Self-Regulating Physiologically Based Pharmacokinetic Model and Creation of Drug Concentration Profiles in Plasma and Tissues

Stanislav Polinkevych
Recherche et Education en Mathematique,
101 Meaney Rue, Kirkland, Quebec, H9J 3B9, Canada

Abstract – *A physiologically based pharmacokinetic model is build to determine the dynamics of drug (compound) concentration in the human body. The model consists of two major subsystems. The first subsystem simulates the diffusion of the drug(s) and respiratory gases between plasma and the tissues. Second subsystem controls the processes of the drug and gas delivery to the tissues. The system of control is based on the principles of optimal control theory and the mechanisms of self-regulation. The model allows simulation of a combined influence of multiple clearance factors. The drug is administered intravenously into the human body and goes through phases of Absorption, Distribution, Metabolism, and Excretion (ADME). The results of numerical calculations of drug concentration profiles under renal and hepatic clearance are reported. The model can be tailored to suit the experimental needs in the fields of pharmacological and medical research.*

Keywords: pharmacokinetics, drug, dynamics, ADME, model, profile

1 Introduction

Drug development is a costly and time consuming process [1]. To reduce expenditure of this process, multiple analytical methods and tools are currently used. Attempts were made to integrate the compartments and build physiologically based models [2]. A variety of mathematical models and software tools was created and is available on market today [2]. Most of them are based on traditional concepts of pharmacokinetic modeling [2, 3]. However, physiological regulation mechanisms of the internal state of the system (organism) and the mechanisms of the drug transportation were not modeled.

The complexity of the mechanisms of regulation in the living organism required more sophisticated models (tools) which could represent the organism as a single system. The most important physiological mechanisms and principles of regulation of the drug transport system had to be properly incorporated into the model.

A new approach to the drug kinetics model creation with the use of Functional Respiratory System as a major system of drug transportation was offered [4]. A brief overview of the model simulating renal clearance was given.

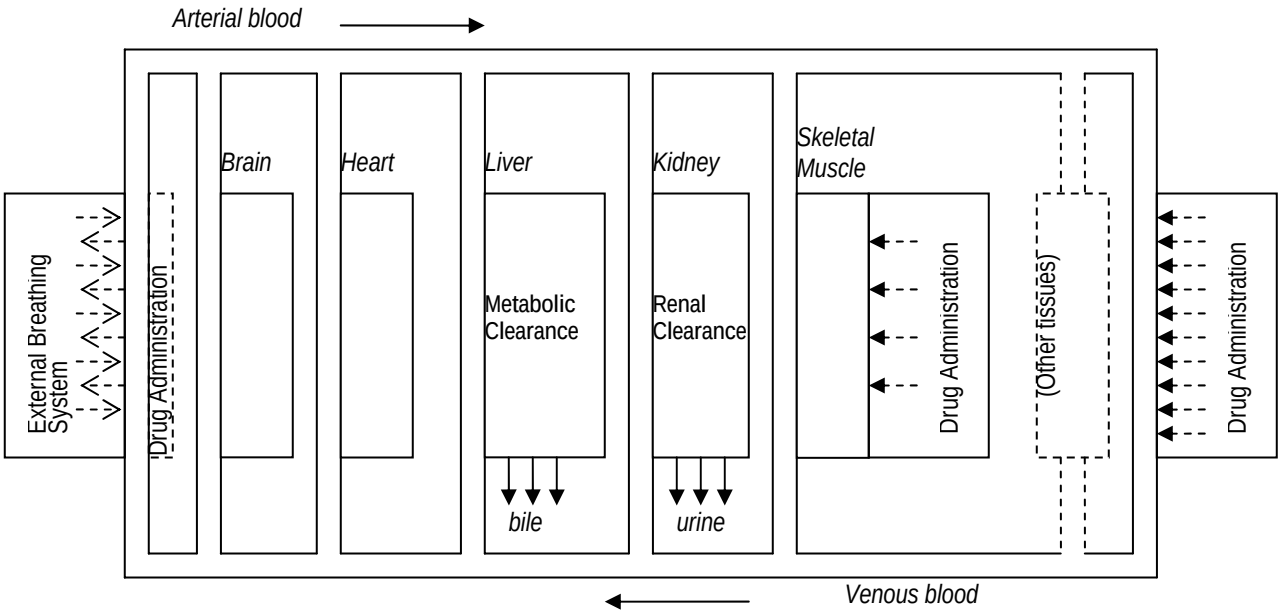
In this paper a new model for drug kinetics simulation is introduced. This model is built on the principles described in [4] and implements the simultaneous influence of two drug elimination factors – renal and hepatic clearance. The control of the model is based on the principles of optimal control theory and the mechanisms of self-regulation.

