

A New Approach of Flow Graph Theory Applied in Physical Chemistry

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An alternative method for solving homogenous and non-homogenous differential equation systems used in chemical kinetics and pharmacokinetics on the basis of flow graph principles has been proposed. The classical method of solving these systems with flow graphs involves the employment of Laplace transform before depicting a flow graph and the inverse Laplace transform after using Mason's rules. A short description of flow graph algebra has been presented. One model very often encountered in pharmacokinetics was solved by both flow graph methods in order to make a comparison. 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: Kinetic graph; Orientated and weighted graph; Flow graph; Laplace transforms; Differential equation system; Chemical kinetics; Reactions mechanism; Pharmacokinetics.

INTRODUCTION

Graphs and diagrams of various types have been used to describe the structure of a chemical substance and the molecular topology¹⁻⁵ as well; after Chi-Hisiung calculated the LCAO-MO energy of open chains,⁶ a graph theory of molecular orbitals was developed.^{7,8} The graph theory has also been used to depict reaction mechanisms in chemistry, such as chain processes, catalyzed processes, and enzyme-catalyzed processes.^{9,10} Temkin¹¹⁻¹³ has proposed a convenient version of cyclic graphs. These graphs incorporate only intermediate species as vertices. They were used to deduce the concentration of reactive intermediates and the overall reaction rate, in a quite simple way. Many chemical chain reactions, photochemical reactions involving chain propagation, enzyme-catalyzed reactions or even heterogeneous catalytic reactions have been classified and mathematically approached on the grounds of graphs associated with these complex mechanisms.¹⁴⁻²⁰ These graphs are called weighted and orientated graphs or kinetic graphs.^{21,22} Bonchev and Rouvray²¹ illustrated the application of kinetic graphs to no-steady state processes when the system of differential equations is transformed into a system of algebraic equations with respect to reciprocal time variable (s), which will be solved based on the Rule of Mason of cy-

cles (1955). The graph of the no-steady state reactions is obtained from the graph of the stationary reaction by the addition of new arcs.

Inspired by the flow graphs used in electronics, physics and engineering,²³⁻²⁵ we tried to use flow graphs to associate them with reaction mechanisms in order to obtain some kinetic characteristics of any reaction scheme. Besides the intermediates, these graphs incorporate also the starting chemical species and the main or secondary products. At the same time, we associated determinants to chemical change and construct the graphs on this base. Such a way has the advantage of offering the opportunity to calculate the concentration of any species involved either being in a quasi-steady-state or a transient concentration. These flow graphs can be used for various types of mechanisms with linear sequence, opposing processes, single route chain reactions, and homogeneous and heterogeneous catalyzed reactions. Graph theory allows us to explain oscillations in reacting systems and is also used to describe kinetics of chemical reactions complicated by diffusion of reagents into the solid catalysts.²¹

Starting from a set of elementary chemical reactions included into a mechanism, a set of simultaneous linear algebraic equations or a linear differential equations system is written. Based on this system a flow graph is derived. By

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using Cramer's method²⁶ one can solve the system with the determinants.

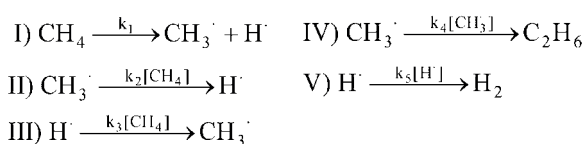
A flow graph consists of a network in which nodes (or vertices) are connected by directed edges (or branches). Each node represents a system variable, and each edge connecting two vertices acts as a signal multiplier. An arrow placed on the edge indicates the direction of the signal flow. The multiplication factor, named transmittance, is indicated along the edge (weighted and orientated graph).^{21,22,27} It can be obtained from the coefficients of the system 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.^{23,28-30} It represents the value of the main determinant of the system.²⁷

For a given system a flow graph is not unique. More than one flow graph can be drawn for a given system by writing the system equations or the corresponding determinants in a different way.²³⁻²⁵

METHODS

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.²⁷ For methane pyrolysis at 1600 °C, for example, the simplified mechanism consists of the following elementary steps, disregarding the reverse reactions.³¹

Scheme I Methane pyrolysis mechanism



Step I (the initiation) indicates the input source (S) of radical species, which, in this case, is common for both of the radicals (CH₄). 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 (C₂H₆ and H₂). The accepted values of the rate constants (k_i) and the value of starting CH₄ concentration are also given,³² so the numerical solutions for radical species can be found after its replacement.

