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A Novel Procedure to Analyse the Kinetics of Multicompartmental Linear Systems. II. Application to the Study of Some Well-known Systems

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Abstract

We analyze the simplification of the general kinetic equations in contribution I of this series and their use when the restrictions corresponding to some particular values of the multiplicities of the eigenvalues of the system matrix and/or some properties of this matrix are considered. The particular cases we have studied are the most frequent in the literature about specific linear compartmental systems, namely: (a) all the eigenvalues of the matrix $\boldsymbol{K}$ (see below) are simple; (b) because $\boldsymbol{K}$ is singular there is a null-eigenvalue of any multiplicity, being simple the remaining non-null eigenvalues; (c) as in (b), but $\boldsymbol{K}$ having some special properties frequent in linear compartmental systems that will be analyzed when this case is treated. To any of these particular cases fit most of the linear multicompartmental systems.

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As example, these particular solutions are applied to three enzymatic systems of biological interest which can be modeled as linear compartmental systems belonging to the cases (a)-(c): 1) autocatalytic activation of a zymogen; 2) non- autocatalytic activation of a zymogen; and 3) reversible, competitive inhibition. Obviously, the power and utility of the equations obtained here for each of the three cases is revealed when they are applied to complex systems. However, and without loss of generality of the procedures, it is easier its illustration when they are applied to simple examples.

Finally, we handle matrix determinant (MD) which is a generalization of determinant concept, where the elements of one of its columns are matrix so that the determinant is also a matrix. We generalize the well known Vandermonde´s determinant and some other types of determinants.

1. Introduction

In paper I of this series we have presented a new procedure to solve the homogeneous set of linear, ordinary, first order, differential equations with constant coefficients, corresponding to any linear compartmental system with zero input. The kinetic equations give the instantaneous amount of matter in any of the compartments of the system. These equations are completely general and easy to apply to any linear compartmental system irrespective that it is open or closed, with or without traps, simple or complex. This is due to the fact that they were derived with no restrictions regarding the properties of the matrix of coefficients of the set of linear differential equations (in the following denoted as ***K***) or the multiplicities of the eigenvalues of this matrix.

Nevertheless, in the literature concerning the kinetic behavior of abstract linear compartmental systems there are many cases (engineering, chemical, biochemical, enzymatic, physical, pharmacological, etc.) that can be modeled as a linear compartmental system [1, 1-29], and whose matrix ***K*** has some special properties [30-32], and/or the multiplicities of its eigenvalues have particular values. Thus, is often assumed that the non-null eigenvalues are simple [18, 27, 30, 33], and that if a null eigenvalue exists this is of any multiplicity [27, 30, 33]. Overlapped with the assumptions above, about the multiplicities of the eigenvalues, other additional assumptions about matrix ***K*** are normally made, e.g. that is singular, non-singular, diagonal dominant [1, 8-10, 26], etc. Obviously, when restrictions about the properties of matrix ***K*** and the multiplicities of its eigenvalues are introduced, the general kinetic equations obtained in contribution I of this series remain valid because they have been obtained without restrictions, but they become considerably simplified and easier to use if these frequent restrictions are inserted into them.

In this paper we analyze the simplification of the general kinetic equations in contribution I of this series and their use when the restriction corresponding to some particular values of the multiplicities of the eigenvalues of matrix $\boldsymbol{K}$ and/or some properties of this matrix are taken into account. The particular cases we consider here are the most frequent in the literature about specific linear compartmental systems. These cases are: (a) all the eigenvalues of $\boldsymbol{K}$ are simple; (b) because $\boldsymbol{K}$ is singular there is a null-eigenvalue of any multiplicity, being simple the remaining non-null eigenvalues; (c) as in (b) but matrix $\boldsymbol{K}$ having some special properties frequent in linear compartmental systems [7, 18, 22, 27, 30, 33] that will be discussed below when this case is treated. Case (c) has widely been treated in the literature in a individualized form [9, 26], and here we find the same results but as particular cases of the general equations obtained in (b) and in paper I of this series.

2. Notation/definitions

To facilitate the development and understanding of this paper we use the notation and definitions in paper I of this series and the following additional one:

$\boldsymbol{\omega}$: Set whose elements are the subindices of the compartments with zero inputs. For example, if in a linear compartmental system the zero inputs are made in compartments X_2 and X_5, then $\omega = \{2,5\}$

$\sum_{k\in\omega} k - \text{dependent expression}$: Sum extended to all and each of the elements of the set ω

$D(\lambda)$: Characteristic determinant of matrix $\boldsymbol{K}$., i.e. $D(\lambda) = \det(\boldsymbol{K} - \lambda \boldsymbol{I})$. It is also called as characteristic polynomial. This determinant is given by the following expression:

$$D(\lambda)=\begin{vmatrix} K_{1,1}-\lambda & K_{2,1} & \cdots & K_{n,1} \\ K_{1,2} & K_{2,2}-\lambda & \cdots & K_{n,2} \\ \vdots & \vdots & \cdots & \vdots \\ K_{1,n} & K_{2,n} & \cdots & K_{n,n}-\lambda \end{vmatrix} \tag{1}$$

The expansion of this determinant origins its polynomic form, i.e. the characteristic polynomial which can be expressed as:

$$D(\lambda)=(-1)^n(F_0\lambda^n+F_1\lambda^{n-1}+\cdots+F_n) \qquad (F_0=1) \tag{2}$$

In eq. (2) Fq are expressions containing the different transfer constants $K_{i,j}$'s. In the following we will refer to $D(\lambda)$ as a determinant or also as a polynomial.

λ_j (j=1, 2,..., n): Eigenvalues of matrix $\boldsymbol{K}$ and, therefore, they coincide with the roots of $D(\lambda)$, that can also be expressed as:

$$D(\lambda)=(-1)^n(\lambda-\lambda_1)(\lambda-\lambda_2)\cdots(\lambda-\lambda_n) \tag{3}$$

u: Number of non-null eigenvalues of matrix $\boldsymbol{K}$. In this contribution we assume that they are simple. If no null eigenvalue exists, then $u=n$.

λ_1, λ_1, …, λ_u: Non-null roots of $D(\lambda)$, i.e. the non-null eigenvalues of matrix $\boldsymbol{K}$. Hearon [7] showed that when $\boldsymbol{K}$ is diagonal dominant, then its non-null eigenvalues are real and negative or complex with a negative real part and they are never purely imaginary.

c: Number of null eigenvalues of $\boldsymbol{K}$. Because the number of eigenvalues of K is n, we have:

$$n=u+c \tag{4}$$

If $D(\lambda)$ has u non-null roots, all of them simple, and a null-root of multiplicity c, it can be written, according to eq. (3):

$$D(\lambda) = (-1)^n \lambda^c (\lambda - \lambda_1)(\lambda - \lambda_2)\cdots(\lambda - \lambda_u) \tag{5}$$

that can also be expressed as:

$$D(\lambda) = (-1)^n \lambda^c T(\lambda) \tag{6}$$

$T(\lambda)$ being:

$$T(\lambda) = (\lambda - \lambda_1)(\lambda - \lambda_2)\cdots(\lambda - \lambda_u) \tag{7}$$

or also as:

$$T(\lambda) = \sum_{q=0}^{u} F_q \lambda^{u-q} \quad (F_0 = 1) \tag{8}$$

In any case, the characteristic equation of $\boldsymbol{K}$, the roots of which are the eigenvalues of $\boldsymbol{K}$, is:

$$D(\lambda) = 0 \tag{9}$$

According to the polynomial theory, the eigenvalues λ_h (h = 1,2,...,u), which are the roots of the polynomial $T(\lambda)$, have the following properties [33, 34]:

$$\left.\begin{array}{l} \lambda_1 + \lambda_2 + \cdots + \lambda_u = -F_1 \\ \lambda_1\lambda_2 + \lambda_1\lambda_3 + \cdots + \lambda_{u-1}\lambda_n = F_2 \\ \qquad\qquad\vdots \\ \lambda_1\lambda_2\cdots\lambda_u = (-1)^u F_u \end{array}\right\} \tag{10}$$

We denote as P_q (q=1,2,...,u) the sum of all of the different q-arys products involving the eigenvalues λ_h (h=1,2,...,u). For completeness, we set P_0=F_0=1. The following relationship between P_q and F_q will be useful below:

$$P_q = (-1)^q F_q \qquad (q=0,1,2,...,u) \tag{11}$$

$D_{k,i}(\lambda)$ (k,i=1, 2, ..., n): Determinant of n-1 order resulting after removing in eq.(1) the k-th row and the i-th column. Expansion of $D_{k,i}(\lambda)$ leads to a polynomial of degree, at maximum, n-1 (what will be happens if $k = i$), i.e.:

$$D_{k,i}(\lambda) = (a_{k,i})_0 \lambda^{n-1} + (a_{k,i})_1 \lambda^{n-2} + \cdots (a_{k,i})_{n-1} \qquad [(a_{k,i})_0 = 0 \text{ if } k \neq i \ ] \tag{12}$$

$D_{k,i}(\lambda_h)$ (k,i = 1, 2, ..., n): $D_{k,i}(\lambda)$ when λ replaced by any of the eigenvalues λ_h (h=1,2,…n) (which has already been defined by eq.(12))

$adj(\boldsymbol{K} - \lambda_h \boldsymbol{I})$: Adjoint matrix (in non-hermitic sense) of the matrix $\boldsymbol{K} - \lambda_h \boldsymbol{I}$, i.e.

$$adj(\boldsymbol{K} - \lambda_h \boldsymbol{I}) = \begin{bmatrix} D_{1,1}(\lambda_h) & -D_{2,1}(\lambda_h) & \cdots & (-1)^{n+1} D_{n,1}(\lambda_h) \\ -D_{1,2}(\lambda_h) & D_{2,2}(\lambda_h) & \cdots & (-1)^{n+2} D_{n,2}(\lambda) \\ \vdots & \vdots & \cdots & \vdots \\ (-1)^{1+n} D_{1,n}(\lambda_h) & (-1)^{2+n} D_{2,n}(\lambda_h) & \cdots & D_{n,n}(\lambda_h) \end{bmatrix} \tag{13}$$

whose element on the k-th row and i-th column is $(-1)^{k+i} D_{k,i}(\lambda_h)$ (k,i=1,2,…,n).

$\boldsymbol{K}^c$: c-th power of matrix $\boldsymbol{K}$:

$\boldsymbol{K}^{p_h}$: p_h-th (p_h=0,1,2,…,c-1) power of matrix $\boldsymbol{K}$, which we denote as:

$$\boldsymbol{K}^{p_h} = \begin{bmatrix} \alpha_{1,1}^{(p_h)} & \alpha_{2,1}^{(p_h)} & \cdots & \alpha_{n,1}^{(p_h)} \\ \alpha_{1,2}^{(p_h)} & \alpha_{2,2}^{(p_h)} & \cdots & \alpha_{n,2}^{(p_h)} \\ \vdots & \vdots & & \vdots \\ \alpha_{1,n}^{(p_h)} & \alpha_{2,n}^{(p_h)} & & \alpha_{n,n}^{(p_h)} \end{bmatrix} \tag{14}$$

$\boldsymbol{K}_i^{p_h}$: row matrix 1 x n whose elements are those on the i-th row in matrix $\boldsymbol{K}^{p_h}$, i.e.:

$$\boldsymbol{K}_i^{p_h} = \begin{bmatrix} \alpha_{1,i}^{(p_h)} & \alpha_{2,i}^{(p_h)} & \cdots & \alpha_{n,i}^{(p_h)} \end{bmatrix} \tag{15}$$

3. Particular cases of the general kinetics equation in paper i of this series.

Eq. (26) and associated eq. (25) in paper I of this series become considerably simplified in the three particular cases which arise by considering the nature of matrix ***K*** and the multiplicities of its eigenvalues. This will be illustrated by studying the cases (a)-(c) described in the Introduction section.

