**MATCH**
*Communications in Mathematical and in Computer Chemistry*

MATCH Commun. Math. Comput. Chem. **68** (2012) 477-502

ISSN 0340 - 6253

# A Novel Procedure to Analyse the Kinetics of Multicompartmental Linear Systems. I. General Equations

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(Received December 22, 2011)

## Abstract

A new, alternative, procedure for determining the kinetic behaviour of any linear compartmental systems with inputs zero, open or closed, with or without traps, is proposed. The equations for the time course of the amount of matter in the different compartments of the system have been derived without any restriction as regards the properties of the matrix of the corresponding set of linear differential equations or the multiplicities of its eigenvalues which circumvents some of the limitations of previous contributions. The equations obtained are general and can be applied to any engineering, chemical, biological, biochemical, pharmacological, physical and other systems that can be modelized as a linear compartmental system, irrespective of its complexity and/or structure.

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# 1. Introduction

Linear multicompartmental models are applicable to many fields of the Chemistry, Biology, Biochemistry, Physics, Pharmacology and Engineering [1-29]. The kinetic studies of these models require to solve a set of differential equations, ordinary, linear, first order and with constant coefficients [2,3,8,9,12,30,31]. From the analytical solution and experimental data can be proposed kinetic data analyses and experimental designs for evaluation of the kinetic parameters involved in the linear compartmental system under study. From an operational point of view a linear multicompartmental model could be defined as any physical, chemical, engineering, pharmacological, etc. system whose kinetic behaviour, i.e., the instantaneous amount of matter in each of the compartments, can be described by a linear set of differential equations. In this contribution we will limit ourselves to consider the most frequent case in literature, i.e., that the system of differential equations is homogeneous [30, 32-34].

For simple linear compartmental systems, usually with two, three or four compartments, there are many contributions in the literature that provide the explicit expressions of the instantaneous amount of matter in the compartments [9,16,35,36]. However, to our knowledge, the analytical solutions for a general model of this type of system respond to the following two situations:

(a) The kinetic equations are not given in a general way since do not contain explicitly the transfer or excretion constants, and this requires a considerable additional mathematical work when these equations are applied to specific linear compartmental systems. Moreover, in their derivation it is generally assumed that all the eigenvalues of the matrix of the coefficients, ***K*,** are simple. In practice, open compartmental systems without traps, whose matrix K is non-singular, are the most frequently studied because they are easier to analyze, apart of their intrinsic importance [7-9,13,18]. As regards closed compartmental systems, the matrix ***K*** of which always is singular, they have been also studied [1,12,31], but in this case the null eigenvalue of ***K*** can have a multiplicity higher than the unity what complicates the obtaining of the corresponding analytical solution as it happens in some enzyme systems which can be modeled as linear compartmental systems [12,30,31]. Obviously, the assumption of no multiplicity of the eigenvalues of the matrix ***K*** greatly facilitates the derivation of the equations. But besides its theoretical interest, the existence of multiple eigenvalues, although not very frequent, occurs in real systems depending on the structure of the compartment system and the relative values of the transfer and excretion constants involved. Thus, as above commented, some real closed compartmental systems have a null eigenvalue of multiplicity greater than the unity. It is also possible to find non null eigenvalues of multiplicity greater than the unity in certain compartmental systems and for certain values of the transfer constants (see, for example the case 2 of the example given below in this contribution). Segre [7] rejects the possibility of the existence of multiple eigenvalues in real systems, which obviously, is not always satisfied.

(b) The equations are in an explicit general way showing the dependence of the instant amount of matter in the compartments on time, as well as their relationship with the fractional transfer or excretion (if any) coefficients and the initial quantities of matter in each compartment. These expressions, however, are limited to compartmental systems where the matrix $\boldsymbol{K}$ has two simplifying features: (1) each element of its main diagonal is non positive and equal, in absolute value, to the sum of the remaining elements of the same column, that are non negative [2,30]; and (2) it is arbitrarily assumed that its non-null eigenvalues are simple, and its null eigenvalue (that always exits, in these cases) being of any multiplicity [12,30,31]. However, there are systems, such as enzyme systems of zymogen activation, which under certain experimental conditions can be modelized as a linear systems of compartments, in which the condition (1) is not satisfied [37-40]. Moreover, the multiplicity of one or more of the non-null eigenvalues, although unlikely in practice, can occur, and its consideration has the interest of increasing the generality of the results.

To overcome the limitations outlined above, the purpose of this contribution is to propose a new procedure for determining the explicit kinetic equations amount of matter-time in the linear compartmental systems without any restriction with regard to the properties of the matrix of the set of differential equations and the multiplicities of its eigenvalues. Obviously, these equations contain, as particular cases, the compartmental linear systems in which one or both of the above conditions (1) and (2) are fulfilled, and those cases in which all eigenvalues or only the non-null one are simple, regardless of the other properties of the system matrix. From these results, the equations for the various situations indicated are obtained in a companion contribution.

## 2. Notation/Definitions

$n$: Number of the compartments of the system

$X_i$ (i=1,2,…,$n$): *i-th* compartment of the compartmental system

$t$: time

$x_i$ ($i$=1,2,…,$n$): Instantaneous amount of matter in the compartment $X_i$

$x_i^0$ ($i$=1,2,…,$n$): Value of $x_i$ at $t$=0

$x_i^{(m)}$ ($i$=1,2,…,$n$; $m$=0,1,2,….): $m$-th time derivative of $x_i$ ($x_i^{(0)} = x_i$)

$\boldsymbol{X}$ : $n$ x 1 column vector the $i$-th element of which is $x_i$

$\boldsymbol{X}^0$ : $n$ x 1 column vector the $i$-th component of which is $x_i^0$

$\boldsymbol{X}^{(m)}$ : $n$ x 1 column vector the $i$-th component of which is $x_i^{(m)}$

$\boldsymbol{K}$ : a $n$-th order square, constant matrix

$K_{i,j}$ ($i$,$j$=1,2,…,$n$; $i \neq j$): Transfer constant from compartment $X_i$ to the compartment $X_j$. It is always a non-negative quantity. It coincides also with the element of matrix $\boldsymbol{K}$ on the $j$-th column and on the $i$-th row