Considering that the quasi-steady-state approximation is valid^{33,34} (the concentrations of radical species are very low and at steady-state) the system of differential equations, based on the mechanism from Scheme of reactions 1, is:

$$\begin{cases} -\frac{d[\text{CH}_3\cdot]}{dt} = 0 = (k_2[\text{CH}_4] + 2k_4[\text{CH}_3\cdot]) \cdot [\text{CH}_3\cdot] \\ \qquad \qquad \qquad - k_3[\text{CH}_4] \cdot [\text{H}\cdot] - k_1[\text{CH}_4] \\ -\frac{d[\text{H}\cdot]}{dt} = 0 = -k_2[\text{CH}_4] \cdot [\text{CH}_3\cdot] + (k_3[\text{CH}_4] \\ \qquad \qquad \qquad + 2k_4[\text{H}\cdot]) \cdot [\text{H}\cdot] - k_1[\text{CH}_4] \end{cases} \quad (1)$$

To simplify, the following symbols are used further on: $B = \text{CH}_3\cdot$, $C = \text{H}\cdot$, the final products C₂H₆, H₂ with I_1 and I_2 respectively; the pseudo-first order rate constants $a = k_1[\text{CH}_4] = d$, $b = k_2[\text{CH}_4]$, $c = k_3[\text{CH}_4]$, $2k_4[\text{CH}_3\cdot] = e$, $2k_5[\text{H}\cdot] = f$. With these, the system (2) becomes:

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

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 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 rules, they both will be kept. These are as follows:²⁷

1. The main determinant is written as:

$$\Delta = \begin{vmatrix} B & C \\ B & b + e & -c \\ C & -b & c + f \end{vmatrix} \quad (3)$$

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 C 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 the same way.

The flow graph is presented in Fig. 1.

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

By using the properties of flow graphs, the global gain, which is the value of the main determinant, can be computed.²⁷ The global gain of the flow graph is defined as the sum of the forward path gain,²⁸⁻³⁰ considering every possible way.²³ Also by definition a forward path is a path from an input node or from a mixed node when the source is missing, to an output node.²³⁻²⁵ Knowing that the path should not go out any node more than once and every node of a given path must have only one outgoing branch,²⁷ the following ways should be considered in our case (see Fig. 1):

$$\Delta = \Delta_1 + \Delta_2 + \Delta_3 = b \cdot f + c \cdot e + e \cdot f \quad (4)$$

A cyclic form cannot be considered because it conflicts with the mass conservation law and has no flux to an output node. If there are more internal nodes, the computation of a flow graph gain could be resumed as:

$$\Delta = \prod_{\substack{i=1 \\ i \notin c}}^r (\sum t_i) \cdot \prod_{c=1}^m \left(\prod_{\substack{j=1 \\ j \in c}}^{p_c} (\sum t_j) - \prod (t_{j,k}) \right) \quad (5)$$

where - r stands for the number of nodes which are not from a cycle,

- m is the possible number of cycles,

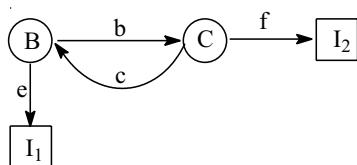


Fig. 1. The flow graph of the main determinant (the consumption flow graph).

- $t_i(t_j)$ stands for the transmittance from node i (j) to the others nodes.

- p_c stands for the number of nodes from a cycle.

- $t_{j,k}$ stands for the transmittance between two nodes j and k from the cycle c .