3.1. Particular case (a): All of the eigenvalues of matrix *K* are simple.

In this case we have:

$$\left.\begin{aligned} & q = n \\ & r_1 = r_2 = \cdots = r_n = 1 \\ & s_h = h \ (h = 1,2,...,n) \\ & p_h = 0 \text{ for each } h\text{-value} \\ & s_h + p_h = h \end{aligned}\right\} \qquad (16)$$

and eqs. (26) and (25) of paper I of this series are simplified to:

$$\boldsymbol{X} = \sum_{h=1}^{n} \boldsymbol{A}_{h,0} e^{\lambda_h t} \qquad (17)$$

with

$$\boldsymbol{A}_{h,0} = \frac{\boldsymbol{\Lambda}_h \boldsymbol{X}^0}{\Lambda} \qquad (18)$$

and where Λ is the following n–order Vandermonde's determinant:

$$\Lambda = \begin{vmatrix} 1 & 1 & \cdots & 1 \\ \lambda_1 & \lambda_2 & \cdots & \lambda_n \\ \lambda_1^2 & \lambda_2^2 & \cdots & \lambda_n^2 \\ \vdots & \vdots & & \vdots \\ \lambda_1^{n-1} & \lambda_2^{n-1} & \cdots & \lambda_n^{n-1} \end{vmatrix} = \prod_{\substack{a,b=1 \\ a>b}}^{n} (\lambda_a - \lambda_b) \qquad (19)$$

Therefore, the MD $\boldsymbol{\Lambda}_h$ (h=1,2,…,n) is:

$$\boldsymbol{\Lambda}_h = \begin{array}{c} \begin{array}{cccccc} \phantom{\lambda_1^{n-1}} & \phantom{\lambda_2^{n-1}} & & \overbrace{\text{h-th mn}} & & \phantom{\lambda_n^{n-1}} \end{array} \\ \begin{vmatrix} 1 & 1 & \cdots & \boldsymbol{I} & \cdots & 1 \\ \lambda_1 & \lambda_2 & \cdots & \boldsymbol{K} & \cdots & \lambda_n \\ \lambda_1^2 & \lambda_2^2 & & \boldsymbol{K}^2 & \cdots & \lambda_n^2 \\ \vdots & \vdots & & \vdots & & \vdots \\ \lambda_1^{n-1} & \lambda_2^{n-1} & \cdots & \boldsymbol{K}^{n-1} & \cdots & \lambda_n^{n-1} \end{vmatrix} \end{array} \tag{20}$$

Note that for a certain h-value (h=1,2,…,n), the same one corresponding to $\boldsymbol{\Lambda}_h$, determinant Λ , given by eq. (19), can be written as:

$$\Lambda = \left\{ \prod_{\substack{a,b=1 \\ a>b \\ a,b\neq h}}^{n} \left(\lambda_a - \lambda_b\right) \right\} \left\{ (-1)^{h-1} \prod_{\substack{p=1 \\ p\neq h}}^{n} \left(\lambda_p - \lambda_h\right) \right\} \qquad (h=1,2,\ldots,n) \tag{21}$$

In turn, if we take into account that the MD in eq. (20) is formally a Vandermonde's determinant, it can be expressed as:

$$\boldsymbol{\Lambda}_h = \left\{ \prod_{\substack{a,b=1 \\ a>b \\ b\neq h}}^{n} \left(\lambda_a - \lambda_b\right) \right\} \left\{ (-1)^{n-h} \prod_{\substack{p=1 \\ p\neq h}}^{n} \left(\boldsymbol{K} - \lambda_p \boldsymbol{I}\right) \right\} \qquad (h=1,2,\ldots,n) \tag{22}$$

If, finally, eqs. (21) and (22) are inserted in eq. (18), it is found:

$$\boldsymbol{A}_{h,0} = \frac{(-1)^{n-1} \prod\limits_{\substack{p=1 \\ p\neq h}}^{n} \left(\boldsymbol{K} - \lambda_p \boldsymbol{I}\right)}{\prod\limits_{\substack{p=1 \\ p\neq h}}^{n} \left(\lambda_p - \lambda_h\right)} \boldsymbol{X}^0 \qquad (h=1,2,...,n) \tag{23}$$

It can be proved (see Appendix A) that:

$$\prod_{\substack{p=1\\p\neq h}}^{n}\left(\boldsymbol{K}-\lambda_p\boldsymbol{I}\right)=(-1)^{n-1}\operatorname{adj}(\boldsymbol{K}-\lambda_h\boldsymbol{I}) \tag{24}$$

where $\operatorname{adj}(\boldsymbol{K}-\lambda_h\boldsymbol{I})$ is given by eq. (13). If eq. (24) is inserted into eq. (23), we have:

$$\boldsymbol{A}_{h,0}=\frac{\operatorname{adj}\left(\boldsymbol{K}-\lambda_h\boldsymbol{I}\right)}{\prod_{\substack{p=1\\p\neq h}}^{n}\left(\lambda_p-\lambda_h\right)}\boldsymbol{X}^0 \qquad (h=1,2,...,n) \tag{25}$$

If we now carry out the multiplication $\operatorname{adj}\left(\boldsymbol{K}-\lambda_h\boldsymbol{I}\right)\cdot\boldsymbol{X}^0$ indicated in eq. (25) we have:

$$\boldsymbol{A}_{h,0}=\begin{bmatrix}\dfrac{\sum_{k=1}^{n}(-1)^{k+1}D_{k,1}(\lambda_h)x_k^0}{\prod_{\substack{p=1\\p\neq h}}^{n}\left(\lambda_p-\lambda_h\right)}\\[2ex] \dfrac{\sum_{k=1}^{n}(-1)^{k+2}D_{k,2}(\lambda_h)x_k^0}{\prod_{\substack{p=1\\p\neq h}}^{n}\left(\lambda_p-\lambda_h\right)}\\ \vdots\\ \dfrac{\sum_{k=1}^{n}(-1)^{k+n}D_{k,n}(\lambda_h)x_k^0}{\prod_{\substack{p=1\\p\neq h}}^{n}\left(\lambda_p-\lambda_h\right)}\end{bmatrix} \qquad (h=1,2,..., n) \tag{26}$$

From eqs. (26) and (17) we have for the instantaneous amount of matter, x_i, in any compartment, X_i , of the system:

$$x_i=\sum_{h=1}^{n}\left(\frac{\sum_{k=1}^{n}(-1)^{k+i}D_{k,i}(\lambda_h)x_k^0}{\prod_{\substack{p=1\\p\neq h}}^{n}\left(\lambda_p-\lambda_h\right)}\right)e^{\lambda_h t} \qquad (i=1,2,\dots,n) \tag{27}$$

If n = 1, i.e. when exists one only compartment, X_1, with zero input and with a excretion constant ti tge environment equal to $K_{1,o}$, then in eq. (27) both $\prod_{\substack{p=1 \\ p\neq h}}^{n}\left(\lambda_p - \lambda_h\right)$ and $D_{1,i}(\lambda_h)$ should be replaced by the unity and eq. (27) is reduced to:

$$x_1 = x_1^0 e^{\lambda_1 t} \tag{28}$$

with $\lambda_1 = -K_{1,o}$. An example where this happens is in the radioactive decay processes. Eq. (28) could also been derived proceeding as previously for any value of n but having into account that u = 1.

3.2. Particular case (b): *K* is singular with a null-eigenvalue of any multiplicity *c* (*c*=1,2,…, *n*-1), being simple all the non-null eigenvalues

If the null eigenvalue has multiplicity c and the remaining eigenvalues are simple, then there are u (u =n-c) non-null eigenvalues that we arbitrarily denote as λ_1, λ_2,…,λ_u and one null eigenvalue of multiplicity c denoted as λ_{u+1}. In this case we have (see notation in paper I of this series):

$$\left.\begin{array}{l}
n = u + c \\
q = u + 1 \\
h = 1,2,...,u+1 \\
r_1 = r_2 = \cdots = r_u = 1 \\
r_{u+1} = c \\
s_h = h \\
p_h = 0 \text{ if } h \le u \\
p_h = 0,1,...,c-1 \text{ if } h = u+1 \\
s_h + p_h = h \text{ if } h \le u \\
s_h + p_h = h + p_h \text{ if } h = u+1
\end{array}\right\} \tag{29}$$

and eqs. (25) and (26) in paper I of this series are simplified to:

$$\boldsymbol{A}_{h,0} = \frac{\boldsymbol{\Lambda}_h \boldsymbol{X}^0}{\Lambda} \qquad (h=1,2,\ldots,u) \tag{30}$$

$$\boldsymbol{A}_{u+1,p_h} = \frac{\boldsymbol{\Lambda}_{u+1+p_h}\boldsymbol{X}^0}{p_h!\Lambda} \qquad (p_h\text{=0,1,}\ldots c\text{-1}) \tag{31}$$

$$\boldsymbol{X} = \sum_{h=1}^{u} \boldsymbol{A}_{h,0} e^{\lambda_h t} + \left(\sum_{p_h=0}^{c-1} \boldsymbol{A}_{u+1,p_h} t^{p_h} \right) \tag{32}$$

When there are u non-null simple eigenvalues, $\lambda_1,\ \lambda_2,\ldots,\lambda_u$ and one eigenvalue, λ_{u+1}, of multiplicity c, determinant Λ is given by:

$$\Lambda = \begin{vmatrix} 1 & 1 & \cdots & & & & & \cdots & \\ \lambda_1 & \lambda_2 & \cdots & \lambda_u & \lambda_{u+1} & 1 & 0 & \cdots & 0 \\ \lambda_1^2 & \lambda_2^2 & \cdots & \lambda_u^2 & \lambda_{u+1}^2 & 2\lambda_{u+1} & 1 & \cdots & 0 \\ \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & & \vdots \\ \lambda_1^{c-2} & \lambda_2^{c-2} & \cdots & \lambda_u^{c-2} & \lambda_{u+1}^{c-2} & (c-2)\lambda_{u+1}^{c-3} & \binom{c-2}{2}\lambda_{u+1}^{c-4} & \cdots & 0 \\ \lambda_1^{c-1} & \lambda_2^{c-1} & \cdots & \lambda_u^{c-1} & \lambda_{u+1}^{c-1} & (c-1)\lambda_{u+1}^{c-2} & \binom{c-1}{2}\lambda_{u+1}^{c-3} & \cdots & 1 \\ \lambda_1^{c} & \lambda_2^{c} & \cdots & \lambda_u^{c} & \lambda_{u+1}^{c} & c\lambda_{u+1}^{c-1} & \binom{c}{2}\lambda_{u+1}^{c-2} & \cdots & \binom{c}{c-1}\lambda_{u+1} \\ \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & & \vdots \\ \lambda_1^{n-1} & \lambda_2^{n-1} & \cdots & \lambda_u^{n-1} & \lambda_{u+1}^{n-1} & (n-1)\lambda_{u+1}^{n-2} & \binom{n-1}{2}\lambda_{u+1}^{n-1} & \cdots & \binom{n-1}{c-1}\lambda_{u+1}^{n-c} \end{vmatrix} \tag{33}$$

(only for the purpose of expressing the above determinant in a general form it has been assumed that $c > 2$; obviously c can take also the values 1 or 2 and then this determinant becomes simpler).