The model allows calculating drug concentration dynamics in plasma and the tissues of the organism, as well the distribution of the dose among the tissues and the re-distribution and elimination of the drug. The model represents a self-regulating system, and is built on modern knowledge of the cardiovascular and respiratory systems. As such, the simulated drug dynamics clearly reflect changes in the internal and external environment of the organism. Note, that traditional pharmacokinetics models attempt to predict the drug concentration under steady-state conditions. However, the newly developed model presented in this paper allows simulating the drug concentration dynamics in the organism in both – steady and disturbed states. A disturbed state is induced by modeling of internal and external stress factors exerted on a steady state of the system (organism).

This model is proven to be a dynamic and adaptable tool to build accurate as well as extensive drug concentration profiles in both plasma and tissues. It allows simulating multiple dosage regimens; determining effective and viable dosage gradients; rates and methods of administration and to simulate various routes of the drug elimination, including renal clearance and multiple schemes of metabolism.

2 General description of the multi-compartmental model

Organ tissues of the body are represented by m compartments, between which the drug d is transported via the closed circulatory system. The compartments represent the following tissues: cardiac, cerebral, hepatic, renal, skeletal muscle, and skin. An additional compartment is allocated for the remaining tissues. The distribution of the drug and respiratory gases through tissue capillaries is represented by a network of pipelines through which arterial and venous blood is pumped.



Scheme 1: Joined multi-compartmental system

The general scheme of the circulatory system is shown in Scheme 1. The sites of administration and routes of drug distribution as well as the compartments chiefly responsible for drug elimination are shown.

3 The system of drug and gas transport and exchange in the compartments

The system consists of a set of differential equations governing drug concentrations in the capillaries and the tissues of the compartments, and a separate set of differential equations that governs the tensions of respiratory gases – O_2 and CO_2.

In this paper, intravenous blood infusion is considered. The model can be adapted to other routes of administration.

Concentration of the drug *d* in the plasma (c_{dct_i}) of tissue capillaries is represented by the following set of differential equations:

$$V_{ct_i}\frac{dc_{dct_i}}{d\tau} = Q_{t_i}c_{fa} - G_{dt_i} - Q_{t_i}c_{dct_i}, \quad (1)$$

$$\mathrm{i} = \overline{1,\mathrm{m}},$$

Index i is assigned to a corresponding tissue, V_{ct_i} - the volume of the blood in the capillary of the tissue i.

Modeling of renal clearance is performed through modification of equation (1).

Concentration of the drug in the tissues (c_{dt_i}) is calculated by:

$$V_{t_i}\frac{dc_{t_i}}{d\tau} = G_{dt_i} - Q_d c_{dt_i} \quad \mathrm{i} = \overline{1,\mathrm{m}}, \quad (2)$$

The multi-compartmental system is governed by the self-regulating control system built on the principles of Optimal Control Theory [9].

Where V_{t_i} - the volume of the tissue i, G_{dt_i} - the flow of the drug from the capillary of the tissue i into the tissue, Q_{t_i} - the blood flow through the capillary of the tissue i, Q_d - the rate of the drug clearance.

G_{dt_i} is calculated by the formula:

$$G_{dt_i} = D_{dt_i}S_{t_i}\left(c_{dct_i} - c_{dt_i}\right) \quad (3)$$

D_{dt_i} is the value of the diffusion coefficient, S_{t_i} - the area of the surface of the diffusion.

The equation of the drug concentration in venous blood is calculated by:

$$V_{\bar{v}}\frac{dc_{d\bar{v}}}{d\tau} = \sum_{t_i}\left(Q_{t_i}c_{dct_i} + Q_{dt_i}\right) - Qc_{d\bar{v}} \quad (4)$$

where $Q = \sum_i Q_{t_i}, i = \overline{1,m}$, $V_{\bar{v}}$ - the volume of the venous blood.

The equations for the tension of oxygen (p_{1ct_i}) and carbon dioxide (p_{2ct_i}) in the blood of tissue (compartment) capillaries are [5]:

$$\frac{dp_{1ct_i}}{d\tau} = \frac{1}{\alpha_1 V_{ct_i}}\Big(\alpha_1 Q_{t_i}\left(p_{1a} - p_{1ct_i}\right) + \gamma Hb Q_{t_i}\left(\eta_a - \eta_{ct_i}\right) - G_{1t_i} - \frac{d\eta_{ct_i}}{d\tau}\gamma Hb \cdot V_{ct_i}\Big), \quad (5)$$

$$\frac{dp_{2ct_i}}{d\tau} = \frac{1}{\alpha_2 V_{ct_i}}\Big(\alpha_2 Q_{t_i}\left(p_{2a} - p_{2ct_i}\right) + \gamma_{BH} BH Q_{t_i}\left(z_a - z_{ct_i}\right) - G_{2t_i} + \gamma Hb Q_{t_i}\left(z_a(1-\eta_a) - z_{ct_i}\left(1-\eta_{ct_i}\right)\right) + \gamma Hb V_{ct_i}\frac{d\eta_{ct_i}}{d\tau} + \gamma_{BH} BH V_{ct_i}\frac{dz_{ct_i}}{d\tau}\Big). \quad (6)$$