$K_{i,o}$: Excretion constant (if any excretion) from compartment $X_i$ to the environment. These excretion constants only can exist in open compartmental systems

$K_{i,i}$ ($i$=1,2,...,$n$): Minus the sum of all the transfer and excretion constants (if any) corresponding to matter leaving the compartment $X_i$ to other compartments or to the environment. $K_{i,i}$ is always a non-positive quantity. It coincides also with the element on the $i$-th row and on the $i$-th column in matrix $\boldsymbol{K}$, i.e., the elements on the principal diagonal of $\boldsymbol{K}$. In many of the linear compartmental systems, but not in all of them, it is fulfilled the following relationship between $K_{i,i}$ and the transfer constants $K_{i,j}$ and the excretion constant (if any) $K_{i,o}$:

$$K_{i,i} = -\left( \sum_{\substack{j=1 \\ j \neq i}}^{n} K_{i,j} + K_{i,o} \right) \qquad (i=1,2,...,n) \qquad (1)$$

Obviously, for a closed compartmental system eq. (1) becomes:

$$K_{i,i} = -\sum_{\substack{j=1 \\ j\neq i}}^{n} K_{i,j} \qquad (i=1,2,...,n) \qquad (2)$$

The analysis carried out in the present contribution is independent of whether eqs. (1) and (2) fulfill or not. The enzyme systems involving zymogen activation under certain conditions are examples of linear compartmental systems in which eq. (1) is not accomplished [38-52].

$\boldsymbol{I}$ : $n$-th order unit matrix

$\boldsymbol{K}^m$ : $m$-th power of $\boldsymbol{K}$ ($m = 0,1,2,\ldots;\ \boldsymbol{K}^0 = \boldsymbol{I}$)

$\boldsymbol{B}_{0,i}$ : 1 x $n$ row matrix whose elements are all zero except the $i$-th one which is the unity

$\boldsymbol{B}_{j,i}$ : matrix define as:

$$\boldsymbol{B}_{j,i} = \boldsymbol{B}_{j-1,i}\boldsymbol{K} \quad (j=1,2,\ldots;\ i=1,2,\ldots,n) \qquad (3)$$

$q$: Number of different eigenvalues of matrix $\boldsymbol{K}$ ($q \leq n$)

$\lambda_h$ ($h$=1,2,…,$q$): an eigenvalue of matrix $\boldsymbol{K}$

$r_h$ ($h$=1,2,…,$q$): multiplicity of $\lambda_h$ ($r_h$=1,2,…, $n$)

$p_h$ : index that depend on $h$ and take values from 0,1,2,…,$r_h$-1

$$s_h = r_1 + r_2 + \cdots + r_{h-1} + 1 \quad (h=1,2,\ldots,q;\ s_1=1) \qquad (4)$$

Of course the notation $h$ for the subindex in the notations above could be replaced by any other figure, such as $j$ or other ones.

$\boldsymbol{A}_{h,p_h}$ ($h$=1,2,…,$q$; $p_h$=1,2,…, $r_{h-1}$): $n$ x 1 column vector the elements of which are constant

$\boldsymbol{G}_h(t)$ ($h$=1,2,…,$q$): Matrix given by the sum:

$$\boldsymbol{G}_h(t) = \left( \sum_{p_h=0}^{r_h-1} \boldsymbol{A}_{h,p_h} t^{p_h} \right) e^{\lambda_h t} \qquad (h=1,2,\ldots,q) \qquad (5)$$

$\boldsymbol{G}_h(t)^{(m)}$ : $m$-th time derivative of $\boldsymbol{G}_h(t)$ [$m$=0,1,…; $\boldsymbol{G}_h(t)^{(0)} = \boldsymbol{G}_h(t)$]

$\boldsymbol{G}_h(t)^{(m)}(0)$ : the matrix $\boldsymbol{G}_h(t)^{(m)}$ at $t = 0$

$\Delta$: $n$-th order determinant whose element on the $i$-th row and $(s_h + p_h)$-th column ($h$=1,2,…,$q$; $p_h$ = 0,1,…, $r_h - 1$) is:

$$\text{Element on the } i\text{-th row and } (s_h + p_h) \text{ column} = \begin{cases} 0 \text{ if } i-1 < p_h \\ 1 \text{ if } i=1 \text{ and } p_h = 0 \\ (i-1)(i-2)\cdots(i-p_h-1)\lambda_h^{i-p_h-1} \text{ in the remaining cases} \end{cases} \quad (6)$$

Note that **a** more compact and convenient way to give eq. (6) is:

$$\text{Element on the } i\text{-th row and } (s_h + p_h) \text{ column} = p_h!\binom{i-1}{p_h}\lambda_h^{i-p_h-1} \quad (7)$$

in which must be taken into account that $\binom{i-1}{p_h} = 0$ if $i$-1 < $p_h$. As an example, if $\lambda_1$, $\lambda_2$ and $\lambda_3$ are the eigenvalues of a 6-th order square matrix $\boldsymbol{K}$, its multiplicities being $r_1$=3, $r_2$=1 y $r_3$=2, respectively, then:

$$\Delta = \begin{vmatrix} 1 & 0 & 0 & 1 & 1 & 0 \\ \lambda_1 & 1 & 0 & \lambda_2 & \lambda_3 & 1 \\ \lambda_1^2 & 2\lambda_1 & 2 & \lambda_2^2 & \lambda_3^2 & 2\lambda_3 \\ \lambda_1^3 & 3\lambda_1^2 & 6\lambda_1 & \lambda_2^3 & \lambda_3^3 & 3\lambda_3^2 \\ \lambda_1^4 & 4\lambda_1^3 & 12\lambda_1^2 & \lambda_2^4 & \lambda_3^4 & 4\lambda_3^3 \\ \lambda_1^5 & 5\lambda_1^4 & 20\lambda_1^3 & \lambda_2^5 & \lambda_3^5 & 5\lambda_3^4 \end{vmatrix} \quad (8)$$

where the values of the combinatory numbers have been used.