Having into account that in this case $\lambda_{u+1} = 0$, eq (33) becomes:

$$\Lambda = \left|\begin{array}{cccc|ccccc} 1 & 1 & \cdots & 1 & 1 & 0 & 0 & \cdots & 0 \\ \lambda_1 & \lambda_2 & \cdots & \lambda_u & 0 & 1 & 0 & \cdots & 0 \\ \lambda_1^2 & \lambda_2^2 & \cdots & \lambda_u^2 & 0 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & & \vdots \\ \lambda_1^{c-2} & \lambda_2^{c-2} & \cdots & \lambda_u^{c-2} & 0 & 0 & 0 & \cdots & 0 \\ \lambda_1^{c-1} & \lambda_2^{c-1} & \cdots & \lambda_u^{c-1} & 0 & 0 & 0 & \cdots & 1 \\ \hdashline \lambda_1^{c} & \lambda_2^{c} & & \lambda_u^{c} & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & & \vdots \\ \lambda_1^{n-1} & \lambda_2^{n-1} & \cdots & \lambda_u^{n-1} & 0 & 0 & 0 & \cdots & 0 \end{array}\right| \tag{34}$$

which has been divided, using the two indicated dashed lines, in four minors which, according to determinants theory, allows us to express the determinant as:

$$\Lambda = (-1)^{u \cdot c} \begin{vmatrix} \lambda_1^c & \lambda_2^c & \cdots & \lambda_u^c \\ \vdots & \vdots & & \vdots \\ \lambda_1^{n-1} & \lambda_2^{n-1} & & \lambda_u^{n-1} \end{vmatrix} \begin{vmatrix} 1 & 0 & 0 & \cdots & 0 \\ 0 & 1 & 0 & \cdots & 0 \\ 0 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & & \vdots \\ 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & \cdots & 1 \end{vmatrix} \tag{35}$$

The second determinant on the right hand side in above equation has null all of its entries except those ones on the main diagonal and, therefore, it is equal to the unity, resulting:

$$\Lambda = (-1)^{u \cdot c} \begin{vmatrix} \lambda_1^c & \lambda_2^c & \cdots & \lambda_u^c \\ \vdots & \vdots & & \vdots \\ \lambda_1^{n-1} & \lambda_2^{n-1} & & \lambda_u^{n-1} \end{vmatrix} \tag{36}$$

In turn, determinant in eq. (36), having into account that $u = n\text{-}c$, adopts the form:

$$\begin{vmatrix} \lambda_1^c & \lambda_2^c & \cdots & \lambda_u^c \\ \vdots & \vdots & & \vdots \\ \lambda_1^{n-1} & \lambda_2^{n-1} & & \lambda_u^{n-1} \end{vmatrix} = \left\{ \prod_{i=1}^{u} \lambda_i^c \right\} \begin{vmatrix} 1 & 1 & \cdots & 1 \\ \vdots & \vdots & & \vdots \\ \lambda_1^{u-1} & \lambda_2^{u-1} & & \lambda_u^{u-1} \end{vmatrix} \tag{37}$$

Note that determinant in the right hand side in eq. (37) is an u-order Vandermonde's determinant and, therefore:

$$\begin{vmatrix} 1 & 1 & \cdots & 1 \\ \vdots & \vdots & & \vdots \\ \lambda_1^{u-1} & \lambda_2^{u-1} & & \lambda_u^{u-1} \end{vmatrix} = \prod_{\substack{a,b \\ a>b}}^{u} (\lambda_a - \lambda_b) \tag{38}$$

and from eqs. (36) and (38), we have:

$$\Lambda = (-1)^{u \cdot c} \left\{ \prod_{i=1}^{u} \lambda_i^c \right\} \left\{ \prod_{\substack{a,b \\ a>b}}^{u} (\lambda_a - \lambda_b) \right\} \tag{39}$$

Note also that determinant Λ , given by eq. (39), can also be written as:

$$\Lambda = (-1)^{u \cdot c} \lambda_h^c \left\{ \prod_{\substack{i=1 \\ i \neq h}}^{u} \lambda_i^c \right\} \left\{ \prod_{\substack{a,b=1 \\ a>b \\ a,b \neq h}}^{u} (\lambda_a - \lambda_b) \right\} \left\{ (-1)^{h-1} \prod_{\substack{p=1 \\ p \neq h}}^{u} (\lambda_p - \lambda_h) \right\} \tag{40}$$

On the other hand, matrix $\boldsymbol{\Lambda}_{s_h+p_h}$ (s_h+p_h = h if $h \le u$ and equal to h+p_h if h=u+1; p_h=1,2,…,c-1) is the MD that results after replacing in determinant Λ , given by eq. (34), column (s_h+p_h)-th by column of matrices $\boldsymbol{I}$, $\boldsymbol{K}$, $\boldsymbol{K}^2$,…$\boldsymbol{K}^n$. In order to determine matrix $\boldsymbol{\Lambda}_{s_h+p_h}$ we distinguish two cases: (1) $s_h + p_h \le u$ and (2) $s_h + p_h > u$.

(1) $s_h + p_h \le u$, i.e. $h \le u$

In this case, $s_h = h$, $p_h = 0$, $s_h+p_h = h$ and the MD $\boldsymbol{\Lambda}_h$ in eq. (30) is given, according to its definition, by:

$$
\boldsymbol{\Lambda}_h = \begin{array}{c}
\qquad\qquad\qquad \overbrace{h-\text{th column}} \qquad\qquad\qquad\qquad\qquad\qquad\qquad \\
\begin{vmatrix}
1 & 1 & \boldsymbol{I} & \cdots & 1 & 1 & 0 & 0 & \cdots & 0 \\
\lambda_1 & \lambda_2 & \boldsymbol{K} & \cdots & \lambda_u & 0 & 1 & 0 & \cdots & 0 \\
\lambda_1^2 & \lambda_2^2 & \boldsymbol{K}^2 & \cdots & \lambda_u^2 & 0 & 0 & 1 & \cdots & 0 \\
\vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & & \vdots \\
\lambda_1^{c-2} & \lambda_2^{c-2} & \boldsymbol{K}^{c-2} & \cdots & \lambda_u^{c-2} & 0 & 0 & 0 & \cdots & 0 \\
\lambda_1^{c-1} & \lambda_2^{c-1} & \boldsymbol{K}^{c-1} & \cdots & \lambda_u^{c-1} & 0 & 0 & 0 & \cdots & 1 \\
\lambda_1^{c} & \lambda_2^{c} & \boldsymbol{K}^{c} & & \lambda_u^{c} & 0 & 0 & 0 & \cdots & 0 \\
\vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & & \vdots \\
\lambda_1^{n-1} & \lambda_2^{n-1} & \boldsymbol{K}^{n-1} & \cdots & \lambda_u^{n-1} & 0 & 0 & 0 & \cdots & 0
\end{vmatrix}
\end{array}
\qquad (h=1,2,\ldots,u) \qquad (41)
$$

and proceeding analogously as in case (a) we have:as previously in the derivation of eq.(36) we have:

$$
\boldsymbol{A}_{h,0} = (-1)^{u-1} \frac{\boldsymbol{K}^c \prod\limits_{\substack{p=1 \\ p\neq h}}^{u} \left(\boldsymbol{K} - \lambda_p \boldsymbol{I}\right)}{\lambda_h^c \prod\limits_{\substack{p=1 \\ p\neq h}}^{u} \left(\lambda_p - \lambda_h\right)} \boldsymbol{X}^0 \qquad (h=1,2,\ldots,u) \qquad (42)
$$

From eq. (24) it is observed that, in this case:

$$
\boldsymbol{K}^c \prod_{\substack{p=1 \\ p\neq h}}^{u} \left(\boldsymbol{K} - \lambda_p \boldsymbol{I}\right) = (-1)^{n-1} \operatorname{adj}(\boldsymbol{K} - \lambda_h \boldsymbol{I}) \qquad (h=1,2,\ldots,u) \qquad (43)
$$

where $\operatorname{adj}(\boldsymbol{K} - \lambda_h \boldsymbol{I})$ is given by eq. (13). If now eq. (46) is inserted in eq. (45), we have:

$$
\boldsymbol{A}_{h,0} = \frac{(-1)^c \operatorname{adj}(\boldsymbol{K} - \lambda_h \boldsymbol{I})}{\lambda_h^c \prod\limits_{\substack{p=1 \\ p\neq h}}^{u} \left(\lambda_p - \lambda_h\right)} \boldsymbol{X}^0 \qquad (h=1,2,\ldots,u) \qquad (44)
$$

If in eq. (44) eq. (13) is taken into account and we carry out the multiplication $\operatorname{adj}(\boldsymbol{K} - \lambda_h \boldsymbol{I}) \cdot \boldsymbol{X}^0$ indicated in it, it results:

$$\boldsymbol{A}_{h,0} = \begin{bmatrix} (-1)^c \dfrac{\sum_{k=1}^{n}(-1)^{k+1} D_{k,1}(\lambda_h) x_k^0}{\lambda_h^c \prod_{\substack{p=1 \\ p\neq h}}^{u} \left(\lambda_p - \lambda_h\right)} \\ \\ (-1)^c \dfrac{\sum_{k=1}^{n}(-1)^{k+2} D_{k,2}(\lambda_h) x_k^0}{\lambda_h^c \prod_{\substack{p=1 \\ p\neq h}}^{u} \left(\lambda_p - \lambda_h\right)} \\ \vdots \\ (-1)^c \dfrac{\sum_{k=1}^{n}(-1)^{k+n} D_{k,n}(\lambda_h) x_k^0}{\lambda_h^c \prod_{\substack{p=1 \\ p\neq h}}^{u} \left(\lambda_p - \lambda_h\right)} \end{bmatrix} \quad (h=1,2,\ldots,u) \tag{45}$$

We will denote as $\mathrm{A}_{i,h}$ the entry on i-th row of matrix $\boldsymbol{A}_{h,0}$, i.e.:

$$\mathrm{A}_{i,h} = (-1)^c \frac{\sum_{k=1}^{n}(-1)^{k+i} D_{k,i}(\lambda_h) x_k^0}{\lambda_h^c \prod_{\substack{p=1 \\ p\neq h}}^{u} \left(\lambda_p - \lambda_h\right)} \tag{46}$$

(2) $s_h + p_h > u$

In Appendix B we show that:

$$\boldsymbol{A}_{u+1,p_h} = \frac{1}{p_h!}\left\{(-1)^{c-1}\sum_{h=1}^{u}\frac{\lambda_h^{p_h}\mathrm{adj}(\boldsymbol{K}-\lambda_h\boldsymbol{I})\boldsymbol{X}^0}{\lambda_h^c \prod_{\substack{p=1 \\ p\neq h}}^{u}(\lambda_p-\lambda_h)} + \boldsymbol{K}^{p_h}\boldsymbol{X}^0\right\} \quad (p_h=0,1,\ldots c\text{-}1) \tag{47}$$

which can also be written, having eq. (44) in mind, as:

$$\boldsymbol{A}_{u+1,p_h}=\frac{1}{p_h!}\left\{-\sum_{h=1}^{u}\lambda_h^{p_h}\boldsymbol{A}_{h,0}+\boldsymbol{K}^{p_h}\boldsymbol{X}^0\right\}\qquad (p_h=0,1,\ldots c\text{-}1)\tag{48}$$