For the considered example ($r = 0$, $m = 1$, $p_1 = 2$) and taking into account the flow graph in Fig. 1, the value of the main determinant could be found based on the eq. (5):

$$\Delta = (b + e)(c + f) - b \cdot c = b \cdot f + e \cdot c + e \cdot f \quad (6)$$

The flow graph derived from the main determinant of the system is named the consumption flow graph. The arrows indicate the direction of the flux from all variables (nodes) to the output nodes. The system evolution brings about a loss in all variable values (B and C) and a gain of the output values (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. The determinants obtained by replacing the column of one unknown with that of free coefficients are:

$$\Delta_B = \begin{matrix} S & C \\ B & \begin{vmatrix} a & -c \\ d & c+f \end{vmatrix} \\ C & \begin{vmatrix} b+e & a \\ -b & d \end{vmatrix} \end{matrix} \quad \text{and} \quad \Delta_C = \begin{matrix} B & S \\ B & \begin{vmatrix} b+e & a \\ -b & d \end{vmatrix} \\ C & \begin{vmatrix} a & -c \\ d & c+f \end{vmatrix} \end{matrix} \quad \text{where} \quad \begin{pmatrix} S \\ a \\ d \end{pmatrix} \quad (7)$$

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

To calculate the gain of a formation determinant we have to choose only the paths which connect the input node with the target species,²⁸⁻³⁰ obeying the definition of "forward way". The flow graph of the formation determinant Δ_B , where B becomes an output node (Fig. 2), and the input node (S) is the source of variable B , is named the formation flow graph for B species (the B species is only forming, not

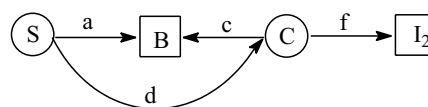


Fig. 2. The formation flow graph for Δ_B .

consuming).

The value of the determinant corresponding to B species is (see Fig. 2):

$$\Delta_B = \Delta_{B_1} + \Delta_{B_2} + \Delta_{B_3} = a \cdot f + a \cdot c + d \cdot c \quad (8)$$

The path through d and f , $\Delta_{B_4} = d \cdot f$, has not been considered since the target species B is not reached (see Fig. 2).

When C is the output node (the target), $\Delta_C = ab + bd + ed$, following the same rules, the corresponding flow graph is obtained in the same way.

This model of transposing the determinants into a flow graph suggests the actual evolution of species involved in a complex reaction scheme (mechanism) as a function of time. The depicted consumption flow graph is therefore the image of the scheme or model, taking into account the coefficients of the reactants (Scheme I and Fig. 1). It follows that all the flow graphs can be depicted directly from the mechanism without having to write the system of the equations.

An alternative way to transpose a determinant into a graph is based on solving the system of differential equations using the Mason rule.²³ Supposing that we deal with a system of two differential equations, the main determinants of the coefficients of the unknowns before (eq. 9a) and after (eq. 9b) transformation into a system of algebraic equations with respect to reciprocal time variable (s)^{21,23-25} are:

$$\Delta = \begin{array}{c|cc} & B & C \\ \hline B_1 & b & c \\ C_1 & b_1 & c_1 \end{array} \quad (9a)$$

$$\Delta^s = \begin{array}{c|cc} & B & C \\ \hline B_1 & b-s & c \\ C_1 & b_1 & c_1-s \end{array} \quad (9b)$$

The branch transmittances are the elements of Δ as follows: a) the element of line 1, column 1 represents the transmittances of the edges which is outgoing from the node B and is incoming to B_1 ; b) the element of line 2, column 1 represents the transmittance of edge outgoing from B and incoming to C_1 . Column 2 is obtained in the same way. The unit value represents the reverse transmittance which is closing a cycle between two equivalent nodes. The graph is presented in Fig. 3.

The formula of calculus of the determinant, based on the flow graph, is:

$$\Delta = \sum (-1)^m \prod_{\substack{c=1 \\ i \in c}}^m (t_i) \quad (10)$$

where m is the number of cycles, t_i represents the transmittance from node i to the other nodes. The cycles belonging to the products are all possible combinations of non-touching loops so that every node is visited and has a single outgoing edge.

