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ORIGINAL PAPER

New method of finding the analytical solutions directly on the base on the reaction mechanism

Marius Socol · Ioan Bâldea

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Abstract An alternative method for solving homogenous and non-homogenous linear differential equation systems used in chemical kinetics and pharmacokinetics on the basis of flow graph principles has been proposed. Classical method of solving these systems with flow graphs involves the employment of Laplace transforms before depicting a flow graph and the inverse Laplace transforms after using the Mason's rules. A short description of flow graph algebra has been presented. One model very often encountered in pharmacokinetics was solved. Our proposed method is simpler and more direct, eliminating the Laplace transforms. The calculus is made directly on the base of the flow graph representing the image of reaction scheme (pharmacokinetic model).

Keywords Flow graph theory · Linear differential equation systems · Chemical kinetics · Reactions mechanism · Pharmacokinetics model

1 Introduction

A flow graph is a diagram that is formed on base of a set of simultaneous linear algebraic equations or a linear differential equations system, which are written starting from a set of elementary chemical reactions included into a mechanism. The flow graph is used to represent the evolution of a physical system and to obtain the relationships

M. Socol (✉) · I. Bâldea
Department of Physical Chemistry, Faculty of Chemistry and Chemical Engineering, Babe-Bolyai University of Cluj-Napoca, 11 Arany Janos Street, Cluj-Napoca, Romania
e-mail: m_socol2000@yahoo.com

I. Bâldea
e-mail: ibaldea@chem.ubbcluj.ro

between the system variables. By using the Cramer's method [1] with determinants one could solve the system.

A flow graph consists of a network in which nodes (or vertices) are connected by directed edges (or branches). Each node represents a system variable, and each edge connecting two vertices acts as a signal multiplier. An arrow placed on the edge indicates the direction of the signal flow and the multiplication factor is indicated along the edge [2,3]. This multiplication factor is named transmittance. It can be obtained from the coefficients of the equations. The signal flow graph depicts the flow of signals from one point of the system to another and gives the relationships between the signals. It represents the value of the determinant of the system [4].

1.1 Definitions related to flow graphs

Before discussing flow graphs certain terms should be defined [4]:

Node (Vertex) is a point representing a variable or a signal. For example, in chemistry it represents a chemical species undergoing some transformation.

Weighting of an edge (transmittance) is a real or complex gain between nodes. Such gains may be expressed in terms of transfer function between two nodes. In chemical kinetics it represents a pseudo-first- or a true first-order rate constant, measuring the frequency with which a chemical event takes place. By multiplying it with the actual concentration of the species in the vertex of the outgoing branch and the volume of the system, the chemical flux in the indicated direction, is obtained.

Edge (branch) is a directed line segment joining two nodes. The gain of a branch is the transmittance.

Input node or source is a node that has only outgoing edges. This corresponds to an independent variable. In chemical kinetics it represents the reactant species.

Output node or sink is a node that has only incoming edges. This corresponds to a dependent variable. In chemical kinetics, it corresponds to a reaction product.

Mixed (internal) node is a node that has both outgoing and incoming branches and corresponds to a dependent variable.

A flow graph example is presented in Fig. 1.

For a given system a flow graph is not unique. More equivalent flow graphs can be drawn for a given system by writing the system equations or the corresponding determinants in a different way [5–7].

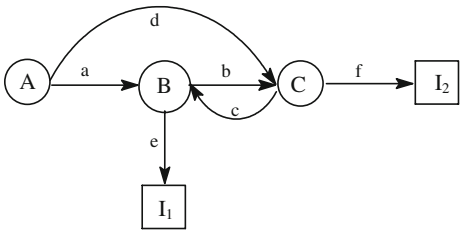


Fig. 1 An example of a flow graph; "A" is an input node (or source); "I_1", "I_2" are output nodes (sinks); a, b, c, d, e and f are weighting of the edges; "B"," C" are the internal nodes

$$\text{I)}\ CH_4 \xrightarrow{k_1} CH_3^{\bullet} + H^{\bullet} \qquad \text{II)}\ CH_3^{\bullet} \xrightarrow{k_2[CH_4]} H^{\bullet} \qquad \text{IV)}\ CH_3^{\bullet} \xrightarrow{k_4[CH_3^{\bullet}]} C_2H_6$$

$$\text{III)}\ H^{\bullet} \xrightarrow{k_3[CH_4]} CH_3^{\bullet} \qquad \text{V)}\ H^{\bullet} \xrightarrow{k_5[H^{\bullet}]} H_2$$