Where

$$\eta_{ct_i} = 1 - 1{,}75\exp(-0{,}048\, m_{cL}\, p_{1cL}) + 0{,}75\exp(-0{,}12\, m_{cL}\, p_{1cL}), \quad (7)$$

$$m_{ct_i} = \delta(pH_{cL} - 7{,}4) + 1, \quad (8)$$

$$pH_{ct_i} = 6{,}1 + \lg\frac{BH}{\alpha_2 p_{2cL}}, \quad (9)$$

$$z_{ct_i} = \frac{p_{2ct_i}}{p_{2ct_i} + 30}, \quad (10)$$

In equations (5)-(10) α - solubility of corresponding gas, *pH* is the acidity of blood, *BH* is the concentration of enzyme carbonic anhydrates, p_{1a} - tension of oxygen (p_{2a} - carbon dioxide) in arterial blood, η_{ct_i} is the degree of saturation of hemoglobin with oxygen, S – the area of the surface of alveoli capillaries in a compartment, q – consumption of oxygen (index 1) or production of carbon dioxide (index 2).

In the compartments (tissues) the dynamics of the parameters of the model are defined by equations:

$$\frac{dp_{1t_i}}{d\tau} = \frac{1}{V_{t_i}\left(\alpha_{1t_i} + \gamma_{Mb} Mb V_{t_i}\frac{\partial\eta_{Mb_i}}{\partial P_{1t_i}}\right)}\left(G_{1t_i} - \dot{q}_{1t_i}\right) \quad (11)$$

$$\frac{dp_{2t_i}}{d\tau} = \frac{1}{\alpha_{2t_i} V_{t_i}}\left(G_{2t_i} + \dot{q}_{2t_i}\right) \quad (12)$$

where

$$\eta_{Mb_i} = 1 - \exp(-0{,}12\, p_{1t_i}) \quad (13)$$

The flows of gases through alveoli-capillary membranes are calculated based on

$$G_{t_i} = D_{t_i} S_{t_i}\left(P_{ct_i} - P_{t_i}\right), \quad (14)$$

D_{t_i} - diffusion coefficient of the corresponding gas.

Scheme 1 and correspondingly, the model can be modified for other possible ways of drug administration.

4 Description of the self-regulating control system

Volumetric blood flows in tissue capillaries Q_{t_i} are considered as control parameters. Then, the general criterion of control of the system (1)-(13) is given as the cost functional:

$$I = \int_{\tau_0}^{\infty}\sum_{i=1}^{m} K_i\left\{\left(G_{1t_i} - q_{1t_i}\right)^2 + \left(G_{2t_i} + q_{2t_i}\right)^2\right\} d\tau. \quad (15)$$

K_i - coefficients dependent on the size and the type of the corresponding compartment.

The task of control of the system (3)-(15) is formulated as the transformation of disturbed trajectories of the system (1)-(12) into the area of attraction of the stationary solution (equilibrium point - if a drug administration is not modeled by a periodic function), defined by inequalities:

$$\left|G_{1t_i} - q_{1t_i}\right| \le \varepsilon_1, \quad (16)$$

$$\left|q_{2t_i} + G_{2t_i}\right| \le \varepsilon_2. \quad (17)$$

The process of control of the system (3)-(15) is provided by the changes of parameters Q_{t_i} in order to minimize the functional (13). The values of Q_{t_i} are calculated using the methods of Optimal Control Theory [9].

If system (1)-(12) is disturbed by the changes in external or internal environments, then the new homeostatic state is determined, and the trajectories of the system (1)-(12) are transferred in the area defined by conditions (16)-(17).

5 Drug concentration profiles calculated by the model for intravenous drug administration

The model was adapted to reflect the characteristics of an average human being of 75 kg weight, including the surface of drug and gas exchange. The steady state of the system was characterized by the oxygen consumption of 4.3 ml/sec. Tensions of respiratory gases in arterial and venous blood were kept constant; O_2 arterial tension was equal to 95 mmHg, CO_2 arterial tension was equal to 42 mmHg.

To conduct the numerical experiments with the model (1)-(17), 200mg of the drug d were introduced intravenously every 5 hours within a 25 hour period. Several series of experiments were conducted with the model. First, the drug distribution and its diffusion to the compartments was simulated under the conditions of no clearance and no physical stress. Thus, benchmark values of the drug dynamics were set, upon which the trajectories of the system with renal and hepatic clearance would be evaluated.