For the considered example, where we have three cycles (I, II and III) the value of Δ is found on the basis of the eq. (10):

$$\begin{aligned} \Delta &= (-1)^1 \cdot 1 \cdot c \cdot 1 \cdot b_1 + (-1)^2 \cdot (1 \cdot b) \cdot (1 \cdot c_1) \\ &= b \cdot c_1 - c \cdot b_1 \end{aligned} \quad (11)$$

Replacing the unit value with $1/s$ in Fig. 3, which represents the connecting factor between the differential and the variable,²³ one obtains the value of the determinant Δ^S divided by the second power of reciprocal time variable s , by the following relation:²³

$\Delta^S/s^2 =$ determinant of graph = 1 - (sum of all individual cycle gains) + (sum of gain products of all possible combinations of two non-touching cycles) - (sum of gain products of all possible combinations of three non-touching cycles) + ...

For the above given example it results in:

$$\begin{aligned} \Delta^S/s^2 &= 1 - \left(\frac{1}{s} \cdot b + \frac{1}{s} \cdot c_1 + \frac{1}{s} \cdot c \cdot \frac{1}{s} \cdot b_1 \right) \\ &\quad + \left[\left(\frac{1}{s} \cdot b \right) \cdot \left(\frac{1}{s} \cdot c_1 \right) \right] \end{aligned} \quad (12)$$

RESULTS AND DISCUSSIONS

Homogenous Linear Differential Equations Systems with Non-equal Eigenvalues

To show how the differential equations³⁵⁻³⁷ character-

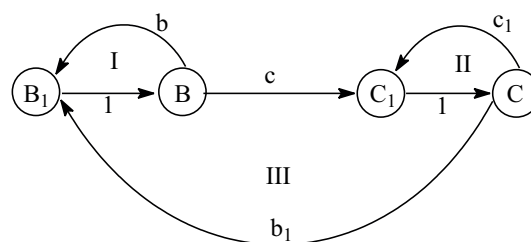
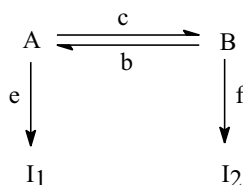


Fig. 3. The graph depicted for Δ .

izing a dynamic system in evolution³⁸ can be solved, an equilibrium scheme between two chemical species *A* and *B* is considered³⁹ (see Scheme II).

Scheme II The equilibrium mechanism



The differential equations describing time evolution of the concentrations of chemical species *A* and *B* are (symbolized by *x* and *y*, respectively):

$$\begin{cases} -\frac{dx}{dt} = (c+e) \cdot x - b \cdot y \\ -\frac{dy}{dt} = -c \cdot x + (b+f) \cdot y \end{cases} \Leftrightarrow \begin{cases} -\frac{dx}{dt} = a \cdot x - b \cdot y \\ -\frac{dy}{dt} = -c \cdot x + d \cdot y \end{cases} \quad (13)$$

The initial conditions are: $x(0) = X_0$ and $y(0) = 0$. The small letters (*b*, *c*, *e*, *f*) represent positive or null constants describing the various rates of transfer or consumption.

The classical method of flow graphs²³⁻²⁵ consists of the following sequence of steps: applying the Laplace transforms in variable (*s*) then the Mason rule and the finding of polynomial coefficients.³⁸ The last step is the reverse transforming in time variable.⁴⁰ In this alternative method, considering that the general mathematical solutions are the sum of the exponential functions^{35-37,39} (here, $x = C_A = A_1 \cdot \exp(-\gamma_1 t) + A_2 \cdot \exp(-\gamma_2 t)$ and $y = C_B = B_1 \cdot \exp(-\gamma_1 t) + B_2 \cdot \exp(-\gamma_2 t)$), the pre-exponential coefficients A_i , B_i , represent the ratio of the corresponding formation and consumption determinants. The exponential factors (γ_1 and γ_2) and the pre-exponential coefficients can be calculated from the gains of flow graphs obtained directly from the reactions scheme. In order to find the exponential factors γ_i , the consumption flow graph is obtained. It is the image of the reaction scheme considering the decrease of the exponential factors from every output transmittance.