Scheme 1 Methane pyrolisys mechanism

2 The alternative flow graphs algebra

In Physical Chemistry, particularly in chemical kinetics, the system of equations and corresponding determinants can be written starting with the reaction mechanism. On the basis of these determinants, the flow graph can be constructed according to a set of rules [5]. For the methane pyrolysis at 1,600 °C, for example, the simplified mechanism consists of the following elementary steps, disregarding the reverse reactions [8]:

Step I (the initiation) indicates the input source (S) of radical species, which, in this case, is commune for both of the radicals (CH_4). Steps II and III describe the interchange of these radical species while the last two steps (IV and V-the interruptions) provide the final output products (C_2H_6 and H_2). The accepted values of the rate constants (k_i) and the value of starting CH_4 concentration are also given [9] so the numerical solutions for radical species can be found, after its replacement.

Considering that the quasi-steady-state approximation is valid [10,11] (the concentrations of radical species are very low and at steady-state) the system of differential equations, based on the mechanism from Scheme 1 of reactions 1, is:

$$\begin{cases} -\dfrac{d\left[CH_3^{\bullet}\right]}{dt} = 0 = (k_2[CH_4] + 2k_4[CH_3^{\bullet}]) \cdot [CH_3^{\bullet}] - k_3[CH_4] \cdot [H^{\bullet}] - k_1[CH_4] \\ -\dfrac{d\,[H^{\bullet}]}{dt} = 0 = -k_2[CH_4] \cdot [CH_3^{\bullet}] + (k_3[CH_4] + 2k_4[H^{\bullet}]) \cdot [H^{\bullet}] - k_1[CH_4] \end{cases} \tag{1}$$

To simplify, the following symbols are used further on: $B = CH_3^{\bullet}$, $C = H^{\bullet}$, the final products C_2H_6, H_2 with I_1 and I_2, respectively; the pseudo-first order rate constants $a = k_1[CH_4] = d$, $b = k_2[CH_4]$, $c = k_3[CH_4]$, $2k_4[CH_3^{\bullet}] = e$, $2k_5[H^{\bullet}] = f$. With these, the system (2) becomes:

$$\begin{cases} (b + e)[B] - c\,[C] = a \\ -b[B] + (c + f)[C] = d \end{cases} \tag{2}$$

The elements on the main diagonal are equal to minus the sum of all other elements of the corresponding column, to which an output value (u_i) is added: e.g., $b_{ii} = -\sum b_{ji} + u_i$, for the first column. The output values are here e and f, respectively. Often, some of the output elements are null, which means that the rates of transformation of the corresponding species in a final product are zero. Although the free coefficients, a and d are identical here, for a better understanding of the flow graph depicting rules, they both will be kept. The rules are as follows [5]:

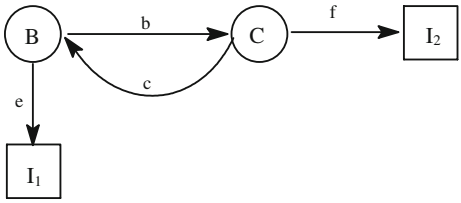


Fig. 2 The flow graph of the main determinant (the consumption flow graph)

1. The main determinant is written as:

$$\Delta = \begin{matrix} & \begin{matrix} \mathrm{B} & \mathrm{C} \end{matrix} \\ \begin{matrix} \mathrm{B} \\ \mathrm{C} \end{matrix} & \begin{vmatrix} \mathrm{b}+\mathrm{e} & -\mathrm{c} \\ -\mathrm{b} & \mathrm{c}+\mathrm{f} \end{vmatrix} \end{matrix} \tag{3}$$

2. The variables become nodes in the graph: the unknowns B and C become the mixed nodes; I_1 and I_2 turn into output nodes (they have only incoming branches).
3. The branch transmittances can be obtained from the coefficients of the system as follows: (a) the element of line 1, column 1 represents all the transmittances of the edges, which are outgoing from the node B with the sign plus in front of it; (b) the element of column 1, line 2 represents the transmittance of edge outgoing from B and incoming to C with the sign minus in front of it, because it means a decrease of the B variable. The output value e becomes the transmittance of the edge connecting B node with the output node I_1. The column 2 is obtained in a similar way.