Second, the calculations with model were performed under the effects of renal clearance exclusively.

The last series of experiments simulated both renal and hepatic methods of drug clearance.

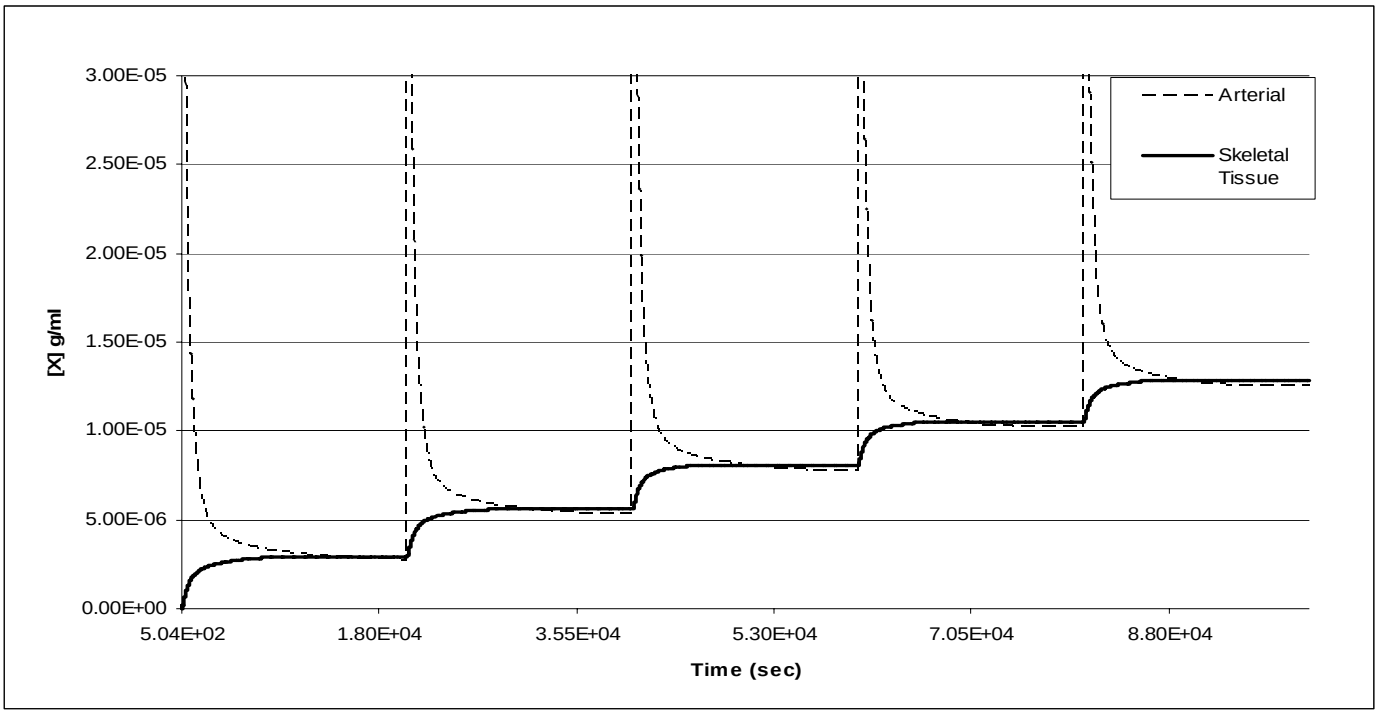


Figure 1A: Drug d Dynamics in Arterial Blood and Skeletal Muscle Tissue

Figures 1A, 1B and 1C display the trajectories of the drug concentration in skeletal, cardiac muscles, cerebral tissue, and arterial blood. The evident peaks on the trajectory that correspond to the drug concentration in arterial blood, show the moments of drug infusion into venous blood. Soon after infusion, the trajectory descends to a much lower level due to the rapid dose distribution to the tissue capillaries and to the tissues themselves. The trajectories of the drug concentration in skeletal muscle (Figure 1A), cardiac muscle (Figure 1B) and cerebral tissue compartments (Figure 1C) show the dynamics of drug accumulation in the corresponding compartment.

The rate of the infusion of the drug can be regulated in the model (1)-(17) according to the dosage requirements.