$\Lambda$: $n$-th order determinant whose element of the $i$-th row and $(s_h + p_h)$-th column ($h$=1,2,…,$q$; $p_h$ = 0,1,…, $r_h - 1$) is:

Element on the $i$-th row and $(s_h + p_h)$ column $= \binom{i-1}{p_h}\lambda_h^{i-p_h-1}$ (9)

in which must be taken into account that $\binom{i-1}{p_h} = 0$ if $i$-1 < $p_h$. As an example, if $\lambda_1$, $\lambda_2$ and $\lambda_3$ are the eigenvalues of a 6-th order square matrix $\boldsymbol{K}$, its multiplicities being $r_1$=3, $r_2$=1 y $r_3$=2, respectively, then:

$$\Lambda = \begin{vmatrix} \binom{0}{0} & 0 & 0 & \binom{0}{0} & \binom{0}{0} & 0 \\ \binom{1}{0}\lambda_1 & \binom{1}{1} & 0 & \binom{1}{0}\lambda_2 & \binom{1}{0}\lambda_3 & \binom{1}{1} \\ \binom{2}{0}\lambda_1^2 & \binom{2}{1}\lambda_1 & \binom{2}{2} & \binom{2}{0}\lambda_2^2 & \binom{2}{0}\lambda_3^2 & \binom{2}{1}\lambda_3 \\ \binom{3}{0}\lambda_1^3 & \binom{3}{1}\lambda_1^2 & \binom{3}{2}\lambda_1 & \binom{3}{0}\lambda_2^3 & \binom{3}{0}\lambda_3^3 & \binom{3}{1}\lambda_3^2 \\ \binom{4}{0}\lambda_1^4 & \binom{4}{1}\lambda_1^3 & \binom{4}{2}\lambda_1^2 & \binom{4}{0}\lambda_2^4 & \binom{4}{0}\lambda_3^4 & \binom{4}{1}\lambda_3^3 \\ \binom{5}{0}\lambda_1^5 & \binom{5}{1}\lambda_1^4 & \binom{5}{2}\lambda_1^3 & \binom{5}{0}\lambda_2^5 & \binom{5}{0}\lambda_3^5 & \binom{5}{1}\lambda_3^4 \end{vmatrix} \qquad (10)$$

or, in this another way where the meaning of the combinatory numbers has been taken into account:

$$\Lambda = \begin{vmatrix} 1 & 0 & 0 & 1 & 1 & 0 \\ \lambda_1 & 1 & 0 & \lambda_2 & \lambda_3 & 1 \\ \lambda_1^2 & 2\lambda_1 & 1 & \lambda_2^2 & \lambda_3^2 & 2\lambda_3 \\ \lambda_1^3 & 3\lambda_1^2 & 3\lambda_1 & \lambda_2^3 & \lambda_3^3 & 3\lambda_3^2 \\ \lambda_1^4 & 4\lambda_1^3 & 6\lambda_1^2 & \lambda_2^4 & \lambda_3^4 & 4\lambda_3^3 \\ \lambda_1^5 & 5\lambda_1^4 & 10\lambda_1^3 & \lambda_2^5 & \lambda_3^5 & 5\lambda_3^4 \end{vmatrix} \qquad (11)$$

$\boldsymbol{\Delta}_{s_h+p_h}$: $n$-th order square matrix arising if in determinant $\Delta$ the $(s_h+p)$-th column is replaced by the column of matrices:

$$\begin{matrix} \boldsymbol{I} \\ \boldsymbol{K} \\ \boldsymbol{K}^2 \\ \vdots \\ \boldsymbol{K}^{n-1} \end{matrix} \tag{12}$$

Hence, for example, if in determinant $\Delta$ the third column ($s_1$=1, $p_h$=2; $s_h$+$p_h$=3) is replaced by column (12), we have:

$$\Delta_3 = \begin{vmatrix} 1 & 0 & \boldsymbol{I} & 1 & 1 & 0 \\ \lambda_1 & 1 & \boldsymbol{K} & \lambda_2 & \lambda_3 & 1 \\ \lambda_1^2 & 2\lambda_1 & \boldsymbol{K}^2 & \lambda_2^2 & \lambda_3^2 & 2\lambda_3 \\ \lambda_1^3 & 3\lambda_1^2 & \boldsymbol{K}^3 & \lambda_2^3 & \lambda_3^3 & 3\lambda_3^2 \\ \lambda_1^4 & 4\lambda_1^3 & \boldsymbol{K}^4 & \lambda_2^4 & \lambda_3^4 & 4\lambda_3^3 \\ \lambda_1^5 & 5\lambda_1^4 & \boldsymbol{K}^5 & \lambda_2^5 & \lambda_3^5 & 5\lambda_3^4 \end{vmatrix} \tag{13}$$

The matrices $\boldsymbol{\Delta}_{s_h+p_h}$ are obtained by replacing in the corresponding determinant $\Delta$ the column $(s_h+p_h)$-th by the column of matrices (12). Thus, the result of this action is a matrix given in the same form as that used for the determinants, but the expansion of this “apparent determinant” is really a $n$-th order square matrix (see example in Results and Discussion section). In the following, we will refer to these kinds of matrices as “matrix-determinant”, abbreviated MD.

$\boldsymbol{\Lambda}_{s_h+p_h}$ : $n$-th order square matrix arising when in in determinant $\Lambda$ the $(s_h+p_h)$-th column is replaced by the column of matrices (12). For example, if in determinant $\Lambda$ the third column ($s_1$=1; $p_h$=2; $s_h$+$p_h$=3) ) is replace by column (12), we have:

$$\boldsymbol{\Lambda}_3 = \begin{vmatrix} 1 & 0 & \boldsymbol{I} & 1 & 1 & 0 \\ \lambda_1 & 1 & \boldsymbol{K} & \lambda_2 & \lambda_3 & 1 \\ \lambda_1^2 & \lambda_1 & \boldsymbol{K}^2 & \lambda_2^2 & \lambda_3^2 & 2\lambda_3 \\ \lambda_1^3 & 3\lambda_1^2 & \boldsymbol{K}^3 & \lambda_2^3 & \lambda_3^3 & 3\lambda_3^2 \\ \lambda_1^4 & 4\lambda_1^3 & \boldsymbol{K}^4 & \lambda_2^4 & \lambda_3^4 & 4\lambda_3^3 \\ \lambda_1^5 & 5\lambda_1^4 & \boldsymbol{K}^5 & \lambda_2^5 & \lambda_3^5 & 5\lambda_3^4 \end{vmatrix} \tag{14}$$

Note that matrices $\boldsymbol{\Lambda}_{s_h+p_h}$ are MD matrices.