The value of the secular determinant³⁵⁻³⁷ Δ , also known as the Laplace determinant,^{5,41-42} yielding the exponential factors (the eigenvalues γ_1 and γ_2), is equal with the gain of the consumption flow graph.

$$\begin{vmatrix} A & B \\ a - \gamma & -b \\ -c & d - \gamma \end{vmatrix} = 0 \quad (14)$$

The characteristic equation results:

$$\Delta = [\gamma^2 - \gamma(a+d) + ad - bc] = (\gamma_1 - \gamma)(\gamma_2 - \gamma) = 0 \quad (15)$$

The consumption determinants $\Delta_c(\gamma_i)$ or Δ_i , which, in this case, are not unique because they depend on γ_i , are derived from the secular determinant, Δ . They have been deduced from the Vandermonde determinant:³⁵

$$\Delta_c(\gamma_i) = \Delta_i = \prod_{\substack{j=1 \\ i \neq j}}^n (\gamma_j - \gamma_i) \neq 0 \quad (16)$$

The formation determinants (eq. 17) have their values equal with the gains of the formation flow graphs:

$$\Delta_A(\gamma) = \begin{vmatrix} S & B \\ A X_0 & -b \\ B & d - \gamma \end{vmatrix} = X_0 \cdot (d - \gamma) \quad \text{and} \quad \Delta_B(\gamma) = \begin{vmatrix} A & S \\ a - \gamma & X_0 \\ -c & 0 \end{vmatrix} = X_0 \cdot c \quad (17)$$

It results in:

$$\begin{aligned}
 A_1 &= \frac{\Delta_A(\gamma_1)}{\Delta_c(\gamma_1)} = \frac{\Delta_{A1}}{\Delta_1} = \frac{X_0(b+f-\gamma_1)}{(\gamma_2-\gamma_1)}; \\
 A_2 &= \frac{\Delta_A(\gamma_2)}{\Delta_c(\gamma_2)} = \frac{\Delta_{A2}}{\Delta_2} = \frac{X_0(b+f-\gamma_2)}{(\gamma_1-\gamma_2)}; \\
 B_1 &= \frac{\Delta_B(\gamma_1)}{\Delta_c(\gamma_1)} = \frac{\Delta_{B1}}{\Delta_1} = \frac{X_0 \cdot c}{(\gamma_2-\gamma_1)}; \\
 B_2 &= \frac{\Delta_B(\gamma_2)}{\Delta_c(\gamma_2)} = \frac{\Delta_{B2}}{\Delta_2} = \frac{X_0 \cdot c}{(\gamma_1-\gamma_2)}; \quad (18)
 \end{aligned}$$

Non-homogenous Differential Equations Systems

The above system (see system from eq. 13) may be complicated, considering that the species *A* is continuously fed into the system, by decreasing from the first equation of the system, a time dependent function, $f(t)$. This function acts as an input one³⁸ for node *A* and represents a positive gain for it. The differential equations system will become a non-homogenous one.

The role of source is played by the input function $f(t)$. The coefficients will have the same form as in the eq. (18),

except for the source X_0 , which is replaced by the input function $f(t)$. By applying the integral of convolution, which is the link between input and output functions,^{38,43} the final solution will be:

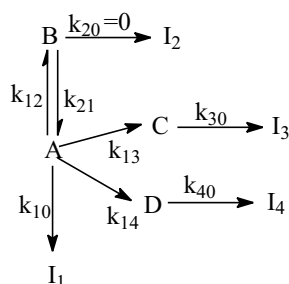
$$C_A = x = \frac{b+f-\gamma_1}{\gamma_2-\gamma_1} \int_0^t f(t-\tau) \cdot \exp(-\gamma_1\tau) d\tau + \frac{b+f-\gamma_2}{\gamma_1-\gamma_2} \int_0^t f(t-\tau) \cdot \exp(-\gamma_2\tau) d\tau \quad (19)$$

$$C_B = y = \frac{c}{\gamma_2-\gamma_1} \int_0^t f(t-\tau) \cdot \exp(-\gamma_1\tau) d\tau + \frac{c}{\gamma_1-\gamma_2} \int_0^t f(t-\tau) \cdot \exp(-\gamma_2\tau) d\tau \quad (20)$$

where the above integrals are applied to the convolution product,^{23-25,38,43} $f(t) * \exp(-\gamma t)$.

