Mariana BEŇOVÁ, Daniela GOMBÁRSKA, Branislav DOBRUCKÝ

University of Žilina

Using Euler's and Taylor's expansion method for solution of non-linear differential equation system in pharmacokinetics

Abstract. *The paper deals with Euler's- and Taylor's expansion methods for next numerical solution in Matlab environment. There are many applications in pharmacokinetic described and modelled by linear or non-linear differential equation (DE) systems. These non-linarities can be considered in drug absorption, distribution, metabolism and excretion, and the pharmacokinetics of drug action. A fictitious exciting functions method makes possible numerical solution of this DE system with non-stationary matrices. The solutions of simple example are presented as well.*

Streszczenie. *Praca pokazuje zastosowanie rozwinięcia Eulera i Taylora w rozwiązaniu równań różniczkowych zwyczajnych w środowisku Matlaba. W szczególności rozważono równania różniczkowe liniowe i nieliniowe zapisane w formie równań stanu. Symulacje numeryczne potwierdzające prawidłowość proponowanej metody dotyczyły praktycznego przykłady równań farmakokinetycznych występujących przy badaniach leku stosowanego w angioplastyce wieńcowej (**Rozwinięcie Eulera i Taylora w rozwiązaniu nieliniowych równań w farmakokinetyce**).*

Keywords: non-linear pharmacokinetic models, non-linear equations, Euler´s and Taylor´s expansion method
Słowa kluczowe: modele farmakokinetyczne, równania rózniczkowe nieliniowe, rozwinięcie Taylora.

Introduction

Pharmacokinetic modelling uses systems of ordinary differential equations (ODE) derived from biological considerations along with statistical models to model the time course for example of drug in the body. From these sources we can obtain simply one-compartment models or multi-compartments model.

There are many applications in pharmacokinetic described and modelled by linear or non-linear ODE systems. Evidence of non-linarities in pharmacokinetics goes back to the early 1930's with the origination of the concept that ethyl alcohol is eliminated at a fixed rate independent of its concentration in the body, [1]. Pharmacokinetics is the study of the course of absorption, distribution, metabolism, and elimination of some substance in a living body and it is especially important in the development of drugs. Sources of non-linearities are for example absorption and elimination parameters, systemic clearance, enzymatic metabolic activity, plasma binding, renal clearance, and cerebrospinal fluid drug concentration, [2], [3].

Solution of non-linear ODEs

A fictitious exciting functions method makes possible numerical solution of this DE system with non-stationary matrices. The paper deals with Euler's- and Taylor's expansion methods for next numerical solution in Matlab.

Let's have system of DEs

$$(1)\quad \frac{\mathrm{d}x_1}{\mathrm{d}t} - a_{11}x_1 - a_{12}x_2 = b_{11}u_1\,, \quad \frac{\mathrm{d}x_2}{\mathrm{d}t} - a_{21}x_1 - a_{22}x_2 = b_{22}u_2$$

It can be also presented in matrix state-space form

$$(2)\quad \frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} b_{11} & b_{12} \\ b_{21} & b_{22} \end{pmatrix}\begin{pmatrix} u_1 \\ u_2 \end{pmatrix} \rightarrow$$

$$\rightarrow \frac{\mathrm{d}\bar{x}}{\mathrm{d}t} = \mathbf{A}\,\bar{x} + \mathbf{B}\,\bar{u}$$

where $\mathbf{A}$, $\mathbf{B}$ are the system- and transition matrices; $\bar{x}$, $\bar{u}$ are state-variables- and exciting vectors.

If a_{11} and a_{12} elements of $\mathbf{A}$ matrix are non-stationary and b_{12}, b_{21}, b_{22} and u_2 = 0 then

$$(3)\quad \frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ a_{21} & a_{22} \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + \begin{pmatrix} b_{11} & 1 & 1 \\ 0 & 0 & 0 \end{pmatrix}\begin{pmatrix} u_1 \\ a_{11}x_1 \\ a_{12}x_2 \end{pmatrix} \rightarrow$$

$$\rightarrow \frac{\mathrm{d}\bar{x}}{\mathrm{d}t} = \mathbf{A}_f\,\bar{x} + \mathbf{B}_f\,\bar{u}_f$$

where $\mathbf{A}_f$, $\mathbf{B}_f$ are the modified (fictitious) system- and transition matrices; $\bar{u}_f$ is fictitious exciting vector, and $a_{11}x_1$, $a_{12}x_2$ are fictitious exciting functions.