## 3. Theory

The kinetic behaviour of a linear compartmental system with inputs zero can be described by the following homogeneous system of differential, ordinary, linear, first order and constant coefficients:

$$\boldsymbol{X}^{(1)} = \boldsymbol{KX} \tag{15}$$

Integrating this system with the initial condition t = $0, \boldsymbol{X} = \boldsymbol{X}^0$, the Laplace transformation method allows us to write:

$$\boldsymbol{X} = \sum_{h=1}^{q} \boldsymbol{G}_h(t) \tag{16}$$

where $\boldsymbol{G}_h(t)$ is given by eq. (4).

From eq. (15) and taking eq. (16) into account, it results:

$$\boldsymbol{X}^{(m)} = \sum_{h=1}^{q} \boldsymbol{G}_h(t)^{(m)} \qquad (m = 0,1,\ldots;\ h = 1,2,\ldots,q) \tag{17}$$

The elements of the matrix $\boldsymbol{K}$ are constant, and we find by recurrence:

$$\boldsymbol{X}^{(m)} = \boldsymbol{K}^m \boldsymbol{X} \tag{18}$$

and by combining eqs. (17) and (18):

$$\boldsymbol{K}^m \boldsymbol{X} = \sum_{h=1}^{q} \boldsymbol{G}_h(t)^{(m)} \quad (m = 0,1,2,\ldots) \tag{19}$$

On the other hand, elementary algebra gives:

$$\boldsymbol{G}_h(t)^{(m)}(0) = \sum_{w=0}^{m} c_{m,w} \lambda_h^{m-w} \boldsymbol{A}_{h,w} \qquad (m{=}0,1,2,...) \tag{20}$$

where:

$$c_{m,w} = \begin{cases} w!\binom{m}{w} & \text{if } w \le r_h\text{-}1 \\ 0 & \text{if } w > r_h\text{-}1 \end{cases} \tag{21}$$

If $m \le r_h$-1 the number of terms on the right side of eq. (13) is $m$+1, and if $m > r_h$-1 this number is $r_h$.

If in eq. (19) $m$ takes the values 0,1..,$n$-1 and for each $m$ value we set t=0, it is obtained, taking eq. (20) into account, a system of algebraic linear equations, the unknowns of which are the columns matrices $\boldsymbol{A}_{h,p_h}$ ($h$ =1,2,…, $q$; $p_h$ =1,2,…, $r_h - 1$). Using the Cramer's rule, the solution of this system is:

$$\boldsymbol{A}_{h,p_h} = \frac{\boldsymbol{\Delta}_{s_h+p_h}\boldsymbol{X}^0}{\Delta} \quad (h=1,2,\ldots,q;\, p_h=0,1,2,\ldots,\, r_h-1) \tag{22}$$

If each of the $s_j+p_j$ ($j$=1,2,...,$q$; $p_j$ = 0,1,2,...,$r_j$-1) columns in determinant $\Lambda$ is multiplied by the corresponding $p_j!$ , determinant $\Lambda$ becomes determinant $\Delta$ , i.e.:

$$\Delta = \left[\prod_{j=1}^{q}\left(\prod_{p_j=0}^{r_j-1} p_j!\right)\right]\Lambda \tag{23}$$

Hence, if each of the $s_j+p_j$ ($j$=1,2,...,$q$; $p_j$ = 0,1,2,...,$r_j$-1) columns in this matrix $\boldsymbol{\Lambda}_{s_h+p_h}$ is multiplied by the corresponding $p_j!$, and the column $(s_h+p_h)$-th divided by $p_h!$, matrix $\boldsymbol{\Lambda}_{s_h+p_h}$ becomes matrix $\boldsymbol{\Delta}_{s_h+p_h}$ , i.e.:

$$\boldsymbol{\Delta}_{s_h+p_h} = \frac{1}{p_h!}\left[\prod_{j=1}^{q}\left(\prod_{p_j=0}^{r_j-1} p_j!\right)\right]\boldsymbol{\Lambda}_{s_h+p_h} \quad (s_h+p_h=1,2,\ldots,n) \tag{24}$$

Eqs. (23) and (24) allows us to write eq. (22) as:

$$\boldsymbol{A}_{h,p_h} = \frac{\boldsymbol{\Lambda}_{s_h+p_h}\boldsymbol{X}^0}{p_h!\Lambda} \quad (h = 1,2,\ldots,q;\, p_h = 0,1,2,\ldots,\, r_h-1) \tag{25}$$

Eq. (25) allows us to calculate the matrices $\boldsymbol{A}_{h,p_h}$ .

By combining eqs. (16) and (5) it is obtained the following expression for the matrix $\boldsymbol{X}$ as a function of $t$, the matrices $\boldsymbol{A}_{h,p_h}$ given by eq. (25), the eigenvalues and the corresponding initial conditions given by the matrix $\boldsymbol{X}^0$ :

$$\boldsymbol{X} = \sum_{h=1}^{q}\left(\sum_{p_h=0}^{r_h-1} \boldsymbol{A}_{h,p_h} t^{p_h}\right)e^{\lambda_h t} \tag{26}$$

To assess the validity of the method it is necessary to prove that determinants type $\Lambda$ are non-zero. In Appendix we prove that these determinants can be expressed as:

$$\Lambda = \prod_{\substack{a,b \\ a>b}}^{q} \left(\lambda_a - \lambda_b\right)^{r_a r_b} \qquad (\Lambda = 1 \text{ if } q = 1) \tag{27}$$

and because $a \neq b$, and therefore $\lambda_a \neq \lambda_b$, it follows $\Lambda \neq 0$. For example, the determinant of eq. (11), from eq. (27), and having into account that $r_1$=3, $r_2$=1, $r_3$=2, is equal to $\left(\lambda_2 - \lambda_1\right)^3 \left(\lambda_3 - \lambda_1\right)^6 \left(\lambda_3 - \lambda_2\right)^2$.