The flow graph is presented in Fig. 2:

The reciprocal of the above discussion is also valid (the main determinant of the system can be derived from this flow graph).

The main flow graph, which is derived from the main determinant of the system, is named *the consumption flow graph* [5]. The arrows indicate the direction of the flux from variables (nodes) to the outputs nodes. The system evolution brings about a loss in a variable values (B and C) and a gain of the values of the output nodes (I_1 and I_2).

As stated above, in order to calculate the dependent variables of the system, these are considered target species or output nodes [5]. The corresponding determinants for their formation are:

$$\Delta_{\mathrm{B}} = \begin{matrix} & \begin{matrix} \mathrm{A} & \mathrm{C} \end{matrix} \\ \begin{matrix} \mathrm{B} \\ \mathrm{C} \end{matrix} & \begin{vmatrix} \mathrm{a} & -\mathrm{c} \\ \mathrm{d} & \mathrm{c}+\mathrm{f} \end{vmatrix} \end{matrix} \quad \text{and} \quad \Delta = \begin{matrix} & \begin{matrix} \mathrm{B} & \mathrm{A} \end{matrix} \\ \begin{matrix} \mathrm{B} \\ \mathrm{C} \end{matrix} & \begin{vmatrix} \mathrm{b}+\mathrm{e} & \mathrm{a} \\ -\mathrm{b} & \mathrm{d} \end{vmatrix} \end{matrix} \quad \text{where} \quad \begin{matrix} \mathrm{A} \\ \begin{pmatrix} \mathrm{a} \\ \mathrm{d} \end{pmatrix} \end{matrix} \tag{4}$$

is the matrix of the free coefficients. They are the transmittances of the independent variable (the input node or source A). The plus sign is attributed to a and d in the determinant and in its corresponding flow graph because positive gains of B and C occur from the input node A. These determinants are named *the formation determinants* because their flow graphs indicate a gain of the chosen variable starting from the input node.

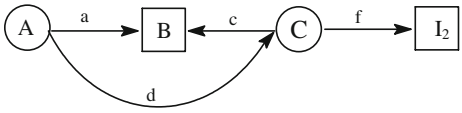


Fig. 3 The formation flow graph for Δ_B

For example, *the flow graph of the formation* determinant Δ_B, where B becomes an output node (Fig. 3), and the input node (A) is the source of variable B, is:

This model of transposing the determinants into flow graphs suggests the evolution of species involved in a complex reaction scheme (mechanism) as a function of time. It also results that the flow graph, depicted in this way, is the image of the scheme or the model. The reciprocal of the above discussion is also valid. The determinants of the system can be derived from the corresponding flow graphs. In the case of the differential equation systems the determinant deduced from the consumption flow graph is the secular determinant from which we can extract the eigenvalues [5].

3 Pharmacokinetic model

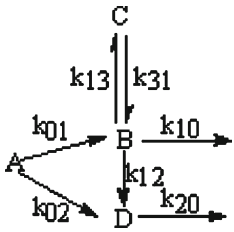
In the pharmacokinetic (PK) analysis, there appear numerous cases in which the drug absorption and disposition are quite complex and therefore cannot be characterized by classical pharmacokinetic models. For example, the case by monitoring the drug and its metabolite is complex one because there are involved a presystemic metabolization to form also an active substances and distribution processes [12–14]. In that case one has to write a linear system of differential equations describing each kinetic process and to use them for finding the corresponding pharmacokinetic parameters.

The differential equations are easy to write and implement in specialized software, this being the main advantage of the numerical analysis procedure [15]. However, this technique has also some limitations. Numerical solutions are always approximations, and this may cause errors, e.g., in the estimation of derivatives (as required for many fitting algorithms). Another disadvantage of using differential equations is that the process to reach convergence is rather slower as compared to the one with analytical solution. This may be important when we deal with a great amount of data, especially in population PK analysis.