Let's consider Euler's- and Taylor's expansion methods for numerical solution by [4]. We obtain:

a) Euler explicit method yields

$$(4)\quad \bar{x}_{n+1} = \left(\mathbf{E} + h\mathbf{A}_f\right)\bar{x}_n + h\mathbf{B}_f\,\bar{u}_{fn}\,,$$

where h is integration step and $\mathbf{E}$ is unity matrix.

b) Euler implicit method yields

$$(5)\quad \bar{x}_{n+1} = \left(\mathbf{E} - h\mathbf{A}_f\right)^{-1}\left[\bar{x}_n + h\mathbf{B}_f\,\bar{u}_{fn}\right],$$

where $\mathbf{F} = (\mathbf{E} - h\mathbf{A}_f)^{-1}$ is fundamental matrix of the system.

c) Taylor expansion yields

$$\mathbf{F} = \exp(h\mathbf{A}) = \sum_{n=0}^{\infty}\frac{h^n\mathbf{A}^n}{n!} \quad \text{and similarly} \quad \mathbf{G} = h\sum_{n=0}^{\infty}\frac{h^n\mathbf{A}^n}{(n+1)!}$$

So, choosing appropriated number of series member n is

$$(6)\quad \bar{x}_{n+1} = \mathbf{F}\,\bar{x}_n + \mathbf{G}\,\bar{u}_{fn}$$

The discrete equations carried-out by Euler explicit-, implicit- and Taylor expansion methods are easily solvable by numerical computing because their modified (fictitious) matrices are stationary ones. The solutions of simple examples are presented in [5].

Pharmacokinetics

Pharmacokinetics is the study of drug disposition in the body and focuses on the changes in drug plasma concentration. For any given drug and dose, the plasma concentration of the drug will rise and fall according to the rates of three processes: absorption, distribution, and elimination.

Absorption of a drug refers to the movement of drug into the bloodstream, with the rate dependent on the physical characteristics of the drug and its formulation.

Distribution of a drug refers to the process of a drug leaving the bloodstream and going into the organs and tissues.

Elimination of a drug from the blood relies on two processes: biotransformation (metabolism) of a drug to one or more metabolites, primarily in the liver; and the excretion of the parent drug or its metabolites, primarily by the kidneys.

The relationship between these processes is shown in Fig.1, [6]. In the case of intravenous administration is scheme more simply, it is without absorption from the blood.

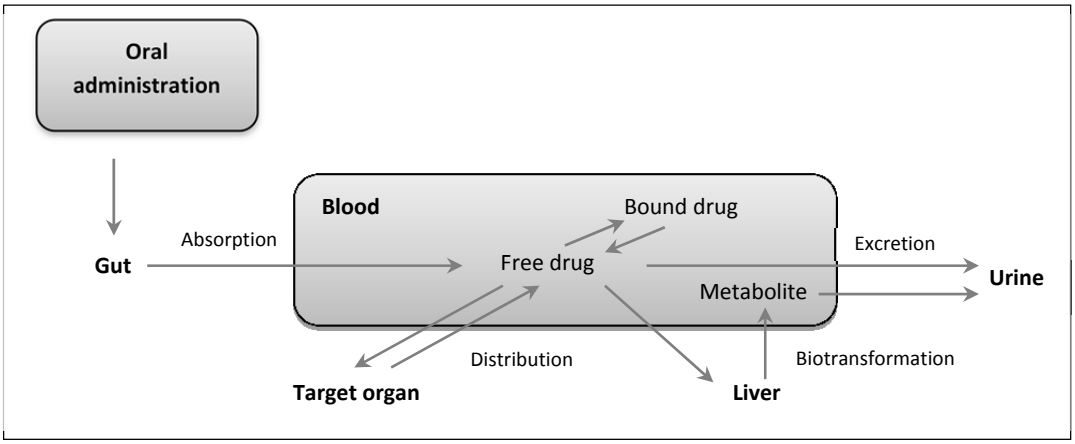


Fig.1. The absorption, distribution, biotransformation (metabolism), and excretion of a typical drug after its oral administration [6]

Linear and non-linear ODEs in pharmacokinetics

As is mentioned above the distribution of drugs in organism is doing across different biological membranes. The major and usually the only process that controls the passage of drugs across membranes is passive diffusion. It comes to this that the directed movement of a chemical through a barrier from a higher to lower concentration (no energy is necessary). Passive diffusion reflects the natural tendency for chemical concentrations to move towards equilibrium and stability. That mathematical modelling is going out from first Fick's low [6].

Traditional pharmacokinetic models are based on the assumption of a linear relationship between the dose of a drug and its concentration. The body is divided into physiological compartments (different biological areas) bounded to membranes, and a drug's journey between two different compartments is described by a rate coefficient. In a linear model, these rate coefficients called *k* are assumed to be constant. The concentration in each compartment *C* can be described by the following differential transport equations for example for two compartment model

$$\frac{dC_1}{dt} = -k_{12}C_1 + k_{21}C_2\,,\quad \frac{dC_2}{dt} = k_{12}C_1 - k_{21}C_2\,, \tag{7}$$

where C_1, C_2 are concentrations in compartments 1, 2, $k_{12} = \frac{P \cdot S}{V_1}$, $k_{21} = \frac{P \cdot S}{V_2}$ are rate coefficients, P is coefficient of permeability, S is membrane area and V_1, V_2 are distribution bulks.