We will now extend the use of both the above presented methods to a more complex practical application in pharmacokinetics describing the time-evolution of a drug in the human body after intake. If one attempts to solve literally on computer programs, e.g. the Mathematica 5.1 program,⁴⁴ some unknowns, such as z and w variables (see eq. 21) will have a very complex expression. When a constant perfusion (source) is used, the drug enters the blood or other tissues and is either eliminated by the kidneys or is metabolized.⁴⁵ The enzyme transformation of the drug is in the range of first-order dependence because of low concentration. The k values represent some constants describing the various rates of transfer or consumption (Scheme III).

Scheme III The pharmacokinetic mechanism



The system of differential equations describing this complex scheme is presented in eq. (21); we denote with x , y , z and w the respective concentrations of A, B, C and D species which are time functions:

$$\begin{cases} -\frac{dx}{dt} = (k_{10} + k_{12} + k_{13} + k_{14}) \cdot x - k_{21} \cdot y - k_0; & -\frac{dy}{dt} = -k_{12} \cdot x + k_{21} \cdot y \\ -\frac{dz}{dt} = -k_{13} \cdot x + k_{30} \cdot z; & -\frac{dw}{dt} = -k_{14} \cdot x + k_{40} \cdot w \end{cases} \quad (21)$$

The initial conditions are: $x(0) = y(0) = z(0) = w(0) = 0$ and the non-homogenous term $k_0 = f(t)$ which is a constant.

a) The classical flow graph method using the Mason rule and Laplace transforms

Supposing that C is the species of interest, the flow graph²³ and the solution for the z variable are presented in Fig. 4 and eqs. (22)-(24) respectively.

Applying the Mason rule,²³⁻²⁵ one obtains:

$$\frac{v(s)}{u(s)} = \frac{k_0 \cdot \frac{1}{s} \cdot k_{13} \cdot \frac{1}{s} \cdot [1 - \frac{1}{s} \cdot (-k_{21})]}{1 - (\frac{1}{s} \cdot (-k)) - (\frac{1}{s} \cdot (-k_{21})) - (\frac{1}{s} \cdot (-k_{30})) - \frac{1}{s} \cdot k_{12} \cdot \frac{1}{s} \cdot k_{21} + (\frac{1}{s} \cdot (-k))(\frac{1}{s} \cdot (-k_{21})) + (\frac{1}{s} \cdot (-k))(\frac{1}{s} \cdot (-k_{30})) + (\frac{1}{s} \cdot (-k_{21}))(\frac{1}{s} \cdot (-k_{30})) + \frac{1}{s} \cdot k_{12} \cdot \frac{1}{s} \cdot k_{21} \cdot \frac{1}{s} \cdot (-k_{30}) - (\frac{1}{s} \cdot (-k)) \cdot (\frac{1}{s} \cdot (-k_{21})) \cdot (\frac{1}{s} \cdot (-k_{30}))} \quad (22)$$

$$v(s) = \frac{1}{s} \cdot \frac{k_0 \cdot \frac{1}{s^3} \cdot k_{13} \cdot (s + k_{21})}{1 + \frac{k}{s} + \frac{k_{21}}{s} + \frac{k_{30}}{s} - \frac{k_{12} \cdot k_{21}}{s^2} + \frac{k \cdot k_{21}}{s^2} + \frac{k \cdot k_{30}}{s^2} + \frac{k_{21} \cdot k_{30}}{s^2} - \frac{k_{12} \cdot k_{21} \cdot k_{30}}{s^3} + \frac{k \cdot k_{21} \cdot k_{30}}{s^3}} \quad (23)$$