Eq. (26) provides the time variation of the amount of matter in each of the compartments of a linear compartmental system with inputs zero irrespective of the properties of the matrix $\boldsymbol{K}$ and the multiplicities of its eigenvalues. For example, in the case of a linear compartmental system whose determinant $\Lambda$ is by **given** eq. (11), the application of eq. (26) leads to the following eq. (28):

$$\boldsymbol{X} = \left(\boldsymbol{A}_{1,0} + \boldsymbol{A}_{1,1}t + \boldsymbol{A}_{1,2}A_3 t^2\right)e^{\lambda_1 t} + \boldsymbol{A}_{2,0}e^{\lambda_2 t} + \left(\boldsymbol{A}_{3,0} + \boldsymbol{A}_{3,1}t\right)e^{\lambda_3 t} \tag{28}$$

where the expressions of the amplitudes $\boldsymbol{A}_{h,p_h}$ ($h$=1,2,3; $p_1$=0,1,2; $p_2$=0; $p_3$=0,1) are obtained using eq. (25) with $\boldsymbol{\Lambda}_1, \boldsymbol{\Lambda}_2, \ldots, \boldsymbol{\Lambda}_6$ being the resulting matrices when the first, second, sixth column in the determinant $\Lambda$ are replaced, respectively, by the column of matrices (12). For example, $\boldsymbol{A}_{1,2}$ (in this case $s_1$=$h$=1 y $p_h$=2) is given by:

$$\boldsymbol{A}_{1,2} = \frac{\boldsymbol{\Lambda}_3 \boldsymbol{X}^0}{2\Lambda} \tag{29}$$

with the DM matrix $\boldsymbol{\Lambda}_3$ and the determinant $\Lambda$ given by eq. (14) and (11), respectively.

## 4. Results and Discussion

We used the method of Laplace transform to obtain eq. (15), and from it, we have developed our own method to derive the general solution [eq. (26)].

Because the differential equations solved here belong to an ordinary first order, homogeneous, linear, with constant coefficients, system, our procedure can be also applied to solve analytically all sets of differential equations as the above described, independently of whether they are associated or not with a linear compartmental system.

In those cases where the complete solution of the set of differential equations (8) **is not required**, but only the t-dependence of $x_i$ (the $i$-th element of matrix $\boldsymbol{X}$; $i$=1,2,…,), the work can be simplified substituting in eq. (22) the square matrices $\boldsymbol{I}$, $\boldsymbol{K}$, $\boldsymbol{K}^2$,…, $\boldsymbol{K}^{n-1}$ by the row matrices $\boldsymbol{B}_{0,i}$, $\boldsymbol{B}_{1,i}$, $\boldsymbol{B}_{2,i}$,…, $\boldsymbol{B}_{n-1,i}$, respectively, and so we directly obtain the row element $i$-th of the column matrices $\boldsymbol{A}_{h,p_h}$

We want also to show that the method proposed here allows expressing $e^{t\boldsymbol{K}}$ in an alternative form. Indeed, since a particular solution of eq. (8) can also be expressed [53] as:

$$\boldsymbol{X} = e^{t\boldsymbol{K}}\boldsymbol{X}^0 \tag{30}$$

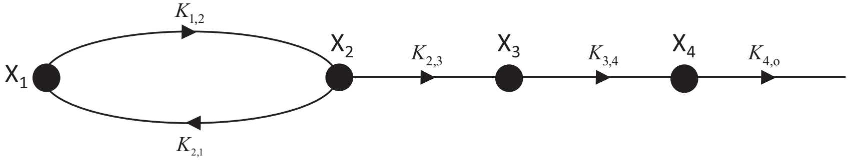
The comparison between eqs. (26) and (30) allows us to write, taking into account eq. (19):

$$e^{t\boldsymbol{K}} = \frac{1}{\Lambda}\sum_{h=1}^{q}\left(\sum_{p_h=0}^{r_h-1}\frac{1}{p_h!}\boldsymbol{\Lambda}_{s_h+p_h}t^{p_h}\right)e^{\lambda_h t} \tag{31}$$

Eq. (31) provides an alternative and explicit development of $e^{t\boldsymbol{K}}$ as a function of time and of the eigenvalues of the matrix $\boldsymbol{K}$. This general expression includes, as particular cases, other similar expressions which are only valid when all the eigenvalues are different ($q=n$, $p_h=0$, $r_h=1$, $s_h = h$ and $\Lambda$ the $n$-order Vandermonde's determinant whose 2nd row is $\lambda_1\ \lambda_2 \cdots \lambda_n$) [8,54]. According to Anderson [8] it is preferable to compute exp($t\boldsymbol{K}$) by using eigenvalues and functions of a matrix [54] rather than expand exp($t\boldsymbol{K}$) as an infinite series. On the other hand, a comparison of our results with the classical way of computing the matrix exponential by taking the inverse Laplace transform of the resolvent $(s\boldsymbol{I} - \boldsymbol{K})^{-1}$ shows: 1) for the case that all eigenvalues of $\boldsymbol{K}$ are simple, the calculation of the resolvent array $(s\boldsymbol{I} - \boldsymbol{K})^{-1}$ requires the same number of iterations that the method proposed by us; 2) If there is an eigenvalue with multiplicity greater than 1, the calculation of the resolvent matrix needs the same number of iterations but our method use less, because they are simultaneously managed; 3) In addition, resolvent matrix method also requires implementation of the inverse Laplace transform to move into the time domain, whereas our method directly gives the result in the variable $t$ [55-59].