From eq. (48) we have that matrix $\boldsymbol{A}_{u+1,p_h}$, in terms of its entries is, having in mind eqs. (45), (13) and (14):

$$\boldsymbol{A}_{u+1,p_h}=\frac{1}{p_h!}\begin{bmatrix} (-1)^{c-1}\sum_{h=1}^{u}\dfrac{\sum_{k=1}^{n}(-1)^{k+1}D_{k,1}(\lambda_h)x_k^0}{\lambda_h^{c-p_h}\prod_{\substack{p=1\\p\neq h}}^{u}\left(\lambda_p-\lambda_h\right)}+\sum_{k=1}^{n}\alpha_{k,1}^{(p_h)}x_k^0 \\ (-1)^{c-1}\sum_{h=1}^{u}\dfrac{\sum_{k=1}^{n}(-1)^{k+2}D_{k,2}(\lambda_h)x_k^0}{\lambda_h^{c-p_h}\prod_{\substack{p=1\\p\neq h}}^{u}\left(\lambda_p-\lambda_h\right)}+\sum_{k=1}^{n}\alpha_{k,2}^{(p_h)}x_k^0 \\ \vdots \\ (-1)^{c-1}\sum_{h=1}^{u}\dfrac{\sum_{k=1}^{n}(-1)^{k+n}D_{k,n}(\lambda_h)x_k^0}{\lambda_h^{c-p_h}\prod_{\substack{p=1\\p\neq h}}^{u}\left(\lambda_p-\lambda_h\right)}+\sum_{k=1}^{n}\alpha_{k,n}^{(p_h)}x_k^0 \end{bmatrix}\qquad (p_h=0,1,\ldots c\text{-}1)\tag{49}$$

We will denote as $\mathrm{A}_{i,0,p_h}$ the entry on i-th row of matrix $\boldsymbol{A}_{u+1,p_h}$, i.e.:

$$\mathrm{A}_{i,0,p_h}=\frac{1}{p_h!}\left((-1)^{c-1}\sum_{h=1}^{u}\frac{\sum_{k=1}^{n}(-1)^{k+i}D_{k,i}(\lambda_h)x_k^0}{\lambda_h^{c-p_h}\prod_{\substack{p=1\\p\neq h}}^{u}\left(\lambda_p-\lambda_h\right)}+\sum_{k=1}^{n}\alpha_{k,i}^{(p_h)}x_k^0\right)\quad (i=1,2,\ldots,n;\ p_h=0,1,\ldots c\text{-}1)\tag{50}$$

From eqs. (32), (45) and (48), one obtains:

$$x_i=\sum_{h=1}^{u}\mathrm{A}_{i,h}\,e^{\lambda_h t}+\sum_{p_h=0}^{c-1}\mathrm{A}_{i,0,p_h}t^{p_h}\tag{51}$$

where $\mathrm{A}_{i,h}$ and $\mathrm{A}_{i,0,p_h}$ are given by eqs. (45) and (49). If all of the minors $D_{k,i}(\lambda)$ of determinant $D(\lambda)$ would have a null root, the lower multiplicity of this null root in the different minors being m (m=1,2,…,c), then all of the minors can be expressed as:

$$D_{k,i}(\lambda) = \lambda^m d_{k,i}(\lambda) \tag{52}$$

and, in this case, it can be shown (see Appendix C) that eq. (32) becomes:

$$\boldsymbol{X} = \sum_{h=1}^{u} \boldsymbol{A}_{h,0} e^{\lambda_h t} + \left(\sum_{p_h=0}^{c'-1} \boldsymbol{A}_{u+1,p_h} t^{p_h} \right) \tag{53}$$

being

$$c' = c\text{-}m \tag{53}$$

and the expressions for $\boldsymbol{A}_{h,0}$ and $\boldsymbol{A}_{u+1,p_h}$ being those ones given by eqs. (44) and (48). On the other hand, according to eq. (12), if all of the minors $D_{k,i}(\lambda_h)$ have a null root of multiplicity m, this means that:

$$(a_{k,i})_{n-m} = (a_{k,i})_{n-m+1} = \cdots = (a_{k,i})_{n-1} = 0 \tag{55}$$

and therefore, from eqs. (55) and (12) one gets:

$$D_{k,i}(\lambda) = \lambda^m \left((a_{k,i})_0 \lambda^{n-m-1} + (a_{k,i})_1 \lambda^{n-m-2} + \cdots (a_{k,i})_{n-m-1} \right) \tag{56}$$

Thus, eqs. (45) and (49) are simplified to:

$$\boldsymbol{A}_{h,0} = \begin{bmatrix} (-1)^c \dfrac{\sum_{k=1}^{n} (-1)^{k+1} x_k^0 \sum_{q=0}^{n-m-1} (a_{k,1})_q \lambda_h^{n-m-1-q}}{\lambda_h^{c'} \prod_{\substack{p=1 \\ p\neq h}}^{u} (\lambda_p - \lambda_h)} \\ (-1)^c \dfrac{\sum_{k=1}^{n} (-1)^{k+2} x_k^0 \sum_{q=0}^{n-m-1} (a_{k,2})_q \lambda_h^{n-m-1-q}}{\lambda_h^{c'} \prod_{\substack{p=1 \\ p\neq h}}^{u} (\lambda_p - \lambda_h)} \\ \vdots \\ (-1)^c \dfrac{\sum_{k=1}^{n} (-1)^{k+n} x_k^0 \sum_{q=0}^{n-m-1} (a_{k,n})_q \lambda_h^{n-m-1-q}}{\lambda_h^{c'} \prod_{\substack{p=1 \\ p\neq h}}^{u} (\lambda_p - \lambda_h)} \end{bmatrix} \qquad (h=1,2,\ldots,u) \tag{57}$$

and

$$\boldsymbol{A}_{u+1,p_h}=\frac{1}{p_h!}\begin{bmatrix} (-1)^{c-1}\sum_{h=1}^{u}\dfrac{\sum_{k=1}^{n}(-1)^{k+1}x_k^0\sum_{q=0}^{n-m-1}(a_{k,1})_q\lambda_h^{n-m-1-q}}{\lambda_h^{c'-p_h}\prod_{\substack{p=1\\p\neq h}}^{u}\left(\lambda_p-\lambda_h\right)}+\sum_{k=1}^{n}\alpha_{k,1}^{(p_h)}x_k^0 \\ (-1)^{c-1}\sum_{h=1}^{u}\dfrac{\sum_{k=1}^{n}(-1)^{k+2}x_k^0\sum_{q=0}^{n-m-1}(a_{k,2})_q\lambda_h^{n-m-1-q}}{\lambda_h^{c'-p_h}\prod_{\substack{p=1\\p\neq h}}^{u}\left(\lambda_p-\lambda_h\right)}+\sum_{k=1}^{n}\alpha_{k,2}^{(p_h)}x_k^0 \\ \vdots \\ (-1)^{c-1}\sum_{h=1}^{u}\dfrac{\sum_{k=1}^{n}(-1)^{k+n}x_k^0\sum_{q=0}^{n-m-1}(a_{k,n})_q\lambda_h^{n-m-1-q}}{\lambda_h^{c'-p_h}\prod_{\substack{p=1\\p\neq h}}^{u}\left(\lambda_p-\lambda_h\right)}+\sum_{k=1}^{n}\alpha_{k,n}^{(p_h)}x_k^0 \end{bmatrix}\quad (p_h=0,1,\ldots c\text{-}1) \tag{58}$$

and eq. (51) is reduced to:

$$x_i=\sum_{h=1}^{u}\mathrm{A}_{i,h}\,e^{\lambda_h t}+\sum_{p_h=0}^{c'-1}\mathrm{A}_{i,0,p_h}t^{p_h} \tag{59}$$

where $\mathrm{A}_{i,h}$ **y** $\mathrm{A}_{i,0,p_h}$ are given, having eqs. (57) and (58) into account, by:

$$\mathrm{A}_{i,h}=(-1)^{c}\frac{\sum_{k=1}^{n}(-1)^{k+i}x_k^0\sum_{q=0}^{n-m-1}(a_{k,i})_q\lambda_h^{n-m-1-q}}{\lambda_h^{c'}\prod_{\substack{p=1\\p\neq h}}^{u}\left(\lambda_p-\lambda_h\right)}\qquad (i=1,2,\ldots,n;\ h=1,2,\ldots,u) \tag{60}$$

$$\mathrm{A}_{i,0,p_h}=\frac{1}{p_h!}\left((-1)^{c-1}\sum_{h=1}^{u}\frac{\sum_{k=1}^{n}(-1)^{k+i}x_k^0\sum_{q=0}^{n-m-1}(a_{k,i})_q\lambda_h^{n-m-1-q}}{\lambda_h^{c'-p_h}\prod_{\substack{p=1\\p\neq h}}^{u}\left(\lambda_p-\lambda_h\right)}+\sum_{k=1}^{n}\alpha_{k,i}^{(p_h)}x_k^0\right)\quad (i=1,2,\ldots,n;\ p_h=0,1,\ldots,c'\text{-}1) \tag{61}$$

If in this particular case (b) happens that u=1, then all those derived equations implicitly assuming that $u > 1$, remain valid, but in those one in which appears $\prod_{\substack{p=1 \\ p\neq h}}^{u}\left(\lambda_p - \lambda_h\right)$ this expression must be replaced by the unity, i.e. by 1, and obviously u must be also replaced by 1. After this action, it results the same equations which would be obtained initially assuming that $u = 1$ and then reasoning analogously as for derivation of the equations corresponding to this particular case.

3.3. Particular case (c). As in (b) but matrix *K* having some special properties frequent in linear compartmental systems.

This case, the most frequent concerning with closed linear compartmental systems, is characterized by the following features:

(1) The matrix ***K*** is singular, being c (c=1,2,…,n-1) the multiplicity of the null eigenvalue. This situation can be considered as a particular case of case (b) but with the following additional characteristics.

(2) The elements of matrix ***K*** outside of the principal diagonal are non-negative

(3) The elements of matrix ***K*** on the principal diagonal are non-positive

(4) Each element on the principal diagonal of matrix ***K*** is, in absolute value, equal to the sum of the remaining elements on the same column to which belongs this element.

This case has been extensively analyzed by Galvez and Varon (1981), Varon et al. (1995) and Garcia-Meseguer et al. (2001) in an individualized way. Here we show that the kinetic equations resulting for this case are a particular result of the kinetic expressions obtained in (b) introducing into them the features (2)-(4).

Under these conditions the non-null eigenvalues λ_1, λ_2, …, λ_u are real and negative or complex with a negative real part [7, 18, 22, 27, 30, 33]. Coefficients F_q (q=0, 1,

..., u) in eq. (8) can be obtained by expanding the characteristic polynomial $D(\lambda)$ (see eq.(1)). [Nevertheless, this procedure may become very tedious and prone to human errors, even when applied to compartmental systems not excessively complex. Varon *et al*. [27] and Garcia-Meseguer et al. [33] have suggested an alternative simple and systematic method to obtain these coefficients. This method circumvents the above mentioned limitations. Moreover Garcia-Meseguer *et al*. [33] implemented a software, named COEFICOM (available in http://oretano.iele-ab.uclm.es/%7Efgarcia/COEFICOM/), which easily furnishes these coefficients and the values of u and c].