$$v(s) = \frac{k_0 \cdot k_{13} \cdot (s + k_{21})}{s \cdot (s^3 + s^2 \cdot (k + k_{21} + k_{30}) + s \cdot (-k_{12} \cdot k_{21} + k \cdot k_{21} + k \cdot k_{30} + k_{21} \cdot k_{30}) + k \cdot k_{21} \cdot k_{30} - k_{12} \cdot k_{21} \cdot k_{30})} \quad (24)$$

$$v(s) = \frac{Z_1}{s - s_1} + \frac{Z_2}{s - s_2} + \frac{Z_3}{s - s_3} + \frac{Z_4}{s} \quad (25)$$

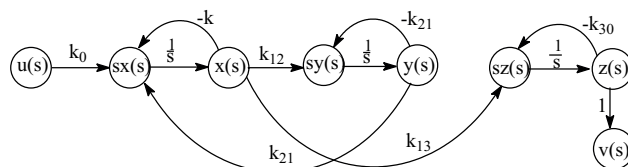


Fig. 4. The flow graph with Laplacian transforms for $z(s)$ variable.

where s_1, s_2, s_3 are the solutions of the following quite complicated equation:

$$s^3 + s^2 \cdot (k + k_{21} + k_{30}) + s(-k_{12} \cdot k_{21} + k \cdot k_{21} + k \cdot k_{30} + k_{21} \cdot k_{30}) + k \cdot k_{21} \cdot k_{30} - k_{12} \cdot k_{21} \cdot k_{30} = 0 \quad (26)$$

Applying the method of coefficient identification,³⁸ Z_i ($i = 1:4$) expressions are found:

$$\begin{aligned} Z_1 &= k_0 k_{13} (k_{21} + s_1) / (s_1 - s_2) (s_1 - s_3) s_1, \\ Z_2 &= k_0 k_{13} (k_{21} + s_2) / (s_2 - s_1) (s_2 - s_3) s_2, \\ Z_3 &= k_0 k_{13} (k_{21} + s_3) / (s_3 - s_1) (s_3 - s_2) s_3 \text{ and } Z_4 = k_0 k_{13} k_{21}. \end{aligned}$$

Knowing that $z(t) = L^{-1}\{v(s)\}$,^{25,40} it results in the final solution expressed in a time variable:

$$z(t) = \frac{k_0 k_{13} (k_{21} + s_1) \cdot \exp(s_1 t)}{(s_1 - s_2)(s_1 - s_3) s_1} + \frac{k_0 k_{13} (k_{21} + s_2) \cdot \exp(s_2 t)}{(s_2 - s_1)(s_2 - s_3) s_2} + \frac{k_0 k_{13} (k_{21} + s_3) \cdot \exp(s_3 t)}{(s_3 - s_1)(s_3 - s_2) s_3} + \frac{k_0 k_{13} k_{21}}{s_1 s_2 s_3} \quad (27)$$

b) The alternative flow graphs method

The consumption flow graph that is the image of the mechanism in Scheme III (with γ decreasing from every output transmittance) is presented in Fig. 5.

Following the eq. (5) the characteristic equation is obtained:

$$\begin{aligned} \Delta &= (k_{30} - \gamma)(k_{40} - \gamma)[(k_{21} - \gamma)(k_{12} + k_{13} + k_{14} + k_{10} - \gamma) - k_{21} k_{12}] = 0 \\ \Delta &= [\gamma^2 - \gamma(k_{12} + k_{13} + k_{14} + k_{10} + k_{21}) + k_{21}(k_{13} + k_{14} + k_{10})] (k_{30} - \gamma)(k_{40} - \gamma) = 0 \end{aligned} \quad (28)$$

From the above equation the exponential factors, γ_1, γ_2 that the solutions of the simple square equation, $\gamma_3 = k_{30}$ and $\gamma_4 =$

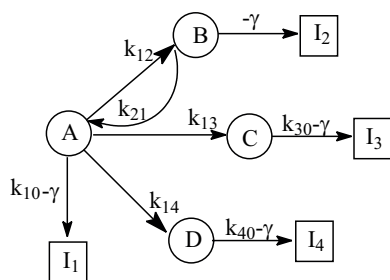


Fig. 5. The consumption flow graph.

k_{40} , are easily obtained.