Analytical solutions provide the calculation of pharmacokinetic parameters with more accuracy, which is indeed an advantage. The analytical solutions could be obtained for linear differential equations systems by using the classical integration [16], the operator method, secular equation and eigenvalues method, constant variation method [17,18] and flow graph method which entails the Laplace transforms [4,6,7,19,20].

By means of our flow graph method for these complex pharmacokinetic models the analytical solution can obtain directly by inspection the graphical representation of the model.

Scheme 2 Pharmacokinetic model for fluoxetine and norfluoxetine



4 Methodology

In order to find the analytical solution with our method using flow graphs, real pharmacokinetic system is chosen. It is an example from a bioequivalence study of fluoxetine, [21,22].

To describe the absorption and disposition of fluoxetine to norfluoxetine, a complex model has been considered. It is presented in Scheme 2. This model involves a first-order kinetic process for absorption of fluoxetine and bicompartmental distribution. Fluoxetine can be transformed into norfluoxetine by both presystemic and systemic metabolism. Fluoxetine and norfluoxetine can be also eliminated from the human body by either metabolic or non-metabolic paths. As the intravenous data for fluoxetine and norfluoxetine were not available, the distribution volume for both drugs was considered equal. A lag time for absorption was also considered (Tlag).

The significance of the notations in this scheme is as follows: *A* stands fluoxetine at administration place, *B* stands for fluoxetine in central compartment, *C* for fluoxetine in peripheral compartment and *D* for norfluoxetine in central compartment; the rate coefficients are: k_{01}-absorption rate constant for fluoxetine, k_{02} and k_{12} presystemic and systemic metabolism rate constant of fluoxetine to norfluoxetine, k_{13} and k_{31} the distribution rate constants for fluoxetine, k_{10} and k_{20} the elimination rate constants for fluoxetine and norfluoxetine.

4.1 The alternative flow graph theory

The system of linear differential equations, which characterize the mechanism from Scheme 2, is presented in the group of Eq. 5. We symbolize the value of concentrations of A, B, C, D species with x, y, z and w, respectively:

$$\begin{cases} \frac{dx}{dt} = -(k_{01} + k_{02}) \cdot x \\ \frac{dy}{dt} = k_{01} \cdot x - (k_{10} + k_{12} + k_{13}) \cdot y + k_{31} \cdot z \\ \frac{dz}{dt} = k_{13} \cdot y - k_{31} \cdot z \\ \frac{dw}{dt} = k_{02} \cdot x + k_{12} \cdot y - k_{20} \cdot w \end{cases} \tag{5}$$

The initial conditions are: $x(0) =$ Dose of administered fluoxetine (X_0); $y(0) = z(0) = w(0) = 0$.

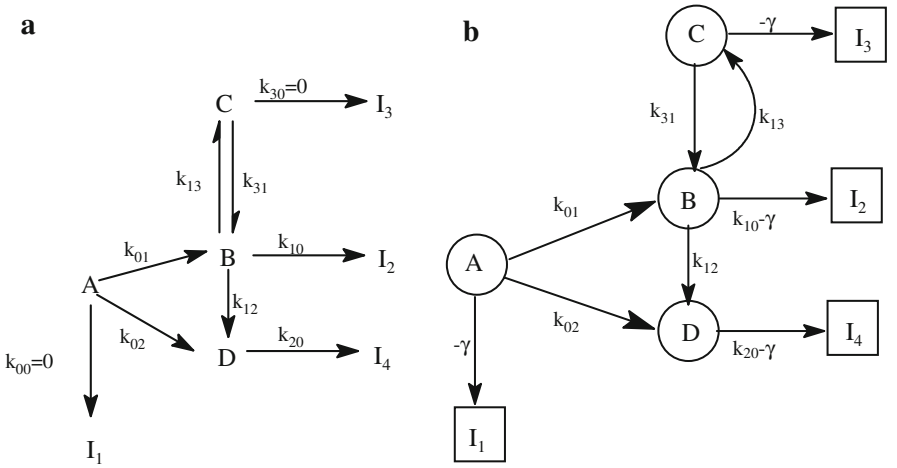


Fig. 4 The equivalent mechanism (**a**) and consumption flow graph (**b**)