Also, the minors $D_{k,i}(\lambda)$ always have a null root of multiplicity c-1 or c [30, 35] and, therefore:

$$m = c\text{-}1, \quad c' = 1, \quad p_h = 0 \tag{62}$$

Moreover, in this case it has been proved [33] that:

$$(a_{k,i})_q = (-1)^{n+i+k-1}(f_{k,i})_q \tag{63}$$

where the coefficients $(f_{k,i})_q$ (q = 1, 2, ..., u) can be obtained by expanding $D_{k,i}(\lambda)$ and using eq. (63), or more easily as described in [33].

If we insert eqs. (62) and (63) into eqs. (59)-(61) and we take into account that $A_{i,0,0}$ is denoted by $A_{i,0}$, we have:

$$x_i = \sum_{h=1}^{u} A_{i,h} e^{\lambda_h t} + A_{i,0} \qquad (i=1,2,\dots,n) \tag{64}$$

$$A_{i,h} = (-1)^{u-1} \frac{\sum_{k=1}^{n} x_k^0 \left(\sum_{q=0}^{u} (f_{k,i})_q \lambda_h^{u-q} \right)}{\lambda_h \prod_{\substack{p=1 \\ p \neq h}}^{u} \left(\lambda_p - \lambda_h \right)} \qquad (i=1,2,\dots,n;\ h=1,2,\dots,u) \tag{65}$$

and

$$A_{i,0} = (-1)^u \sum_{h=1}^{u} \frac{\sum_{k=1}^{n} x_k^0 \left(\sum_{q=0}^{u} (f_{k,i})_q \lambda_h^{u-q} \right)}{\lambda_h \prod_{\substack{p=1 \\ p \neq h}}^{u} (\lambda_p - \lambda_h)} + x_i^0 \qquad (i=1,2,\ldots,n) \tag{66}$$

In Appendix D we show that $A_{i,0}$ can also be expressed as:

$$A_{i,0} = \frac{\sum_{k=1}^{n} x_k^0 \left(\sum_{q=1}^{u} (f_{k,i})_u \right)}{F_u} \qquad (i=1,2,\ldots,n) \tag{68}$$

Finally, eqs. (67) and (65) can be expressed, having in mind that $x_k^0 = 0$ if $x_k^0 \notin \omega$, as:

$$A_{i,0} = \frac{\sum_{k \in \omega} (f_{k,i})_u x_k^0}{F_u} \qquad (i=1,2,\ldots,n) \tag{69}$$

$$A_{i,h} = \frac{(-1)^{u-1} \sum_{k \in \omega} x_k^0 \left(\sum_{q=0}^{u} (f_{k,i})_q \lambda_h^{u-q} \right)}{\lambda_h \prod_{p=1}^{u} (\lambda_p - \lambda_h)} \qquad (i=1,2,\ldots,n;\ h=1,2,\ldots,u) \tag{68}$$

As mentioned above, eqs. (64), (68) and (69) coincide with the expression previously derived in a individualized way described in references [27,30,33].

4. Results and discussion

In this contribution we have derived, starting from the general solutions given in paper I of this series, particular solutions which are much simpler and that can be applied to enzyme, chemical, biochemical, pharmacokinetic, physical, engineering and other frequent systems which can be modeled as some of the linear compartmental systems above described. Of course, other particular cases are possible, and the way to obtain the corresponding expressions is similar to that used here for cases (a)- (c).

Cases (a)-(c) are frequently found. Thus, the situation where all the eigenvalues are simple, none of them being null, appears in open linear compartmental systems without traps [1, 9, 36, 37]. The corresponding matrix ***K*** is non-singular and, therefore, there are no null eigenvalues. Moreover, in this case, the possibility that the some eigenvalues are multiple is little. There are also some enzyme systems involving zymogen autocatalytic activation which belong to this case [37-39]. Case (b), with one null eigenvalue of any multiplicity, and the other ones being simple and without any additional restriction concerning system matrix ***K***, is frequent in enzyme systems involving zymogen non-autocatalytic activation [40, 41] (these processes are of great physiological interest because they occur in digestion, metabolism, immunity, blood coagulation, fibrinolysis, cell apoptosis, tumor growth and metastasis [42] , as well as in applications in biotechnology and possibly treatment of AIDS [43, 44]). Finally, case (c) corresponds to most of closed linear compartmental systems, all of them possessing, at least, one null eigenvalue the multiplicity of which coincides with the number of final classes in the corresponding directed graph [27]. To this particular case fit most of the enzyme reactions once modeled as linear compartmental systems. Actually, case (c) is a particular case of (b) when in matrix ***K*** certain conditions are hold. Nevertheless, due to the important and the large number of physical, chemical and biomedical systems which fit to this case, it has been treated independently.

Also, and because case (a) is applicable when all the eigenvalues are simple, this include those situations in which a simple null eigenvalue exists. As expected, the result for this situation coincides with that obtained in (b) setting c=1.

4.1. The two ways to obtain the results in this contribution

It must be emphasized that in this contribution cases (a)-(c) have been analyzed as particular cases of the general model analyzed in paper I of this series to show the validity, power and completeness of the results there obtained. Nevertheless, these particular cases, frequent in practice and relatively simple due to their restrictive constraints, could also be analyzed in an independent way, by applying any of the methods for analytical integration of linear sets of differential equations. In fact, these procedures were already used early in the literature [30, 33, 45, 46] for case (c). As an example, we discuss two procedures to obtain the results corresponding to case (a).

Procedure 1: In paper I of this series the general equations were obtained from the Laplace transformation and the general form of the solution which relates matrix $\boldsymbol{X}$ with time [eqs. (16) and (4) in paper I] by derivating $\boldsymbol{X}$ with respect to t n-1 times. This gives a set of n linear algebraic equations (after setting t =0 in them) where the unknowns are the column matrices $\boldsymbol{A}_{h,p_h}$ defined by eq. (25) in I. Next, and if it is assumed that the n eigenvalues of matrix $\boldsymbol{K}$ are simple, eqs. (25) and (26) for the matrices $\boldsymbol{A}_{h,0}$ are found.

Procedure 2: Another way to obtain these matrices is shown in Appendix A where $\boldsymbol{A}_{h,0}$ are obtained from the Laplace transformation for $\boldsymbol{X}$, L($\boldsymbol{X}$) [eq. (A4)], setting in it, successively, h=1,2,…,n. Hence, the matrices are not obtained from the $\boldsymbol{X}$ expression as a function of time, but from a previous step, where the inverse transformation of L($\boldsymbol{X}$) has not yet been taken. Finally, once the expressions of the matrices have been obtained, the inverse transformation is taken.

These two procedures to obtain the matrices $\boldsymbol{A}_h$ (h=1,2,…,n) provide the same results.

4.2. Some Mathematical relationships that arise from this contribution

The existence of two procedures that provide the kinetic equations of the particular cases (a)-(c) indicated in this contribution, i.e. either from the general equations derived in paper I or by using an individualized way, allows us to obtain mathematical relationships which, as far as we know, were not established previously.

Thus, relationship (24) has been found, as indicated in Appendix A, by comparison of eqs. (23) in the main text for matrices $\boldsymbol{A}_{h,0}$ (h=1,2,…,n) in case (a), and eq. (A7) in Appendix A. In turn, from relationship (24) derivation of relationship (46) is immediate.

Other useful relationships can be also derived by comparison of results obtained from different ways. Thus, in Appendix C it is shown that when all the minors $D_{k,i}(\lambda)$ have a null root and their lower multiplicities are m, then:

$$\boldsymbol{A}_{u+1,c-m} = \boldsymbol{A}_{u+1,c-m+1} = \ldots = \boldsymbol{A}_{u+1,c-1} = 0 \qquad (70)$$

Therefore, according to eq. (47) which gives the expression of these matrices, it must be fulfilled:

$$(-1)^c \sum_{h=1}^{u} \frac{\mathrm{adj}(\boldsymbol{K}-\lambda_h \boldsymbol{I})}{\lambda_h^{c-p_h} \prod\limits_{\substack{p=1 \\ p\neq h}}^{u} (\lambda_p - \lambda_h)} = \boldsymbol{K}^{p_h} \quad (\text{if } p_h = c\text{-}m,\ c\text{-}m\text{+}1,\ldots,c\text{-}1) \qquad (71)$$

(if all the minors $D_{k,i}(\lambda_h)$ have a null root being m the lower multiplicity of them)

The possibility of obtaining the expression of a same magnitude by using different ways offers great mathematical richness as illustrated in this contribution by deriving relationships (24), (46), (70) and (71). As far as we know, these relationships were not given previously in the literature.

4.3. Examples

Next, we consider three examples of enzyme systems, examples 1, 2 and 3, which can be modeled as linear compartmental systems fitting to particular cases (a), (b) and (c), respectively. Obviously, the full power and utility of the equations obtained here for each of the three cases is revealed when they are applied to more complex systems. However, and without loss of generality of the procedures, it easier its illustration when they are applied to simple examples.

Example 1. *Autocatalytic activation of a zymogen*

We will obtain the kinetic equation corresponding to the active enzyme E for the following reaction mechanism of autocatalytic activation of a zymogen, as occurs in the autocatalytic activation of trypsinogen to trypsin [41, 47], of pepsinogen to pepsin [48-52] and in the activation of prekalicrein to kalicrein [53, 54]:

$$E + Z \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} EZ \xrightarrow{k_2} 2E + W$$

Scheme 1

In this scheme E is activating enzyme, Z is the zymogen and W is a peptide released from Z. If the initial concentration of Z, $[Z]_0$, is much higher than the initial concentration of E, $[E]_0$, and we consider a reaction time so that the instantaneous concentration of Z, [Z], remains approximately equal to $[Z]_0$, i.e. $[Z] \simeq [Z]_0$, then the interconversions between the enzyme forms are of first ($EZ \xrightarrow{k_2} 2E + W$ y $E + Z \xleftarrow[k_{-1}]{} EZ$) or pseudofirst order ($E \xrightarrow{k_1[Z]_0} EZ$), and the system can be modeled as a linear compartmental system whose directed graph is displayed in Fig. 1.

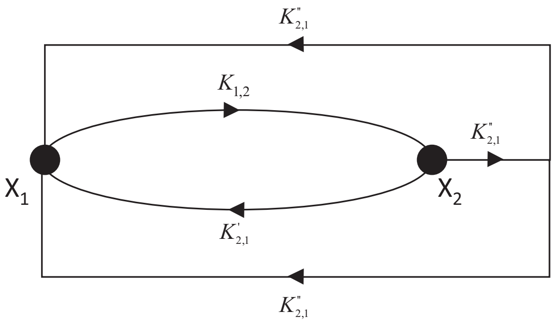

Figure 1. Directed graph showing the linear compartmental system in Scheme 1. X_1 and X_2 correspond to E and EZ, respectively. $K_{1,2} = k_1[Z]_0$, $K'_{2,1}=k_{-1}$, $K''_{2,1}=k_2$.