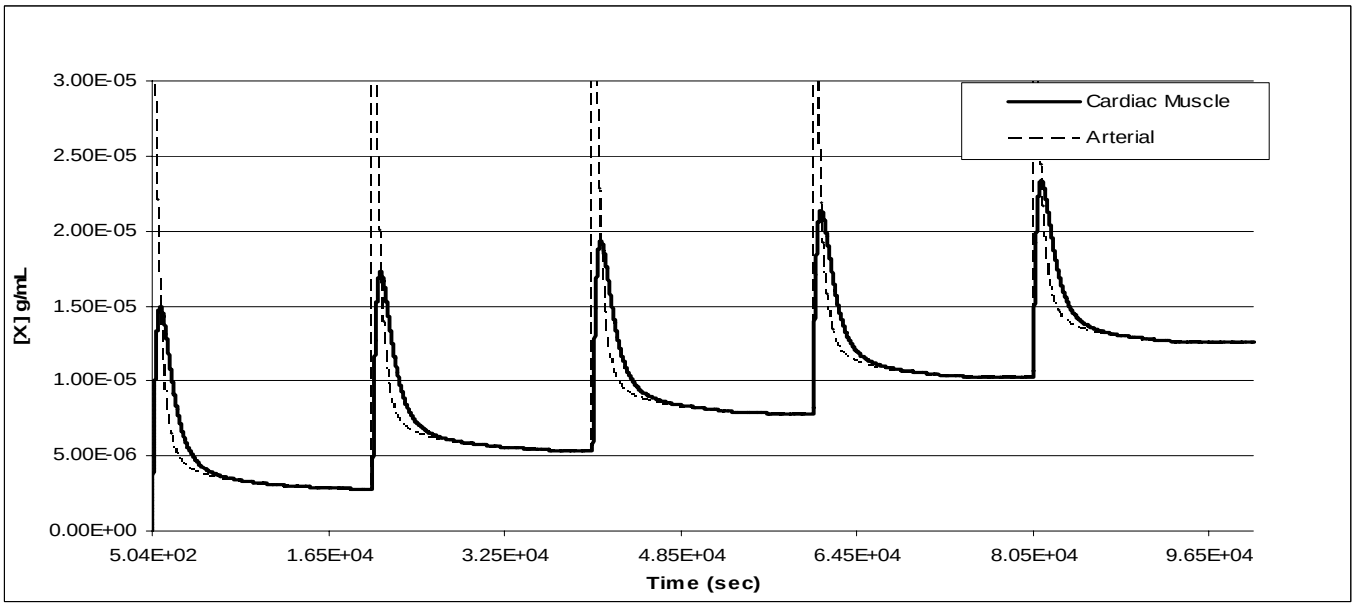


Figure 1B: Drug d Dynamics in Arterial Blood and Cardiac Muscle

The evident peaks on the trajectory of the caridac muscle are observed due to a higher ratio between the volume of the capillaries (V_{cti}) in the cardiac muscle and the volume of the tissue compartment in comparison to the same ratio in skeletal muscle or cerebral tissue. Once the concentration of the drug in the capillaries becomes lower than the concentration of the

drug in the tissue, the diffusion of the drug back to the capillaries from the tissue begins.

