problem 2.4b. A muscle being contracted with a speed of $v = 9$ mm s^{-1} develops the total power equal to $N_{\text{total}} = 3$ mW. The load during isometric contraction P_0 for this muscle is equal to 0.78 N, the constant b is equal to 25 mm s^{-1}. Calculate the work W done by the muscle for the time interval $t = 0.5$ s.

Data:	***Solution:***

Answer: ____

Problem 2.5b. During contraction of a muscle the quantity of heat $Q = 6.25$ kJ has been liberated for the time interval of $t = 0.7$ s. Calculate the useful power N_{useful} developed by the muscle, if its efficiency is $\eta = 25$ %.

Data:	***Solution:***

Answer: ____

Problem 2.6b. The maximal total power developed by a muscle is $N_{\text{total max}} = 10$ W, the load during isometric contraction is $P_0 = 300$ N. Calculate the total power N_{total} of the muscle at the at load of $P = 180$ N.

Data:	***Solution:***

Answer: ____

Control questions

1. Between which parameters does the relationship of Hill's equation establish?
2. Muscle contraction involves ....
3. What constants does the Hill's equation contain? What is the difference?
4. Which parameter does change in the isotonic mode of muscle contraction?
5. Which parameter does change in the isometric mode of muscle contraction?
6. Indicate the energy characteristics of the muscle contraction process.

Individual assignments

1. A muscle is contracted with a speed of v =40 mm s^{-1} at a load of P = 0.75 N. It is known that the load during isometric contraction P_0 is equal to 1.35 N; the constant a is equal to 0.54 N. Calculate the maximal speed v_{max} of contraction.
2. A muscle being contracted with a speed of v = 37 mm s^{-1} develops the total power equal to N_{total} = 2.3 mW. The load during isometric contraction P_0 for this muscle is equal to 0.95 N, the constant b is equal to 33 mm s^{-1}. Calculate the work W done by the muscle for the time interval t = 0.45 s.
3. During contraction of a muscle the quantity of heat Q = 7.05 kJ has been liberated for the time interval of t = 1.0 s. Calculate the useful power N_{useful} developed by the muscle, if its efficiency is η = 20 %.
4. The maximal total power developed by a muscle is $N_{total\ max}$ = 8 W, the load during isometric contraction is P_0 = 250 N. Calculate the total power N_{total} of the muscle at the at load of P = 110 N.
5. A muscle is contracted with a speed of v =23 mm s^{-1} at a load of P = 0.32 N. It is known that the load during isometric contraction P_0 is equal to 0.9 N; the constant a is equal to 0.14 N. Calculate the maximal speed v_{max} of contraction.
6. A muscle being contracted with a speed of v = 19 mm s^{-1} develops the total power equal to N_{total} = 1.3 mW. The load during isometric contraction P_0 for this muscle is equal to 0.43 N, the constant b is equal to 15 mm s^{-1}. Calculate the work W done by the muscle for the time interval t = 0.1 s.
7. During contraction of a muscle the quantity of heat Q = 4.25 kJ has been liberated for the time interval of t = 0.47 s. Calculate the useful power N_{useful} developed by the muscle, if its efficiency is η = 30 %.
8. The maximal total power developed by a muscle is $N_{total\ max}$ = 12 W, the load during isometric contraction is P_0 = 280 N. Calculate the total power N_{total} of the muscle at the at load of P = 155 N.