Thus for multiple simultaneous processes in a number of compartments, a series of coupled differential equations is obtained. Since all of these equations are linear, it is easy to solute them.

Non-linear pharmacokinetics are said to exist when the parameters are dose- or time-dependent. With dose-dependence, an increase in the administered dose results in a disproportionate increase in the absorbed dose. The most common type of dose-dependence discussed in the literature follows Michaelis-Menten (M-M) kinetics, where the clearance of a drug changes with concentration *C* due to saturation of the drug action site by following equation

$$-\frac{dC}{dt} = v_{\max}\frac{C}{K_m + C}\,, \tag{8}$$

where $v_{\max}$ is maximal velocity of metabolism and K_m is Michaelis constant. Those parameters are possible obtained by experimental way. M-M kinetics is also called capacity-limited metabolism, saturable metabolism, or mixed-order kinetics.

References to time-dependent nonlinearity are much less frequent, though Levy [7] lists the following possible sources: absorption and elimination parameters, systemic clearance, enzymatic metabolic activity, plasma binding, renal clearance, and cerebrospinal fluid drug concentration. Both dose and time dependencies can be present simultaneously.

Because the body is a complex system, the observed concentration values are the end product of many intricate interactions. In all likelihood, there is one dominant process responsible [3].

Practical example - Modeling of Abciximab Concentrations in Patients Undergoing Coronary Angioplasty

Abciximab, a monoclonal antibody Fab fragment, was the first approved agent in this class of drugs and has been shown to prevent acute cardiac ischemic complications from percutaneous transluminal coronary angioplasty (PTCA) and atherectomy (EPIC Investigators, 1994). Typical dosing regimens include a weight-normalized intravenous (i.v.) bolus dose of 0.25 mg/kg, followed by an i.v. infusion of 0.125 μg/kg/min (up to a maximum of 10 μg/min) for 12 to 24 hours, depending on the indication. Abciximab is a drug with a narrow therapeutic index, with serious complications resulting from under treatment (lack of antithrombotic effect) or over treatment (e.g. bleeding episodes). The standard administration regimen results in substantial inter-patient variability in dose concentration and concentration-effect relationships. These observations suggest a role for the individualization of abciximab pharmacotherapy as well as the potential for therapeutic drug monitoring, [8].

The classical description of abciximab pharmacokinetics, including a rapid distribution phase, a prolonged terminal phase, and high-affinity binding to its pharmacological receptor, is consistent with that of target-mediated drug disposition, where drug-target interactions may impact the pharmacokinetics of the drug in just such a manner. The schematic of the model is shown in Fig. 2 and the differential equations that define it by [8] are:

$$\frac{dC_1}{dt} = \frac{K_0/V + k_{21}\cdot C_2 - \left(k_{12} + k_{el}\right)\cdot C_1}{1 + \dfrac{R_T \cdot K_D}{V\cdot\left(K_D/V + C_1\right)^2}}\,, \tag{9}$$

$$\frac{dC_2}{dt} = k_{12}\cdot C_1 - k_{21}\cdot C_2\,, \tag{10}$$

where C_1 and C_2 represent drug concentrations (nM) in the central (#1) and peripheral (#2) compartments, R_T is

maximum receptor density (nM), k_{12}, k_{21} are first order distribution constants (h^{-1}), k_{el} is the first order elimination rate constant (h^{-1}), V is the volume of both compartments (L/kg). The zero-order drug infusion rate (K_0) is zero for the first study, and a constant value (K_0 = 0.158 nmol/kg/hr) when time is less than the infusion time (T_{inf}) for the second study (K_0 = 0 when time $t > T_{inf}$).

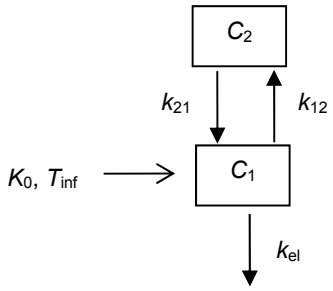


Fig.2. Schematic of the pharmacokinetic component of the final model for abciximab. It´s infusion (K_0, T_{inf}) is connected to the central compartment (C_1) and free drug can transfer between the peripheral compartment (C_2, k_{12}, k_{21}) or be eliminated (k_{el}).