In this case n=2, and x_1 and x_2 represent the instantaneous concentrations of the enzyme species E and EZ and x_1^0 and x_2^0 their initial concentrations, respectively. We will assume that the only species present at the onset of the reaction are E and Z and therefore $x_2^0 = 0$. The matrix $\boldsymbol{K}$ is:

$$\boldsymbol{K} = \begin{bmatrix} K_{1,1} & K_{2,1} \\ K_{1,2} & K_{2,2} \end{bmatrix} \tag{72}$$

being:

$$\left.\begin{aligned} K_{1,1} &= -K_{1,2} \\ K_{1,2} &= k_1[Z]_0 \\ K_{2,2} &= -K_{2,1} \\ K_{2,1} &= K^{'}_{2,1} + 2K^{"}_{2,1} \\ K^{'}_{2,1} &= k_{-1} \\ K^{"}_{2,1} &= k_2 \end{aligned}\right\} \tag{73}$$

and $D(\lambda)$ is:

$$D(\lambda)=\begin{vmatrix} K_{1,2}-\lambda & K_{2,1} \\ K_{1,2} & K_{2,2}-\lambda \end{vmatrix} \tag{74}$$

The eigenvalues of ***K*** are the roots of $D(\lambda)$, i.e.:

$$\lambda_1=\frac{-\left(k_1[Z]_0+k_{-1}+k_2\right)+\sqrt{\left(k_1[Z]_0+k_{-1}+k_2\right)^2+4k_1k_2[Z]_0}}{2} \tag{75}$$

and

$$\lambda_2=\frac{-\left(k_1[Z]_0+k_{-1}+k_2\right)-\sqrt{\left(k_1[Z]_0+k_{-1}+k_2\right)^2+4k_1k_2[Z]_0}}{2} \tag{76}$$

Note that λ_1 is positive whereas λ_2 is negative. Because of these two eigenvalues are simple, the results obtained for particular case (a) are applicable to this system. From eq. (27) and having into account that i=1, k=1 y u=2 one obtains:

$$x_1=\frac{D_{1,1}(\lambda_1)x_1^0}{\left(\lambda_2-\lambda_1\right)}e^{\lambda_1 t}+\frac{D_{1,1}(\lambda_2)x_1^0}{\left(\lambda_1-\lambda_2\right)}e^{\lambda_2 t} \tag{77}$$

From eq. (75) we find:

$$D_{1,1}(\lambda)=K_{2,2}-\lambda \tag{78}$$

and, therefore:

$$D_{1,1}(\lambda_1)=K_{2,2}-\lambda_1 \tag{79}$$

$$D_{1,1}(\lambda_2)=K_{2,2}-\lambda_2 \tag{80}$$

Finally, if in eq. (76), eqs. (78) and (79) and the expression of $K_{2,2}$ are taken into account, we have:

$$x_1 = \frac{x_1^0}{\lambda_1 - \lambda_2}\left\{(k_{-1} + k_2 + \lambda_1)e^{\lambda_1 t} - (k_{-1} + k_2 + \lambda_2)e^{\lambda_2 t}\right\} \tag{81}$$

Example 2. *Non-autocatalytic activation of a zymogen*

In this example we will obtain the kinetic equation corresponding to the instantaneous concentration of the activated enzyme in a non-autocatalytic zymogen activation such as the activation of plasminogen to plasmin [43, 55-58] which takes place according to the following scheme of reaction:

$$E + Z \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} EZ \xrightarrow{k_2} E + E_a + W$$

Scheme 2

In this scheme E and Z are the activating enzyme and the zymogen, respectively, E_a is the activated enzyme and W is a peptide released from Z.

If $[Z]_0 >> [E]_0$, and we consider a reaction time during which $[Z] \simeq [Z]_0$, then the interconversions between the enzyme forms are of first ($EZ \xrightarrow{k_2} E + E_a + W$, $E + Z \xleftarrow[k_{-1}]{} EZ$) or pseudofirst order ($E \xrightarrow{k_1[Z]_0} EZ$). Under these conditions, the system under study can be modeled as a linear compartmental system whose directed graph is shown in Fig. 2.:

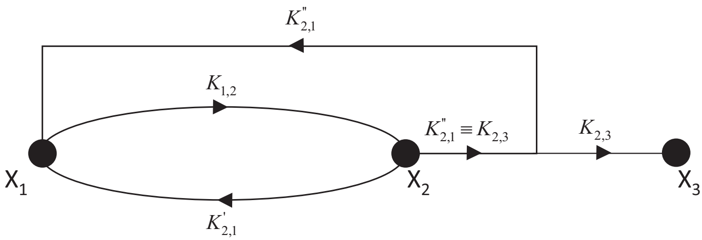

Figure 2. Directed graph showing the linear compartmental system in Scheme 2. X_1, X_2 and X_3 correspond to E, EZ and Ea, respectively. $K_{1,2} = k_1[Z]_0$, $K'_{2,1}=k_{-1}$, $K''_{2,1}= K_{2,3} = k_2$.

In this case n=3 and x_1, x_2 and x_3 represent the instantaneous concentrations of the enzyme species E, EZ and E_a. The initial concentrations of these species are x_1^0, x_2^0 and x_3^0, respectively. By assuming that the only species present at the onset of the reaction are E and Z, i. e., $x_2^0 = x_3^0 = 0$, the matrix $\boldsymbol{K}$ is:

$$\boldsymbol{K} = \begin{bmatrix} K_{1,1} & K_{2,1} & 0 \\ K_{1,2} & K_{2,2} & 0 \\ 0 & K_{2,3} & 0 \end{bmatrix} \tag{82}$$

where

$$\left.\begin{aligned} K_{1,1} &= -K_{1,2} \\ K_{1,2} &= k_1[Z]_0 \\ K_{2,2} &= -K_{2,1} \\ K_{2,1} &= K_{2,1}^{'} + K_{2,1}^{"} \\ K_{2,1}^{'} &= k_{-1} \\ K_{2,1}^{"} &= k_2 \\ K_{2,3} &= k_2 \end{aligned}\right\} \tag{83}$$

and $D(\lambda)$ is:

$$D(\lambda) = \begin{bmatrix} K_{1,1} - \lambda & K_{2,1} & 0 \\ K_{1,2} & K_{2,2} - \lambda & 0 \\ 0 & K_{2,3} & -\lambda \end{bmatrix} \tag{84}$$

The matrix $\boldsymbol{K}$ has two different eigenvalues, one of them non-null, λ_1, given by:

$$\lambda_1 = K_{1,1} + K_{2,2} \tag{85}$$

and another null, λ_2, of multiplicity 2. In this example:

$$\left.\begin{aligned} u &= 1 \\ c &= 2 \\ s_2 &= 2 \\ p_2 &= 0 \text{ and } 1 \end{aligned}\right\} \tag{86}$$

Because the non-null eigenvalue is simple and the null eigenvalue is of multiplicity *c*, one can apply to this situation, in principle, the results of the particular cases (b) or (c). But since $\left|K_{2,2}\right| < K_{2,1}$+$K_{2,3}$ the requisite (4) above mentioned for case (c) is not fulfilled. In other words, the results obtained for case (b) must be used in this example.

We want to determine x_3 and taking into account that the only enzyme species present at the onset of the reaction is E, i.e. X_1, it follows according to eq. (51):

$$x_3 = A_{3,1}e^{\lambda_1 t} + A_{3,0} + A_{3,0,1}t \tag{87}$$

where $A_{3,1}$, $A_{3,0}$ and $A_{3,0,1}$ are given by eqs. (46) and (50) (note that $A_{3,0,0}$ is denoted by $A_{3,0}$) with i =3, u=1 y c=2, i.e.:

$$A_{3,1} = \frac{D_{1,3}(\lambda_1)x_1^0}{\lambda_1^2} \tag{88}$$

$$A_{3,0} = \left(-\frac{D_{1,3}(\lambda_1)}{\lambda_1^2} + \alpha_{1,3}^{(0)}\right)x_1^0 \tag{89}$$

$$A_{3,0,1} = \left(-\frac{D_{1,3}(\lambda_1)}{\lambda_1} + \alpha_{1,3}^{(1)}\right)x_1^0 \tag{90}$$

From eq. (95) we find:

$$D_{1,3}(\lambda_1) = \begin{bmatrix} K_{1,2} & K_{2,2} - \lambda \\ 0 & K_{2,3} \end{bmatrix} = K_{1,2}K_{2,3} \tag{91}$$

Also, according to matrices ***I*** and ***K*** and the meaning of $\alpha_{1,3}^{(0)}$ and $\alpha_{1,3}^{(1)}$, we have:

$$\alpha_{1,3}^{(0)} = \alpha_{1,3}^{(1)} = 0 \tag{92}$$

and, therefore, eq. (98) adopts the form:

$$x_3 = \frac{K_{1,2}K_{2,3}x_1^0}{\lambda_1}\left\{\frac{1}{\lambda_1}\left(e^{\lambda_1 t}-1\right)-t\right\} \tag{93}$$

If in this equation are taken into account the expressions for $K_{1,2}$ and $K_{2,3}$ given by eqs. (82), and that $x_3 = [E_a]$, $x_1^0 = [E]_0$, one finds:

$$[E_a] = \frac{k_1k_2[Z]_0[E]_0}{k_1[Z]_0 + k_{-1} + k_2}\left\{\frac{1}{k_1[Z]_0 + k_{-1} + k_2}\left(e^{-(k_1[Z]_0+k_{-1}+k_2)t}-1\right)+t\right\} \tag{94}$$

Example 3. *Reversible, competitive inhibition*

In this example we will obtain the kinetic equation corresponding to the enzyme-substrate complex, *ES*, belonging to an enzyme system with reversible, competitive inhibition [41, 49, 50, 59-62] according to the following scheme of reaction mechanism:

$$\begin{array}{l} E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E + P \\ + \\ \mathrm{I} \\ k_3 \downarrow\uparrow k_{-3} \\ EI \end{array}$$

Scheme 3

In this scheme E, S, ES, P, I and EI are the free enzyme, the substrate, the enzyme-substrate complex, the product of the reaction, the inhibitor and the enzyme-inhibitor complex, respectively

If $[S]_0$ and $[I]_0 >> [E]_0$, and the reaction time is such that $[S] \simeq [S]_0$ and $[I] \simeq [I]_0$, then the interconversions between the enzyme forms are of first ($ES \xrightarrow{k_2} E + P$, $ES \xrightarrow{k_2} E + P, E + S \xleftarrow[k_{-1}]{} ES$ and $EI \xrightarrow{k_{-3}} E + I$) or pseudofirst order ($E \xrightarrow{k_1[S]_0} ES$ y $E \xrightarrow{k_1[I]_0} EI$).

Under these conditions, the enzyme system can be modeled as a linear compartmental system described by the directed graph displayed in Fig. 3.

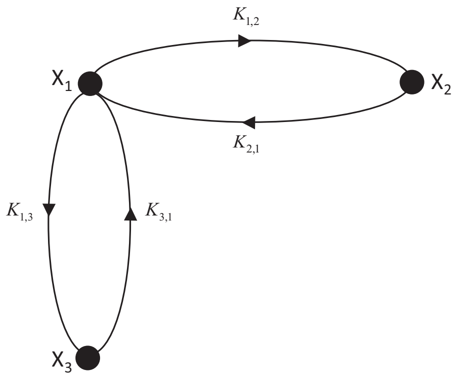

Figure 3. Directed graph describing the linear compartmental system shown in Scheme 3. X_1, X_2 and X_3 correspond to E, ES and EI, respectively. $K_{1,2}$ = $k_1[S]_0$, $K_{2,1}$=k_{-1}+k_2, $K_{1,3}$= $k_{,3}[I]_0$ y $K_{3,2}$ = k_{-3}.