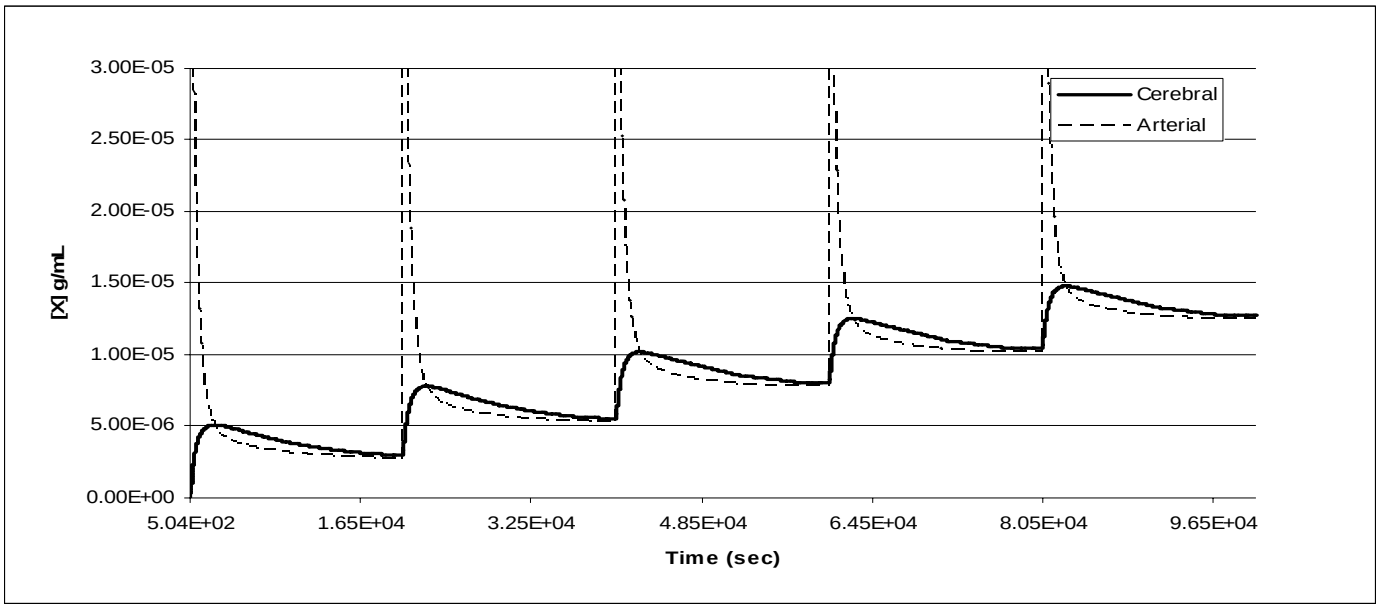


Figure 1C: Drug d Dynamics in Arterial Blood and Cerebral Tissue

Figure (2) presents the drug dynamics within skeletal muscle tissue under varying degrees of renal clearance in a steady state. It is apparent, that the dynamics of the drug concentration trajectory changes significantly. The calculations show significant decrease in the levels of the drug concentration in the skeletal muscle. Under the same rate of infusion, lower clearance rates show more rapid drug accumulation in the skeletal muscle, than under higher clearance rates.

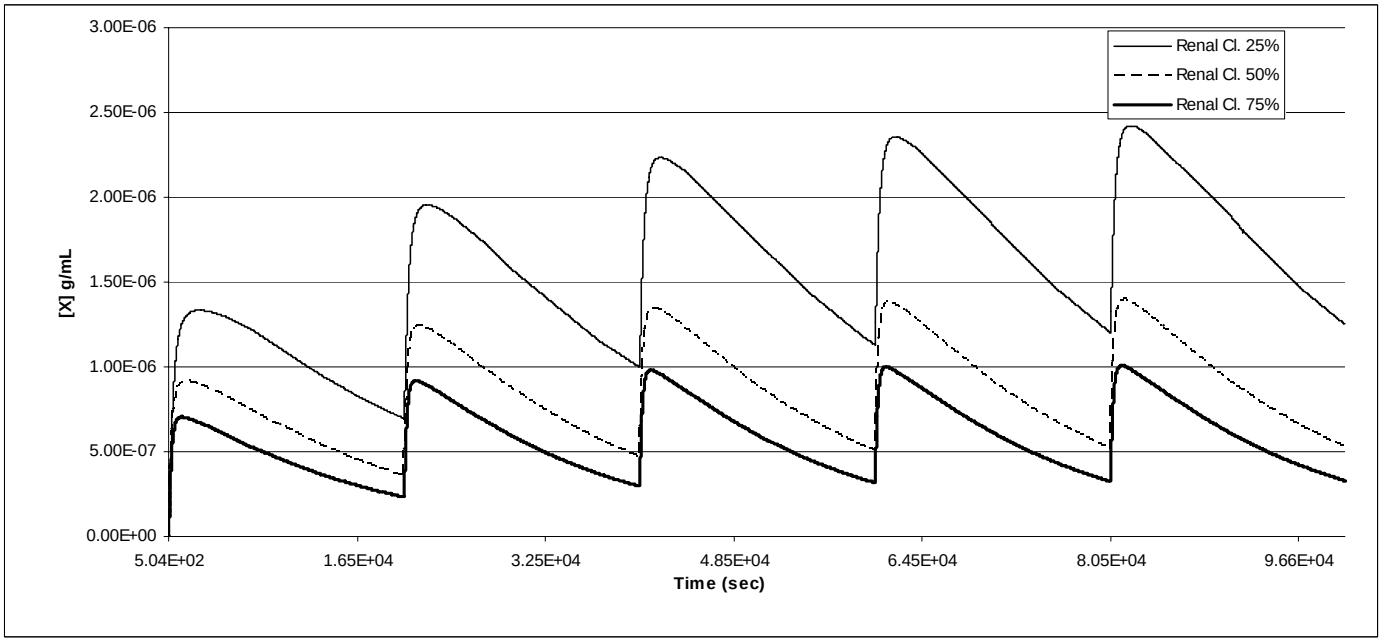


Figure 2: Effect of Renal Clearance on Drug d Dynamics in Skeletal Tissue.

Figure (3) presents the effects of renal and renal and hepatic (metabolic) clearance of the drug concentration in skeletal muscle. Two trajectories of drug concentration in skeletal muscle were simulated. One was simulated solely under renal clearance. The second was simulated under a combination of renal and hepatic methods of clearance. The dynamics clearly demonstrate the difference in the levels of the drug concentration between two trajectories. The trajectory that

was calculated in the result of simulation of the joined effect of both ways of clearance displays significantly lower values of the drug concentration.