On the base on the graph theory [3,23], the determinants of the above system can be found [5]. The general mathematical solutions for this kind of systems are the sum of exponential functions [5–8] (e.g, $y = C_B = B_1 \cdot \exp(-\gamma_1 t) + B_2 \cdot \exp(-\gamma_2 t) + B_3 \cdot \exp(-\gamma_3 t)$). In our theory [5], the pre-exponential coefficients (in this case, B_i) represent the ratio of the corresponding formation and consumption determinants (in accordance with Cramer's rule [1]); the exponential factors (e.g., γ_1, γ_2 and γ_3) and the consumption determinants are calculated from the consumption flow graphs which is the image of a equivalent mechanism.

In this approach a new mechanism equivalent to the model from Scheme 2 is drawn considering that every substance is transforming in a final product (a substance which doesn't transform any more) with a constant rate, even it is zero (see Fig. 4a). The "consumption" flow graph [5] is the image of the new mechanism with the γ decreased from every output transmittance (see Fig. 4b). Its name suggests that the system evolution bring about a loss (consumption) in all variable values and a gain of the output values (the final products I_1, I_2, I_3 and I_4) in how the arrows indicate the direction of the flux from all nodes to the output nodes.

The "formation" flow graph [5] for a species is constructed considering the species of interest as being a target one (the final product; it has no output edges) and by adding a new node (the input node or the source which represents the initial conditions). They are named like this because indicate a formation and a gain of the chosen variable starting from the input node (the source *S*).

Considering the flow graph from Fig. 4b and using the reciprocal rules of depicting a flow graph, we obtain in the Eq. 6 the secular determinant of the system (5):

$$\Delta = \begin{array}{c} \\ \mathrm{A} \\ \mathrm{B} \\ \mathrm{C} \\ \mathrm{D} \end{array} \begin{vmatrix} \mathrm{A} & \mathrm{B} & \mathrm{C} & \mathrm{D} \\ k_{01}+k_{02}-\gamma & 0 & 0 & 0 \\ -k_{01} & k_{12}+k_{13}+k_{10}-\gamma & -k_{31} & 0 \\ 0 & -k_{13} & k_{31}-\gamma & 0 \\ -k_{02} & -k_{12} & 0 & k_{20}-\gamma \end{vmatrix} = 0 \qquad (6)$$

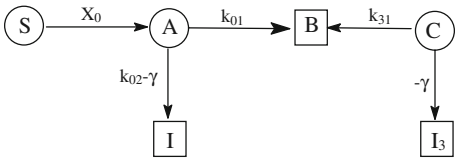


Fig. 5 The formation flow graph for B species

It results immediately that:

$$\begin{aligned}\Delta &= (k_{20}-\gamma)(k_{01}+k_{02}-\gamma)[(-\gamma)(k_{12}+k_{13}+k_{10}-\gamma)\\ &\quad + k_{31}(k_{12}+k_{10}-\gamma)] = 0\\ \Delta &= (k_{01}+k_{02}-\gamma)[\gamma^2-\gamma(k_{12}+k_{13}+k_{14}+k_{10}+k_{31})\\ &\quad + k_{31}(k_{12}+k_{10})](k_{20}-\gamma) = 0\end{aligned} \tag{7}$$

From the above equation it can be found the exponential factors and the expressions of consumption determinants [5] (Δ_c): $\gamma_1 = k_{01} + k_{02}$; γ_2, γ_3 (the solutions of the square equation), and $\gamma_4 = k_{20}$.

$$\text{And } \Delta_c(\gamma_i) = \prod_{\substack{j=1\\ i\neq j}}^{n} (\gamma_j - \gamma_i), \text{ where } n \text{ is number of the species involved} \tag{8}$$

The formation flow graph for B (Fig. 5) is depicted from the consumption flow graph, considering the interest species being a target one (a final product, one eliminates the output edges of B species) and by adding the new input node (the source, which represents the initial conditions). Also, considering the *Scheme 2*, it could be noticed that there are not any connections starting from the node D in the direction of the node B. For this reason, the D species and its outgoing branches, which are not participating at B formation, will not be appearing in the formation flow graph of B species; in this case, n becomes 3 (A, B and C: species involved).