In this example $n = 3$ and x_1, x_2 and x_3 represent the instantaneous concentrations of the enzyme species E, ES and EI, respectively and x_1^0, x_2^0 and x_3^0 their initial concentrations. We will assume that the only species present at the onset of the reaction are E, S and I so that $x_2^0 = x_3^0 = 0$. Matrix $\boldsymbol{K}$ corresponding to Fig. 3 is:

$$\boldsymbol{K} = \begin{bmatrix} K_{1,1} & K_{2,1} & K_{3,1} \\ K_{1,2} & K_{2,2} & 0 \\ K_{1,3} & 0 & K_{3,3} \end{bmatrix} \tag{95}$$

being:

$$\left.\begin{aligned} K_{1,1} &= -(K_{1,2} + K_{1,3}) \\ K_{1,2} &= k_1[S]_0 \\ K_{1,3} &= k_3[I]_0 \\ K_{2,2} &= -K_{2,1} \\ K_{2,1} &= k_{-1} + k_2 \\ K_{3,3} &= -K_{3,1} \\ K_{3,1} &= k_{-3} \end{aligned}\right\} \tag{96}$$

and $D(\lambda)$ is:

$$D(\lambda) = \begin{vmatrix} K_{1,1} - \lambda & K_{2,1} & K_{3,1} \\ K_{1,2} & K_{2,2} - \lambda & 0 \\ K_{1,3} & 0 & K_{3,3} - \lambda \end{vmatrix} \qquad (97)$$

Hence, the eigenvalues of matrix ***K*** are:

$$\lambda_1 = \frac{-F_1 + \sqrt{F_1^2 - 4F_2}}{2} \qquad (98)$$

$$\lambda_2 = \frac{-F_1 - \sqrt{F_1^2 - 4F_2}}{2} \qquad (99)$$

and

$$\lambda_3 = 0 \qquad (100)$$

where:

$$F_1 = k_{-1} + k_2 + k_{-3} + k_1[S]_0 + k_3[I]_0 \qquad (101)$$

and

$$F_2 = k_{-3}(k_{-1} + k_2) + k_1 k_{-3}[S]_0 + k_3(k_{-1} + k_2)[I]_0 \qquad (102)$$

Thus, in this example there are two simple eigenvalues (u=2) and one null eigenvalue of multiplicity c=1. Therefore, in principle, the results for cases (b) or (c) could be applied. But in this example the four requirements that allow us to apply the much simpler equations for case (c) are hold. For this reason we will use these expressions. Briefly, in this example:

$$\left.\begin{matrix} u = 2 \\ c = 1 \end{matrix}\right\} \qquad (103)$$

We are interested in obtaining the time course of x_2. According to eq. (64) and having into account that $x_2^0 = x_3^0 = 0$, i =2, u=2 and c=1, one obtains:

$$x_2 = \mathrm{A}_{2,0} + \mathrm{A}_{2,1} e^{\lambda_1 t} + \mathrm{A}_{2,2} e^{\lambda_2 t} \tag{104}$$

where $\mathrm{A}_{2,0}$ is given by eq. (67) and $\mathrm{A}_{2,1}$ and $\mathrm{A}_{2,2}$ by eq. (68) with i =2, u=2 and h = 1 and 2 respectively, i.e.:

$$A_{2,0} = \frac{(f_{1,2})_2 x_1^0}{F_2} \tag{105}$$

$$A_{2,1} = \frac{-x_1^0\left((f_{1,2})_0 \lambda_1^2 + (f_{1,2})_1 \lambda_1 + (f_{1,2})_2\right)}{\lambda_1\left(\lambda_2 - \lambda_1\right)} \tag{106}$$

and

$$A_{2,2} = \frac{-x_1^0\left((f_{1,2})_0 \lambda_2^2 + (f_{1,2})_1 \lambda_2 + (f_{1,2})_2\right)}{\lambda_2\left(\lambda_1 - \lambda_2\right)} \tag{107}$$

Coefficients $(f_{1,2})_q$ (q=0,1,2) involved in above equations are obtained by expanding the minor $D_{1,2}(\lambda)$ given by

$$D_{1,2}(\lambda) = \begin{vmatrix} K_{1,2} & 0 \\ K_{1,3} & K_{3,3} - \lambda \end{vmatrix} \tag{108}$$

and from eq. (75):

$$(f_{1,2})_0 = 0 \tag{109}$$

$$(f_{1,2})_1 = K_{1,2} \tag{110}$$

$$(f_{1,2})_2 = K_{1,2}K_{3,1} \tag{111}$$

Inserting eqs. (109)-(111) into eqs. (105) and (107), and taking into account the expressions for $K_{1,2}$, $K_{3,1}$ and F_2 and that $x_1^0 = [E]_0$, it results:

$$A_{2,0} = \frac{k_1 k_{-3}[E]_0}{k_{-3}(k_{-1}+k_2)+k_1 k_{-3}[S]_0 + k_3(k_{-1}+k_2)[I]_0} \tag{112}$$

$$A_{2,1} = \frac{-k_1\left(\lambda_1 + k_{-3}\right)[S]_0[E]_0}{\lambda_1\left(\lambda_2 - \lambda_1\right)} \tag{113}$$

$$A_{2,1} = \frac{-k_1\left(\lambda_2 + k_{-3}\right)[S]_0[E]_0}{\lambda_2\left(\lambda_1 - \lambda_2\right)} \tag{114}$$

Appendix A

Derivation of relationship (24) in the main text

If in eq. (15) of paper I, $\mathbf{X}^{(1)}=\boldsymbol{K}\mathbf{X}$, we take Laplace transformation, we have:

$$-\boldsymbol{X}^0 = (\boldsymbol{K} - \lambda \boldsymbol{I})\cdot L(\boldsymbol{X}) \tag{A1}$$

with

$$L(\boldsymbol{X}) = \begin{bmatrix} L(x_1) \\ L(x_2) \\ \vdots \\ L(x_n) \end{bmatrix} \tag{A2}$$

and where L(x_i) is the Laplace transformated of the function x_i giving the instantaneous amount of matter in compartment X_i.

From eq. (A1) and having into account that $\det(\boldsymbol{K} - \lambda \boldsymbol{I}) = D(\lambda)$ we have:

$$L(\boldsymbol{X}) = -\frac{adj(\boldsymbol{K} - \lambda \boldsymbol{I})\cdot \boldsymbol{X}^0}{D(\lambda)} \tag{A3}$$

If we assume that the n eigenvalues of matrix $\boldsymbol{K}$ are simple, then the right side of eq. (A3) can be expressed as the following sum:

$$-\frac{adj(\boldsymbol{K} - \lambda \boldsymbol{I})\cdot \boldsymbol{X}^0}{D(\lambda)} = \sum_{h=1}^{n} \frac{\boldsymbol{A}_{h,0}}{\lambda - \lambda_h} \tag{A4}$$

If we carry out the sum in the right side of eq. (A4) and we have into account the expression of $D(\lambda)$ given by eq. (3), we have:

$$(-1)^{n-1}\frac{adj(\boldsymbol{K}-\lambda\boldsymbol{I})\cdot\boldsymbol{X}^0}{\prod_{p=1}^{n}\left(\lambda-\lambda_p\right)}=\frac{\sum_{h=1}^{n}\left(\boldsymbol{A}_{h,0}\prod_{\substack{p=1\\p\neq h}}^{n}\left(\lambda-\lambda_p\right)\right)}{\prod_{p=1}^{n}\left(\lambda-\lambda_p\right)} \tag{A5}$$

and hence:

$$(-1)^{n-1}adj(\boldsymbol{K}-\lambda\boldsymbol{I})\cdot\boldsymbol{X}^0=\sum_{h=1}^{n}\left(\boldsymbol{A}_{h,0}\prod_{\substack{p=1\\p\neq h}}^{n}\left(\lambda-\lambda_p\right)\right) \tag{A6}$$

Eq. (A6) is accomplished for any λ-value and, therefore, also for each of the *n* different λ_h-values (h=1,2,…,n). If in eq. (A6) we replace λ for any of the possible λ_h's, all the summands in the bracket on the right side of eq. (A6) vanish except $\boldsymbol{A}_{h,0}\prod_{\substack{p=1\\p\neq h}}^{n}\left(\lambda_h-\lambda_p\right)=$ $(-1)^{n-1}\boldsymbol{A}_{h,0}\prod_{\substack{p=1\\p\neq h}}^{n}\left(\lambda_p-\lambda_h\right)$. Thus, we have:

$$\boldsymbol{A}_{h,0}=\frac{adj(\boldsymbol{K}-\lambda\boldsymbol{I})\cdot\boldsymbol{X}^0}{\prod_{\substack{p=1\\p\neq h}}^{n}\left(\lambda_p-\lambda_h\right)} \tag{A7}$$

By comparing eqs. (A7) and (23) we have immediately relationship (24).

Appendix B

Derivation of eq. (47) in the main text

In this case, h=u+1, s_h=h=u+1, p_h=0,1,2,…,c-1, $s_h + p_h$=u+1+p_h and, therefore, matrix $\boldsymbol{\Lambda}_{u+1+p_h}$ (p_h=0,1,2,…,c-1) is:

$$
{}_{s_h+p_h} = {}_{u+1+p_h} =
\begin{array}{c}
\begin{array}{cccccccccccc}
 & & & & & & & & \overbrace{\quad (u+1+p_h)-\text{th} \quad} & & \\
\end{array}\\
\begin{vmatrix}
1 & 1 & \cdots & 1 & 1 & 0 & 0 & \cdots & \boldsymbol{I} & \cdots & 0\\
\lambda_1 & \lambda_2 & \cdots & \lambda_u & 0 & 1 & 0 & \cdots & \boldsymbol{K} & \cdots & 0\\
\lambda_1^2 & \lambda_2^2 & \cdots & \lambda_u^2 & 0 & 0 & 1 & \cdots & \boldsymbol{K}^2 & \cdots & 0\\
\vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & & \vdots & & \vdots\\
\lambda_1^{c-2} & \lambda_2^{c-2} & \cdots & \lambda_u^{c-2} & 0 & 0 & 0 & \cdots & \boldsymbol{K}^{c-2} & \cdots & 0\\
\lambda_1^{c-1} & \lambda_2^{c-1} & \cdots & \lambda_u^{c-1} & 0 & 0 & 0 & \cdots & \boldsymbol{K}^{c-1} & \cdots & \\
\lambda_1^{c} & \lambda_2^{c} & & \lambda_u^{c} & 0 & 0 & 0 & \cdots & \boldsymbol{K}^{c} & \cdots & 0\\
\vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & & \vdots & & \vdots\\
\lambda_1^{n-1} & \lambda_2^{n-1} & \cdots & \lambda_u^{n-1} & 0 & 0 & 0 & & \boldsymbol{K}^{n-1} & \cdots &
\end{vmatrix}
\end{array}
$$

(p_h=0,1,2,…,c-1) (B1)