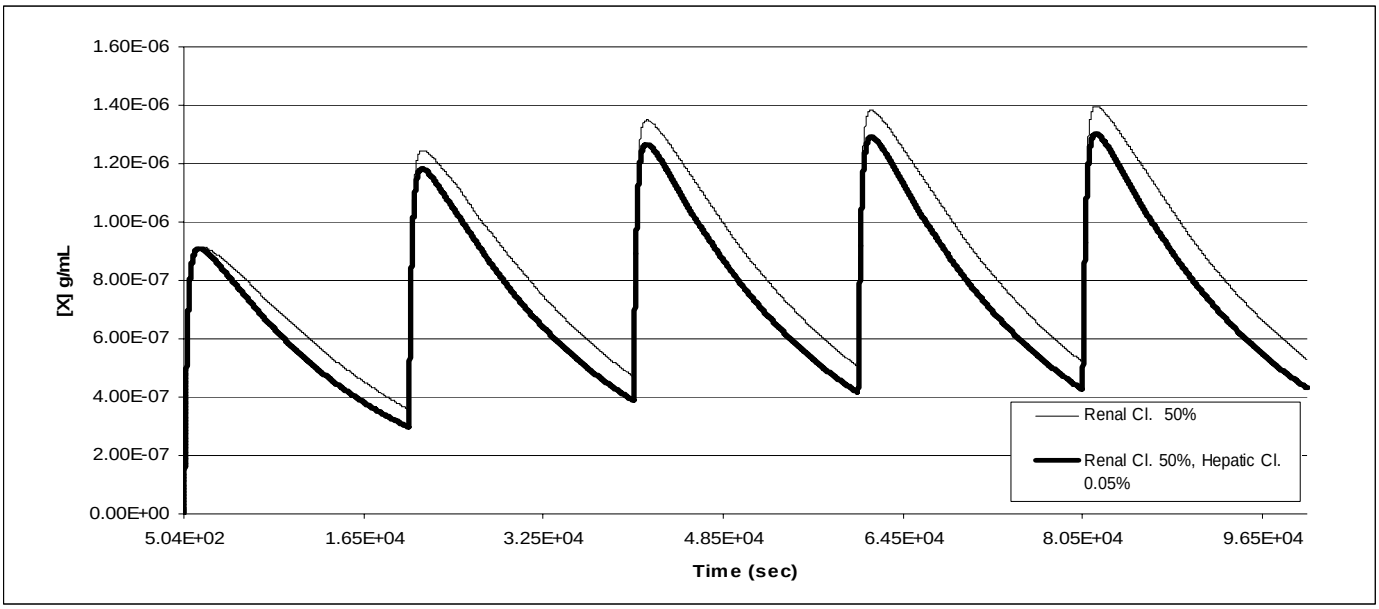


Figure 3: Effect of Hepatic Clearance on Drug d in Skeletal Tissue.