## 4.1. Examples

In this section we will apply the above results to the linear compartmental system shown in Scheme 1. This system is open and consists of four compartments, $X_1$, $X_2$, $X_3$ and $X_4$, with transfer constants $K_{i,j}$ ($i$=1,2,3,4; $j$ =1,2,3; $i \neq j$) between compartments $X_i$ and $X_j$ ($i$=1,2,3,4; j=1,2,3; $i \neq j$) and excretion from compartment $X_4$ with a excretion constant equal to $K_{4,o}$. There is a zero input, $x_1^0$, in compartment $X_1$ and the time course of the amount of matter in the different compartments is derived. This example corresponds to a simple linear compartmental system to no excessively increase the length of the paper. Nevertheless, the example allows illustrating the application of the method without loss of generality. Obviously, the method shows its full power when it is applied to more complex linear compartmental systems.




**Scheme 1**

In this example $n$ = 4 and the matrices $\boldsymbol{X}^0$ y $\boldsymbol{K}$ are given by:

$$\boldsymbol{X}^0 = \begin{bmatrix} x_1^0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{32}$$

and

$$\boldsymbol{K} = \begin{bmatrix} K_{1,1} & K_{2,1} & 0 & 0 \\ K_{1,2} & K_{2,2} & 0 & 0 \\ 0 & K_{2,3} & K_{3,3} & 0 \\ 0 & 0 & K_{3,4} & K_{4,4} \end{bmatrix} \tag{33}$$

where

$$K_{1,1}=-K_{1,2} \tag{34}$$

$$K_{2,2}=-(K_{2,1}+K_{2,3}) \tag{35}$$

$$K_{3,3}=-K_{3,4} \tag{36}$$

$$K_{4,4}=-K_{4,o} \tag{37}$$

The eigenvalues of this matrix are:

$$\lambda_1 = \frac{-(K_{1,2}+K_{2,1}+K_{2,3})+\sqrt{(K_{1,2}+K_{2,1}+K_{2,3})^2-4K_{1,2}K_{2,3}}}{2} \tag{38}$$

$$\lambda_2 = \frac{-(K_{1,2}+K_{2,1}+K_{2,3})-\sqrt{(K_{1,2}+K_{2,1}+K_{2,3})^2-4K_{1,2}K_{2,3}}}{2} \tag{39}$$

$$\lambda_3 = -K_{3,4} \tag{40}$$

$$\lambda_4 = -K_{4,o} \tag{41}$$

Because $(K_{1,2}+K_{2,1}+K_{2,3})^2 - 4K_{1,2}K_{2,3} > 0$, the eigenvalues $\lambda_1$ and $\lambda_2$ are simple, different, real and negatives and between them the two following relationships are fulfilled:

$$\lambda_1 + \lambda_2 = -(K_{1,2}+K_{2,1}+K_{2,3}) \tag{42}$$

$$\lambda_1\lambda_2 = K_{1,2}K_{2,3} \tag{43}$$

It is convenient to distinguish two different cases labeled as cases 1 and 2. In case 1 $K_{3,4} \neq K_{4,0}$, while in case 2 $K_{3,4} = K_{4,0}$.

**Case 1:** $K_{3,4} \neq K_{4,0}$

In this case the four eigenvalues $\lambda_1$, $\lambda_2$, $\lambda_3$ and $\lambda_4$ are simple, i.e.:

$$r_1 = r_2 = r_3 = r_4 = 1 \tag{44}$$

so that from the definition of determinant $\Lambda$ we have:

$$\Lambda = \begin{vmatrix} 1 & 1 & 1 & 1 \\ \lambda_1 & \lambda_2 & \lambda_3 & \lambda_4 \\ \lambda_1^2 & \lambda_2^2 & \lambda_3^2 & \lambda_4^2 \\ \lambda_1^3 & \lambda_2^3 & \lambda_3^3 & \lambda_4^3 \end{vmatrix} \tag{45}$$

Note that, in this case, determinant $\Lambda$ is a Vandermonde's determinant. This happens only if all the eigenvalues are simple. Applying eq. (27), or that one for any Vandermonde's determinant, one obtains:

$$\Lambda = (\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)(\lambda_4 - \lambda_1)(\lambda_3 - \lambda_2)(\lambda_4 - \lambda_2)(\lambda_4 - \lambda_3) \tag{46}$$

Moreover, according to general eq. (26), the solution of the set of differential equations is:

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix} = \boldsymbol{A}_{1,0} e^{\lambda_1 t} + \boldsymbol{A}_{2,0} e^{\lambda_2 t} + \boldsymbol{A}_{3,0} e^{\lambda_1 t} + \boldsymbol{A}_{4,0} e^{\lambda_1 t} \tag{47}$$

where matrices $\boldsymbol{A}_{h,0}$ ($h$=1,2,3,4) are obtained by applying general eq. (25) to this particular case:

$$\boldsymbol{A}_{1,0} = \frac{\begin{vmatrix} \boldsymbol{I} & 1 & 1 & 1 \\ \boldsymbol{K} & \lambda_2 & \lambda_3 & \lambda_4 \\ \boldsymbol{K}^2 & \lambda_2^2 & \lambda_3^2 & \lambda_4^2 \\ \boldsymbol{K}^3 & \lambda_2^3 & \lambda_3^3 & \lambda_4^3 \end{vmatrix} \boldsymbol{X}^0}{\Lambda} \tag{48}$$

$$\boldsymbol{A}_{2,0} = \frac{\begin{vmatrix} 1 & \boldsymbol{I} & 1 & 1 \\ \lambda_1 & \boldsymbol{K} & \lambda_3 & \lambda_4 \\ \lambda_1^2 & \boldsymbol{K}^2 & \lambda_3^2 & \lambda_4^2 \\ \lambda_1^3 & \boldsymbol{K}^3 & \lambda_3^3 & \lambda_4^3 \end{vmatrix} \boldsymbol{X}^0}{\Lambda} \tag{49}$$

$$\boldsymbol{A}_{3,0} = \frac{\begin{vmatrix} 1 & 1 & \boldsymbol{I} & 1 \\ \lambda_1 & \lambda_2 & \boldsymbol{K} & \lambda_4 \\ \lambda_1^2 & \lambda_2^2 & \boldsymbol{K}^2 & \lambda_4^2 \\ \lambda_1^3 & \lambda_2^3 & \boldsymbol{K}^3 & \lambda_4^3 \end{vmatrix} \boldsymbol{X}^0}{\Lambda} \tag{50}$$

$$A_{4,0} = \frac{\begin{vmatrix} 1 & 1 & 1 & \boldsymbol{I} \\ \lambda_1 & \lambda_2 & \lambda_3 & \boldsymbol{K} \\ \lambda_1^2 & \lambda_2^2 & \lambda_3^2 & \boldsymbol{K}^2 \\ \lambda_1^3 & \lambda_2^3 & \lambda_3^3 & \boldsymbol{K}^3 \end{vmatrix} \boldsymbol{X}^0}{\Lambda} \tag{51}$$

In eqs. (48)-(52 ), $\lambda_1$, $\lambda_2$, $\lambda_3$ and $\lambda_4$ are given by eqs. (34)-(37), the matrices $\boldsymbol{K}$ and $\boldsymbol{X}^0$ by eqs. (33) and (32) and $\Lambda$ by eq. (38).