The formation flow graph for C species is depicted in Fig. 6. The D species does not appear since it is not involved in the formation of C species. I symbolizes the global output node from A and the output transmittance from A node is the sum of remaining outgoing transmittances, when the D node is missing.

By choosing only the ways that connect the species S with the species of interest C , the formation determinant comes to be:

$$\begin{aligned} \Delta_C(\gamma_i) &= k_0 \cdot k_{13} \cdot k_{21} + k_0 \cdot k_{13} \cdot (-\gamma_i) \\ &= k_0 \cdot [k_{13} \cdot (k_{21} - \gamma_i)] \quad i = \overline{1,3} \end{aligned} \quad (29)$$

Knowing that $C_C = C_1 \cdot \exp(-\gamma_1 t) + C_2 \cdot \exp(-\gamma_2 t) + C_3 \cdot \exp(-\gamma_3 t)$, $C_i = \Delta_C(\gamma_i) / \Delta_i$ and taking into account the eqs. (19) and (20), the concentration of C species is:

$$\begin{aligned} C_C &= \frac{k_{13}(k_{21} - \gamma_1) \int_0^t k_0 \exp(-\gamma_1 \tau) d\tau}{(\gamma_2 - \gamma_1)(\gamma_3 - \gamma_1)} \\ &+ \frac{k_{13}(k_{21} - \gamma_2) \int_0^t k_0 \exp(-\gamma_2 \tau) d\tau}{(\gamma_1 - \gamma_2)(\gamma_3 - \gamma_2)} \\ &+ \frac{k_{13}(k_{21} - \gamma_3) \int_0^t k_0 \exp(-\gamma_3 \tau) d\tau}{(\gamma_1 - \gamma_3)(\gamma_2 - \gamma_3)} \end{aligned} \quad (30)$$

$$\begin{aligned} C_C &= \frac{k_0 k_{13} (k_{21} - \gamma_1) (\exp(-\gamma_1 \tau) - 1)}{(\gamma_2 - \gamma_1)(\gamma_3 - \gamma_1)(-\gamma_1)} \\ &+ \frac{k_0 k_{13} (k_{21} - \gamma_2) (\exp(-\gamma_2 \tau) - 1)}{(\gamma_1 - \gamma_2)(\gamma_3 - \gamma_2)(-\gamma_2)} \\ &+ \frac{k_0 k_{13} (k_{21} - \gamma_3) (\exp(-\gamma_3 \tau) - 1)}{(\gamma_1 - \gamma_3)(\gamma_2 - \gamma_3)(-\gamma_3)} \end{aligned} \quad (31)$$

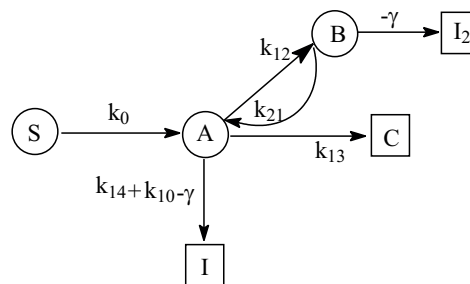


Fig. 6. The formation flow graph for C .

If the substitutions and the final computations are made, eqs. (27) and (31) are identical.

CONCLUSIONS

The advantages of the flow graph method are:

1. The calculation of the solutions is made directly on the grounds of the scheme (mechanism) or pharmacokinetic model. Writing the differential equations is not needed.

2. The rules of drawing a flow graph and its algebra are simpler and more direct than that obtained by using Mason's rules, especially when the scheme (model) contains more than three interdependent species.

3. The Laplace transforms are avoided.

Some disadvantages of the approach reported here as compared to that using Laplace transforms consists in the fact that we deal with convolution integral (eqs. (19), (20)) for non-homogenous systems. In many cases it is a very simple operation and also the classical method requires these integrals when the input function is a complicated one.

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