I and symbolizes the output node of A species and its transmittance is the sum of all its outgoing branches transmittances when the node D is missing.

Using the reciprocal rules of depicting a flow graph, the formation determinant is obtained and has the following form:

$$\Delta = \begin{array}{c|ccc} & \text{A} & \text{S} & \text{C} \\ \text{A} & k_{01}+k_{02}-\gamma & \text{X}_0 & 0 \\ \text{B} & -k_{01} & 0 & -k_{31} \\ \text{C} & 0 & 0 & k_{31}-\gamma \end{array} \tag{9}$$

It results:

$$\Delta_{\text{B}_\text{i}} = \text{X}_0 \cdot \text{k}_{01} \cdot (\text{k}_{31} - \gamma_\text{i}) \quad \text{i} = 1, 2, 3; \text{ (A, B and C)} \tag{10}$$

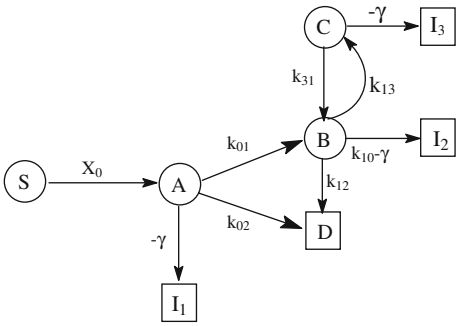


Fig. 6 The formation flow graph for D

The final solution is presented below:

$$C_B = \frac{X_0 k_{01}(k_{31}-\gamma_1)e^{-\gamma_1 t}}{(\gamma_2-\gamma_1)(\gamma_3-\gamma_1)} + \frac{X_0 k_{01}(k_{31}-\gamma_2)e^{-\gamma_2 t}}{(\gamma_1-\gamma_2)(\gamma_3-\gamma_2)} + \frac{X_0 k_{01}(k_{31}-\gamma_3)e^{-\gamma_3 t}}{(\gamma_1-\gamma_3)(\gamma_2-\gamma_3)} \tag{11}$$

The formation graph for D, which provides the formation determinant, is shown in Fig. 6.

The formation determinant for D species is ($n = 4$ species involved: A, B, C, D):

$$\Delta = \begin{array}{c|cccc} & \text{A} & \text{B} & \text{C} & \text{S} \\ \text{A} & k_{01}+k_{02}-\gamma & 0 & 0 & X_0 \\ \text{B} & -k_{01} & k_{12}+k_{13}+k_{10}-\gamma & -k_{31} & 0 \\ \text{C} & 0 & -k_{13} & k_{31}-\gamma & 0 \\ \text{D} & -k_{02} & -k_{12} & 0 & 0 \end{array} \tag{12}$$

The calculus of the above determinant leads to the following expression:

$$\begin{aligned} \Delta_{D_i} &= X_0 \cdot k_{01} \cdot k_{12} \cdot (k_{31}-\gamma_i) + X_0 \cdot k_{02} \cdot [(k_{31}-\gamma_i)(k_{10}+k_{12}-\gamma_i)+k_{13} \cdot (-\gamma)] \\ &= X_0 \cdot k_{01} \cdot k_{12} \cdot (k_{31}-\gamma_i) + X_0 \cdot k_{02} \cdot [\gamma_i^2 - \gamma_i(k_{10}+k_{12}+k_{13}+k_{31}) \\ &\quad + k_{31} \cdot (k_{10}+k_{12})] \\ i &= 1,2,3,4; \end{aligned} \tag{13}$$