If the determinant above is expanded by the entries on the first column, from the (u+1)-th one, and then again by the entries on the first column from the (u+1)-th one different of the column of matrices, and so forth, the result is:

$$
\boldsymbol{\Lambda}_{u+1+p_h} = (-1)^{u\cdot(c-1)}
\begin{vmatrix}
\lambda_1^{p_h} & \lambda_2^{p_h} & \cdots & \lambda_u^{p_h} & \boldsymbol{K}^{p_h}\\
\lambda_1^{c} & \lambda_2^{c} & \cdots & \lambda_u^{c} & \boldsymbol{K}^{c}\\
\lambda_1^{c+1} & \lambda_2^{c+1} & \cdots & \lambda_u^{c+1} & \boldsymbol{K}^{c+1}\\
\vdots & \vdots & & \vdots & \vdots\\
\lambda_1^{n-1} & \lambda_2^{n-1} & \cdots & \lambda_u^{n-1} & \boldsymbol{K}^{n-1}
\end{vmatrix}
\qquad (p_h=0,1,2,\ldots,c-1) \qquad \text{(B2)}
$$

From eq. (B2) one obtains that matrix $\boldsymbol{\Lambda}_{u+1+p_h}$ is given by:

$$\boldsymbol{\Lambda}_{u+1+p_h} = (-1)^{u(c-1)}\left(\prod_{i=1}^{u}\lambda_i^{p_h}\right)\boldsymbol{K}^{p_h}\begin{vmatrix} 1 & 1 & \cdots & 1 & \boldsymbol{I} \\ \lambda_1^{c-p_h} & \lambda_2^{c-p_h} & \cdots & \lambda_u^{c-p_h} & \boldsymbol{K}^{c-p_h} \\ \lambda_1^{c+1-p_h} & \lambda_2^{c+1-p_h} & \cdots & \lambda_u^{c+1-p_h} & \boldsymbol{K}^{c+1-p_h} \\ \vdots & \vdots & & \vdots & \vdots \\ \lambda_1^{n-1-p_h} & \lambda_2^{n-1-p_h} & \cdots & \lambda_u^{n-1-p_h} & \boldsymbol{K}^{n-1-p_h} \end{vmatrix} \quad (p_h=0,1,\ldots,c\text{-}1) \quad \text{(B3)}$$

If the MD in eq. (B2) is expanded by the entries on the first row it yields:

$$\begin{vmatrix} 1 & 1 & \cdots & 1 & \boldsymbol{I} \\ \lambda_1^{c-p_h} & \lambda_2^{c-p_h} & \cdots & \lambda_u^{c-p_h} & \boldsymbol{K}^{c-p_h} \\ \lambda_1^{c+1-p_h} & \lambda_2^{c+1-p_h} & \cdots & \lambda_u^{c+1-p_h} & \boldsymbol{K}^{c+1-p_h} \\ \vdots & \vdots & & \vdots & \vdots \\ \lambda_1^{n-1-p_h} & \lambda_2^{n-1-p_h} & \cdots & \lambda_u^{n-1-p_h} & \boldsymbol{K}^{n-1-p_h} \end{vmatrix} =$$

$$= \sum_{h=1}^{u}\left\{(-1)^{h+1}\left(\prod_{\substack{p=1\\p\neq h}}^{u}\lambda_p^{c-p_h}\right)\left(\prod_{\substack{a,b=1\\a>b\\a,b\neq h}}^{u}(\lambda_a-\lambda_b)\right)\boldsymbol{K}^{c-p_h}\left(\prod_{\substack{p=1\\p\neq h}}^{u}(\boldsymbol{K}-\lambda_p\boldsymbol{I})\right)\right\}+$$

$$+\left\{(-1)^{u}\boldsymbol{I}\left(\prod_{p=1}^{u}\lambda_p^{c-p_h}\right)\left(\prod_{\substack{a,b=1\\a>b}}^{u}(\lambda_a-\lambda_b)\right)\right\} \qquad (c=1,2,\ldots,n\text{-}1;p_h=0,1,\ldots c\text{-}1) \quad \text{(B4)}$$

If now eq. (B4) is inserted into eq. (B3), it is obtained:

$$\boldsymbol{\Lambda}_{u+1+p_h} = (-1)^{u.c}\sum_{h=1}^{u}\left\{(-1)^{u+h+1}\left(\lambda_h^{p_h}\prod_{\substack{p=1\\p\neq h}}^{h}\lambda_p^{c}\right)\left(\prod_{\substack{a,b=1\\a>b\\a,b\neq h}}^{u}(\lambda_a-\lambda_b)\right)\boldsymbol{K}^{c}\left(\prod_{\substack{p=1\\p\neq h}}^{u}(\boldsymbol{K}-\lambda_p\boldsymbol{I})\right)\right\}+$$

$$+(-1)^{u.c}\left\{\boldsymbol{K}^{p_h}\left(\prod_{p=1}^{u}\lambda_p^{c}\right)\left(\prod_{\substack{a,b=1\\a>b}}^{u}(\lambda_a-\lambda_b)\right)\right\} \qquad (p_h=0,1,\ldots c\text{-}1) \quad \text{(B5)}$$

Hence, if eq. (B5) is inserted into eq. (31), we have:

$$\boldsymbol{A}_{u+1,p_h} = \frac{1}{p_h!}\sum_{h=1}^{u}\frac{(-1)^u \lambda_h^{p_h}\boldsymbol{K}^c\left(\prod_{\substack{p=1\\p\neq h}}^{u}(\boldsymbol{K}-\lambda_p\boldsymbol{I})\right)\boldsymbol{X}^0}{\lambda_h^c\prod_{\substack{p=1\\p\neq h}}^{u}\left(\lambda_p-\lambda_h\right)} + \boldsymbol{K}^{p_h}\boldsymbol{X}^0 \quad (p_h=0,1,\ldots c\text{-}1) \tag{B6}$$

and then if eq. (43) is inserted into eq. (B6) eq. (47) in the main text is obtained.

Appendix C

Derivation of eqs. (53) and (70) in the main text

Eq. (32) is obtained as a particular case of eq. (26) in paper I when there are u non-null, simple eigenvalues of $\boldsymbol{K}$ and one null eigenvalue of $\boldsymbol{K}$ of multiplicity c. But, if each minor $D_{k,i}(\lambda)$ has one null root and the less multiplicity of them is m, then eq. (32) becomes simplified. Effectively, reasoning in the same way as in Appendix A we have:

$$L(\boldsymbol{X}) = -\frac{adj(\boldsymbol{K}-\lambda\boldsymbol{I})\cdot\boldsymbol{X}^0}{D(\lambda)} \tag{C1}$$

where $D(\lambda)$ is given by eq. (5). If we take λ^m factor commun in the minors $D_{k,i}(\lambda)$ we obtain:

$$adj(\boldsymbol{K}-\lambda\boldsymbol{I}) = \lambda^m d(\boldsymbol{K}-\lambda\boldsymbol{I}) \tag{C2}$$

eq. (C1) can be written as:

$$L(\boldsymbol{X}) = -\frac{d(\boldsymbol{K}-\lambda\boldsymbol{I})\cdot\boldsymbol{X}^0}{\lambda^{c'}\prod_{p=1}^{u}\left(\lambda-\lambda_p\right)} \tag{C3}$$

with $c'=c-m$

Eq. (C3) can be expressed as the following sum:

$$-\frac{d(\boldsymbol{K}-\lambda\boldsymbol{I})\cdot\boldsymbol{X}^0}{\lambda^{c'}\prod_{p=1}^{u}\left(\lambda-\lambda_p\right)} = \sum_{p_h=0}^{c'-1}\frac{\boldsymbol{A}_{u+1,p_h}}{\lambda^{p_h}} + \sum_{h=1}^{u}\frac{\boldsymbol{A}_{h,0}}{\lambda-\lambda_h} \tag{C4}$$

By combining eqs. (C3) and (C4) one has:

$$L(\boldsymbol{X}) = \sum_{p_h=0}^{c'-1} \frac{\boldsymbol{A}_{u+1,0,p_h}}{\lambda^{p_h}} + \sum_{h=1}^{u} \frac{\boldsymbol{A}_h}{\lambda - \lambda_h} \tag{C5}$$

and taking the Laplace inverse transformation in both sides of eq. (C5), eq. (52) in the main text is found. Finally, by comparing eqs. (53) and (32) eq. (70) results.

Appendix D

Derivation of eq. (67) in the main text.

Eq. (66) can be written as:

$$A_{i,0} = (-1)^u \sum_{k=1}^{n} x_k^0 \left(\sum_{q=0}^{u} (f_{k,i})_q \left(\sum_{h=1}^{u} \frac{1}{\lambda_h^{1-u+q} \prod_{\substack{p=1 \\ p\neq h}}^{u} \left(\lambda_p - \lambda_h\right)} \right)\right) + x_i^0 \qquad \text{(D1)}$$

In eq.(D1) the sum:

$$\sum_{h=1}^{u} \frac{1}{\lambda_h^{1-u+q} \prod_{p=1}^{u} \left(\lambda_p - \lambda_h\right)} \qquad \text{(D2)}$$

adopts the form:

$$\sum_{h=1}^{u} \frac{1}{\lambda_h^{r} \prod_{\substack{p=1 \\ p\neq h}}^{u} (\lambda_p - \lambda_h)} \qquad (u=1,2,3,\ \ldots;\ r \text{ is an integer number}) \qquad \text{(D3)}$$

where r=1-u+q (q=0,1,2,…,u). In the following we will write r_q instead of r to indicate that r depends on q, i.e.:

$$r_q=1-u+q \qquad \text{(D4)}$$

There is a mathematical algorithm [39, 63, 64], which is summarized in Appendix A of ref. [65] (Ap66 in the following), which provides easily the sum indicated in (D2). We make here a little adaptation of the expressions in Ap66 consisting in replacing in them n by

u, r by r_q and v by q. Moreover, this algorithm allows us to express the sum in (D2) as a function of the coefficients F_1, F_2,…, F_u involved in polynomial $T(\lambda)$. The results of the sums depend on the relative values of u and r_q and of whether r_q is positive, negative or null.

If in eq. (D1) we replace the expression for the sum (D2) by that given in eq. (A1) in Ap66, one obtains:

$$\mathrm{A}_{i,0} = (-1)^u \sum_{k=1}^{n} x_k^0 \left(\sum_{q=0}^{u} (f_{k,i})_q Q(u, r_q) \right) + x_i^0 \tag{D5}$$

In turn, the expressions of the sums $Q(u,r_q)$ are given by eqs. (A2)-(A8) in Ap66 mentioned by replacing in them n by u and r por r_q and they depend on u and r_q. In Table D1 we show the values or expressions of Q(u,r_q) corresponding to each of the different possible q-values (0,1,2,…,u).

Table D1

Values of q (q=0,1,…u) in r_q [obtained from eq. (D4)], and values or expressions of the corresponding quantities $Q(u,r_q)$ (obtained as describe in Ap66). On the second row of the table, in light grey shaded, the values of r_q, $-r_q$ and $Q(u,r_q)$ corresponding to q = 0. On the row that follow are indicated in dark grey shaded these same values for those values of q for which r_q is negative and $-r_q < u-1$. On the penultimate row, in white shaded, the above values for the q-value for which r_q = 0. The r_q, $-r_q$ and the expression of $Q(u,r_q)$ for the highest possible value q, i.e. u, are indicated on the last row. Note that, except for q =0 and q=u, it is fulfilled $Q(u,r_q)$=0.

q	r_q	$-r_q$	$Q(u,r_q)$
0	$1-u$	$u-1$	$(-1)^{u-1}$
1	$2-u$		0
⋮	⋮	⋮	⋮
$u-2$	-1	1	0
	0	0	0
u	1	-1	$(-1)^u / F_u$

If the results in Table D1 are taken into account in eq. (D5), eq. (67) in the main text results.

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