Based on above the non-linear dynamical state-space model of the system can be created

$$\frac{d}{dt}\begin{pmatrix} C_1 \\ C_2 \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ -k_{12} & k_{21} \end{pmatrix} \cdot \begin{pmatrix} C_1 \\ C_2 \end{pmatrix} + \tag{11}$$

$$+ \begin{pmatrix} -1/V & (k_{12}+k_{el}) & -k_{21} \\ 0 & 0 & 0 \end{pmatrix} \cdot \begin{pmatrix} K_0/D \\ C_1/D \\ C_2/D \end{pmatrix},$$

and it in discrete form using Euler explicit formula (4)

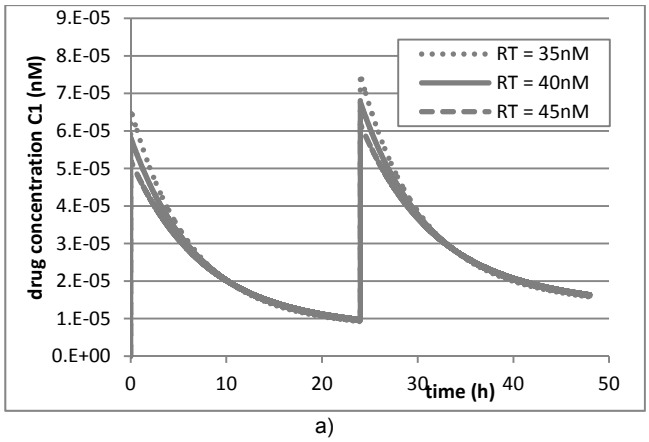
$$\begin{pmatrix} C_1 \\ C_2 \end{pmatrix}_{n+1} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} + h \cdot \begin{pmatrix} 0 & 0 \\ -k_{12} & k_{21} \end{pmatrix} \cdot \begin{pmatrix} C_1 \\ C_2 \end{pmatrix}_n + \tag{12}$$

$$+ h \cdot \begin{pmatrix} -1/V & (k_{12}+k_{el}) & -k_{21} \\ 0 & 0 & 0 \end{pmatrix} \cdot \begin{pmatrix} K_0/D \\ C_1/D \\ C_2/D \end{pmatrix}_n ,$$

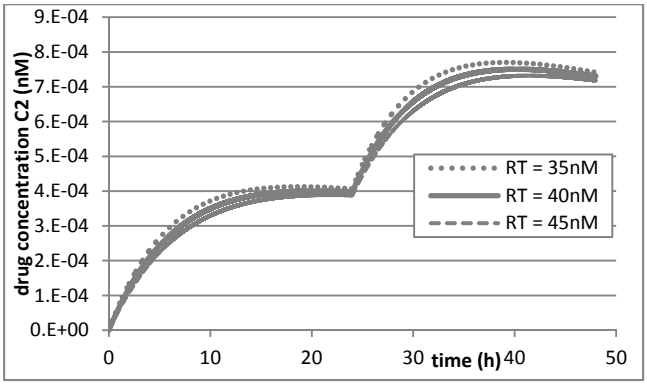
where

$$D = 1 + \frac{R_T \cdot K_D}{V \cdot (K_D/V + C_1)^2} .$$

There are simulation results of drug concentrations C_1 and C_2 in Fig.3 using MatLab simulation environment for three values of R_T (40nM, 35nM, 45nM). Initial conditions are $C_{1(0)}$ = 0, $C_{2(0)}$ = 0 and time for next infusion is 24 hours. The values of parameters used in simulation are defined in the Tab.1. by [8].



a)



b)

Fig.3. Simulation results of time drug concentrations C in the a) central (#1) and b) peripheral (#2) compartments for three different values of maximum receptor density R_T

Tab.1. Estimated abciximab pharmacokinetic parameters [8]

Parameter (units)	Final estimate
k_{12} (h^{-1})	1.21
k_{21} (h^{-1})	0.0326
k_{el} (h^{-1})	0.583
V (L/kg)	0.118
K_D (nmol/kg)	0.0411
T_{inf} (h)	24

Similarly it is possible to create this non-linear dynamic model in discrete form using Euler implicit formula (5) and Taylor expansion method (6) with the same results.

Conclusion

There are many applications in pharmacokinetic described and modelled by non-linear differential equation (DE) systems. The solutions of simple example - modelling of abciximab concentrations in patients undergoing coronary angioplasty was presented with using Euler's expansion method for next numerical solution.

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***Authors**: dr. inż. Mariana Beňová, dr. inż. Daniela Gombárska, prof. dr inż. Branislav Dobrucký, University of Žilina, Faculty of Electrical Engineering, Univerzitná 1, 01 026 Zilina, Slovakia, benova@fel.uniza.sk, gombarska@fel.uniza.sk, dobrucky@fel.uniza.sk.*