So, the analytical solution for D species is:

$$\begin{aligned} C_D = {} & \frac{X_0 \cdot \left(k_{01} \cdot k_{12} \cdot (k_{31}-\gamma_1) + k_{02} \cdot [\gamma_1^2 - \gamma_1(k_{10}+k_{12}+k_{13}+k_{31}) + k_{31} \cdot (k_{10}+k_{12})]\right) \cdot e^{-\gamma_1 t}}{(\gamma_2-\gamma_1)(\gamma_3-\gamma_1)(\gamma_4-\gamma_1)} \\ & + \frac{X_0 \cdot k_{01} \cdot k_{12} \cdot (k_{31}-\gamma_2) \cdot e^{-\gamma_2 t}}{(\gamma_1-\gamma_2)(\gamma_3-\gamma_2)(\gamma_4-\gamma_2)} + \frac{X_0 \cdot k_{01} \cdot k_{12} \cdot (k_{31}-\gamma_3) \cdot e^{-\gamma_3 t}}{(\gamma_1-\gamma_3)(\gamma_2-\gamma_3)(\gamma_4-\gamma_3)} \\ & + \frac{X_0 \cdot \left(k_{01} \cdot k_{12} \cdot (k_{31}-\gamma_4) + k_{02} \cdot [\gamma_4^2 - \gamma_4(k_{10}+k_{12}+k_{13}+k_{31}) + k_{31} \cdot (k_{10}+k_{12})]\right) \cdot e^{-\gamma_4 t}}{(\gamma_1-\gamma_4)(\gamma_2-\gamma_4)(\gamma_3-\gamma_4)} \end{aligned} \tag{14}$$

5 Conclusions

Using the proposed method, based on flow graph theory, one can obtain the analytical solution for complex pharmacokinetic models directly by inspecting the graphical representation of the model. It won't require the writing the homogenous or non-homogenous linear differential equations system but only the solving of the determinants obtained on the base of the pharmacokinetic model.

References

1. A.C. Aitken, *Determinants and Matrices* (Oliver and Boyd, Edinburgh, 1939)
2. M.V. Diudea, O. Ivanciuc, *Topologie Moleculara*, (Ed. Comprex, Cluj, 1995)
3. T. Ionescu, *Grafuri. Aplicatii*, vol 1 (Ed. Didactica si Pedagogica, Bucuresti, 1973)
4. K. Ogata, *Modern Control Engineering* (Prentice Hall International, New Jersey, 1995)
5. M. Socol, I. Baldea, J. Chin. Chem. Soc. **53**(4), 773 (2006)
6. N.S. Nice, *Control System Engineering* (Addison-Westley Publishing Company, 1995)
7. R.C. Dorf, R.H. Bihop, *Modern Control System* (Prentice Hall International, New Jersey, 2001)
8. M. Bodenstein, Z. Physik. Chem. **85**, 329 (1913)
9. G. Come, J. Phys. Chem. **81**, 2560 (1977)
10. T. Turányi, A.S. Tomlin, M.J. Pilling, J. Phys. Chem. **97**, 163 (1993)
11. G.R. Gavalas, Chem. Eng. Sci. **21**, 133 (1966)
12. M. Gex-Fabry, L.P. Balant, Clin. Pharmacokinetics **19**, 241 (1990)
13. M.K. Ma, W.C. Zamboni, K.M. Radomski, W.L. Furman, Clin. Cancer Res. **6**, 813 (2000)
14. H.G. Boxenbaum, S. Riegelman, R.M. Helashoff, J. Pharmacokin Biopharm, **2**, 123 (1974)
15. Pharsight Corporation, Cary, North Carolina, USA
16. C. Udriste, *Aplicatii de algebra, geometrie si ecuatii diferentiale* (Didactica si Pedagogica, Bucuresti, 1993)
17. P. Juergen, *Reaktionskinetische Auswertung Spektroskopischer Hessdaten* (Brauschweig, 1995)
18. K.A. Connors, *Chemical Kinetics: The Study of Reactions Rate in Solutions* (Hardcover, 1998)
19. M.V. Cristea, S.P. Agachi, *Elemente de teoria sistemelor* (Risoprint, Cluj-Napoca, 2002)
20. V. Comnac, I. Tollet, S. Lahti, *System Theory* (Lux Libris, Brasov, 2004)
21. L. Vlase, I. Tomuta, A. Popa, A. Bodiu, S.E. Leucuta, Romanian Farmacia **52**(4), 39 (2004)
22. L. Vlase, S. Imre, S. Leucuta, Talanta, **66**(3), 659 (2005)
23. M.V. Diudea, I. Gutman, L. Jantschi, *Molecular Topology* (Nova, New York, 2002)