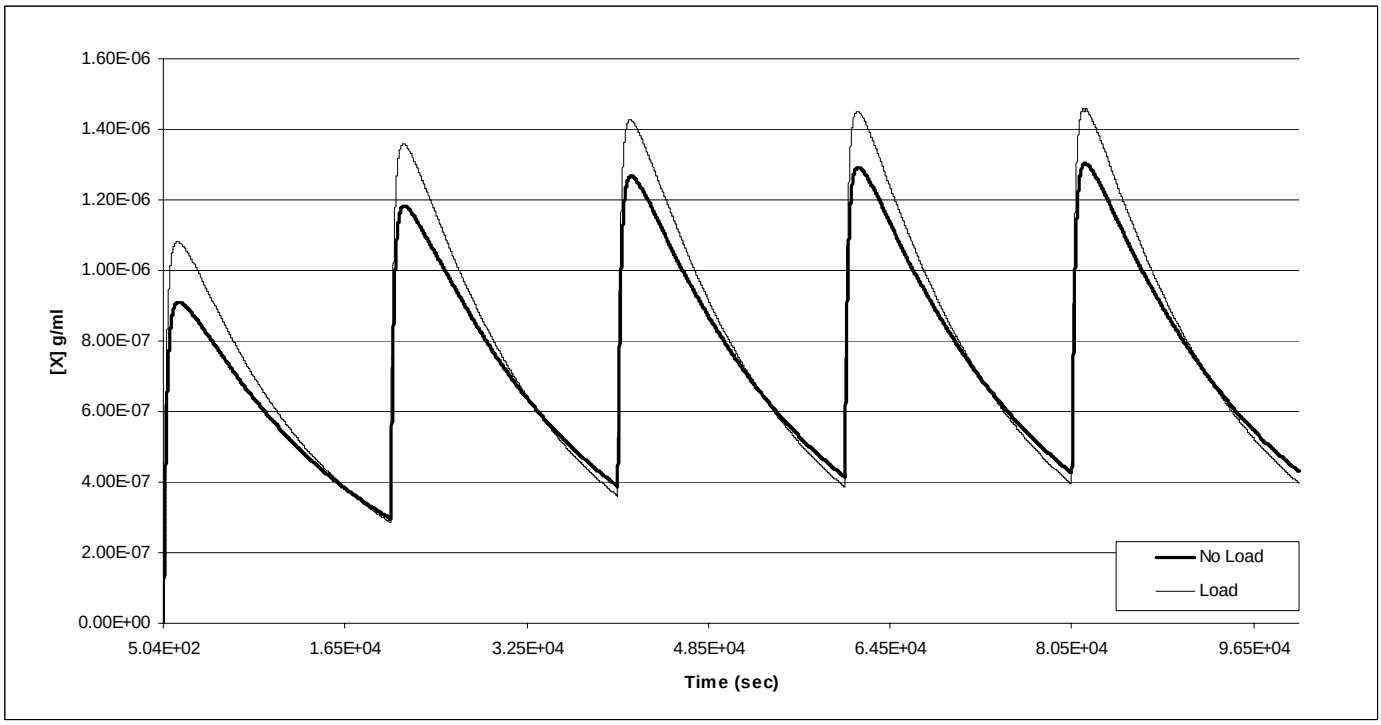


Figure 4: Effect of physical load on the drug concentration dynamics in skeletal muscle along with renal clearance ($K_R = 0.5$) and hepatic clearance ($K_H = 0.0005$).

Figure 4 represents the dynamics of the drug concentration in the skeletal muscle in a steady state ("No load") and under physical load ("Load", oxygen consumption was equal to 15 ml/sec). The dynamics of the trajectory under the load shows higher rate of accumulation of the drug in the muscle as well as higher rate of elimination. These changes

are explained by the increase in the blood flow in the skeletal muscle under the load from 19 ml/sec to approximately 100 ml/sec. Under physical load the blood flow grows due to increased oxygen demand in the skeletal muscle.

6 Conclusion

The results of the experiments with the model (1)-(17) proved that the model can be successfully used for the calculations of drug dynamics in plasma and tissues influenced by several factors of drug clearance. The dynamics of the drug concentration trajectories prove that the combined influence of two clearance factors accelerates elimination of the drug from the system (organism).

The model (1)-(17) allowed to build the accurate pictures of the drug dynamics in every (each) tissue/compartment in a steady and disturbed states. It was proven, that the model allows simulating the influence of several concurrent factors of drug clearance.

The model permits to calculate the dosage and the regimens of the drug for the different routes of its administration and ways of clearance. It can be readily adapted to a specific drug with the defined physical, physiological and chemical properties. Different mechanisms of clearance including multiple schemes of metabolism can be introduced into the model.

The model (1)-(17) is a versatile tool of the simulation of drug kinetics parameters, and can be tailored to suit the experimental needs in the fields of pharmacological and medical research; it considerably reduces the time and the cost of the laboratory studies.

7 References

[1] New Drug Development: Regulatory Paradigms for Clinical Pharmacology and Biopharmaceutics (Drugs and the Pharmaceutical Sciences), Informa Healthcare, 2004

[2] Applied Biopharmaceutics And Pharmacokinetics, 5th Edition, McGraw-Hill Companies Inc., 2005

[3] Dennis A. Smith, Han van de Waterbeemd, K. Don, Pharmacokinetics and Metabolism in Drug Design, second ed., Wiley-VCH, Weinheim, 2006.

[4] K.Polinkevych; G.Onopchuk; S.Polinkevych. Simulation of drug dynamic parameters and optimization models of the functional respiratory system in pharmacokinetic studies. Nonlinear Analysis (December 2009), 71 (12), pg. e936-e941

[5] G. Onopchuk, K. Polinkevich, Mathematical models of the respiratory system and practical problems of medicine, METMBS '04, June 21_24, 2004, CSREA Press, Las Vegas, 2004, pp. 69_74.

[6] G. Onopchuk, Mathematical modeling of hypoxic states of human organism and their pharmacological correction in case of ischemia and atherosclerosis, METMBS 2005, Las Vegas, Nevada, USA, June 20_23, 2005, CSREA Press, Las Vegas, 2005, pp. 201_204.

[7] G. Onopchuk, K. Polinkevych, Integrated approach to system researches of complex problems of medicine and biology, ISFR 2005 - The New Roles of Systems Sciences for a Knowledge-Based Society, Nov. 14_17, 2005, Kobe, Jaist Press, Komatsu, 2005, pp. 287_288.

[8] G. Onopchuk, K. Polinkevych, Mathematical approach to validation of the material balance type simulation models for pharmacokinetics studies, SERP 2007, June 25_28, 2007, CSREA Press, Las Vegas, 2007, pp. 210_216.

[9] Ross, I. M. *A Primer on Pontryagin's Principle in Optimal Control*, Collegiate Publishers, 2009