The matrices MD in the numerator of eqs. (48)-(51) can be obtained applying to them the formalism for expansion of determinants, e.g. the MD in eq. (51) can be expressed, considering that it is formally a Vandermonde's determinant as:

$$\begin{vmatrix} 1 & 1 & 1 & \boldsymbol{I} \\ \lambda_1 & \lambda_2 & \lambda_3 & \boldsymbol{K} \\ \lambda_1^2 & \lambda_2^2 & \lambda_3^2 & \boldsymbol{K}^2 \\ \lambda_1^3 & \lambda_2^3 & \lambda_3^3 & \boldsymbol{K}^3 \end{vmatrix} = (\lambda_2-\lambda_1)(\lambda_3-\lambda_1)(\lambda_3-\lambda_2)(\boldsymbol{K}-\lambda_1\boldsymbol{I})(\boldsymbol{K}-\lambda_2\boldsymbol{I})(\boldsymbol{K}-\lambda_3\boldsymbol{I}) \tag{52}$$

The MD above could also been obtained expanding by the elements of the last column, i.e.:

$$\begin{vmatrix} 1 & 1 & 1 & \boldsymbol{I} \\ \lambda_1 & \lambda_2 & \lambda_3 & \boldsymbol{K} \\ \lambda_1^2 & \lambda_2^2 & \lambda_3^2 & \boldsymbol{K}^2 \\ \lambda_1^3 & \lambda_2^3 & \lambda_3^3 & \boldsymbol{K}^3 \end{vmatrix} = -\lambda_1\lambda_2\lambda_3 \begin{vmatrix} 1 & 1 & 1 \\ \lambda_1 & \lambda_2 & \lambda_3 \\ \lambda_1^2 & \lambda_2^2 & \lambda_3^2 \end{vmatrix} \boldsymbol{I} + \begin{vmatrix} 1 & 1 & 1 \\ \lambda_1^2 & \lambda_2^2 & \lambda_3^2 \\ \lambda_1^3 & \lambda_2^3 & \lambda_3^3 \end{vmatrix} \boldsymbol{K} - \begin{vmatrix} 1 & 1 & 1 \\ \lambda_1 & \lambda_2 & \lambda_3 \\ \lambda_1^3 & \lambda_2^3 & \lambda_3^3 \end{vmatrix} \boldsymbol{K}^2 + \begin{vmatrix} 1 & 1 & 1 \\ \lambda_1 & \lambda_2 & \lambda_3 \\ \lambda_1^2 & \lambda_2^2 & \lambda_3^2 \end{vmatrix} \boldsymbol{K}^3 \tag{53}$$

Right side of eqs. (52) and (53) lead to the same $n$-th square matrix that multiplied by the $n$ x 1 column vector $\boldsymbol{X}^0$ and then dividing the resulting $n$ x 1 column vector by $\Lambda$ defined by eq. (46), provides the $n$ x 1 column vector $\boldsymbol{A}_{4,0}$ . Other possible ways to expand the MD in eqn. (52) are possible leading all of them to the same $n$ x $n$ square matrix.

The relationships (42) and (43) between $\lambda_1$ and $\lambda_2$ are useful to progress in the right side of eq. (51).

**Case 2:** $K_{3,4} = K_{4,0}$

Let be $K_{3,4}=K_{4,0}=k$. In this case the eigenvalues $\lambda_1$ and $\lambda_2$ are simple but $\lambda_3 = \lambda_4$, i.e. the matrix $\boldsymbol{K}$ has three eigenvalues, $\lambda_1$ and $\lambda_2$ given by eqs. (34) and (35) with $K_{3,4}=K_{4,0}=k$, and another eigenvalue, $\lambda_3$, of multiplicity 2, given by:

$$\lambda_3 = -k \qquad (54)$$

Therefore, in this case we have:

$$r_1 = r_2 = 1 \qquad (55)$$

$$r_3 = 2 \qquad (56)$$

$$\Lambda = \begin{vmatrix} 1 & 1 & 1 & 0 \\ \lambda_1 & \lambda_2 & \lambda_3 & 1 \\ \lambda_1^2 & \lambda_2^2 & \lambda_3^2 & 2\lambda_3 \\ \lambda_1^3 & \lambda_2^3 & \lambda_3^3 & 3\lambda_3^2 \end{vmatrix} \qquad (57)$$

Note that from eq. (26) $\Lambda$ adopts the form:

$$\Lambda = (\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)^2(\lambda_3 - \lambda_2)^2 \qquad (58)$$

Moreover, according to general eq. (26), the solution of the set of differential equations is:

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix} = \boldsymbol{A}_{1,0}e^{\lambda_1 t} + \boldsymbol{A}_{2,0}e^{\lambda_2 t} + (\boldsymbol{A}_{3,0} + \boldsymbol{A}_{3,1}e^{\lambda_3 t}) \qquad (59)$$

where matrices $\boldsymbol{A}_{h,0}$ ($h$=1,2,3) and $\boldsymbol{A}_{3,1}$ are obtained by applying general eq. (25) to this particular case:

$$\boldsymbol{A}_{1,0} = \frac{\begin{vmatrix} \boldsymbol{I} & 1 & 1 & 0 \\ \boldsymbol{K} & \lambda_2 & \lambda_3 & \lambda_3 \\ \boldsymbol{K}^2 & \lambda_2^2 & \lambda_3^2 & 2\lambda_3^2 \\ \boldsymbol{K}^3 & \lambda_2^3 & \lambda_3^3 & 3\lambda_3^3 \end{vmatrix} \boldsymbol{X}^0}{\Lambda} \qquad (60)$$

$$A_{2,0} = \frac{\begin{vmatrix} 1 & \boldsymbol{I} & 1 & 0 \\ \lambda_1 & \boldsymbol{K} & \lambda_3 & 1 \\ \lambda_1^2 & \boldsymbol{K}^2 & \lambda_3^2 & 2\lambda_3 \\ \lambda_1^3 & \boldsymbol{K}^3 & \lambda_3^3 & 3\lambda_4^3 \end{vmatrix} \boldsymbol{X}^0}{\Lambda} \tag{61}$$

$$A_{3,0} = \frac{\begin{vmatrix} 1 & 1 & \boldsymbol{I} & 0 \\ \lambda_1 & \lambda_2 & \boldsymbol{K} & 1 \\ \lambda_1^2 & \lambda_2^2 & \boldsymbol{K}^2 & 2\lambda_3 \\ \lambda_1^3 & \lambda_2^3 & \boldsymbol{K}^3 & 3\lambda_3^2 \end{vmatrix} \boldsymbol{X}^0}{\Lambda} \tag{62}$$

$$A_{3,1} = \frac{\begin{vmatrix} 1 & 1 & 1 & \boldsymbol{I} \\ \lambda_1 & \lambda_2 & \lambda_3 & \boldsymbol{K} \\ \lambda_1^2 & \lambda_2^2 & \lambda_3^2 & \boldsymbol{K}^2 \\ \lambda_1^3 & \lambda_2^3 & \lambda_3^3 & \boldsymbol{K}^3 \end{vmatrix} \boldsymbol{X}^0}{\Lambda} \tag{63}$$

In eqs. (60)-(63), $\lambda_1$, $\lambda_2$ and $\lambda_3$ are given by eqs. (38)-(39), the matrix $\boldsymbol{K}$ by eq. (33) where $K_{3,4}$=$K_{4,0}$ = $k$, $\boldsymbol{X}^0$ by eq. (32) and determinant $\Lambda$ by eq. (58). The matrices MD in the numerator of eqs. (60)-(62) can be obtained by applying to them the formalism for expansion of determinants, e.g. the matrix MD in eq. (60) can be expressed, by expanding it by the elements of the first column, as:

$$\begin{vmatrix} \boldsymbol{I} & 1 & 1 & 0 \\ \boldsymbol{K} & \lambda_2 & \lambda_3 & \lambda_3 \\ \boldsymbol{K}^2 & \lambda_2^2 & \lambda_3^2 & 2\lambda_3^2 \\ \boldsymbol{K}^3 & \lambda_2^3 & \lambda_3^3 & 3\lambda_3^3 \end{vmatrix} = \lambda_2\lambda_3^2 \begin{vmatrix} 1 & 1 & 1 \\ \lambda_2 & \lambda_3 & 2\lambda_3 \\ \lambda_2^2 & \lambda_3^2 & 3\lambda_3^2 \end{vmatrix} \boldsymbol{I} - \lambda_3 \begin{vmatrix} 1 & 1 & 0 \\ \lambda_2^2 & \lambda_3^2 & 2\lambda_3 \\ \lambda_2^3 & \lambda_3^3 & 3\lambda_3^2 \end{vmatrix} \boldsymbol{K} + \lambda_3 \begin{vmatrix} 1 & 1 & 0 \\ \lambda_2 & \lambda_3 & 1 \\ \lambda_2^3 & \lambda_3^3 & 3\lambda_3^2 \end{vmatrix} \boldsymbol{K}^2 - \lambda_3 \begin{vmatrix} 1 & 1 & 0 \\ \lambda_2 & \lambda_3 & 1 \\ \lambda_2^2 & \lambda_3^2 & 2\lambda_3 \end{vmatrix} \boldsymbol{K}^3 \tag{64}$$

Right side of eq. (64) leads to a $n$-th order square matrix that multiplied by the $n$ x 1 column vector $\boldsymbol{X}^0$ and then dividing the resulting $n$ x 1 column matrix by determinant $\Lambda$ given by eq. (58), gives the $n$ x 1 column vector $\boldsymbol{A}_{1,0}$.

One could think that the equations corresponding to case 2 can be obtained merely setting in the expressions corresponding to case 1 $\lambda_4 = \lambda_3$, $K_{3,4}$ = k and $K_{4,0}$= k. Proceeding in this way mathematical indeterminations arise which often are difficult and laborious to solve.

## 4.2. Final remarks

In this contribution we obtain the equations that provide the instantaneous amount of matter in the compartments of a linear compartmental system with zero inputs. To our knowledge, the procedure proposed in this paper, which is regardless of the properties of the matrix ***K*** of the system (i.e. if it is invertible or not, diagonal dominant or not, etc.) and the multiplicity of its null or not null eigenvalues, has not been previously described in the literature. The general eq. (26) has a wide applicability and can be directly applied to any open or closed compartmental linear system, with or without traps, simple or complex. However, for certain specific properties of the matrix ***K*** and the multiplicities of its eigenvalues, the general solution can be simplified, in some cases significantly. Simplification of eq. (26) when it is applied to certain linear systems of compartments that are found frequently in the analysis of dynamical systems will be the subject of the contribution II of this series.

# Appendix

### Derivation of eq. (26) in the main text

Let $\Lambda\left(\lambda_1, r_1; \lambda_2, r_2; ...; \lambda_q, r_q\right)$ be the determinant $\Lambda$ defined in the notation section where **there** are $r_1$ columns in which is involved $\lambda_1$, $r_2$ columns in which is involved $\lambda_2$,…,$r_q$ columns in which $\lambda_q$ is involved. In order to prove eq. (26) we proceed as follows:

1) From the second row, we subtract from each row of the determinant $\Lambda\left(\lambda_1, r_1; \lambda_2, r_2; ...; \lambda_q, r_q\right)$ the preceding row multiplied by $\lambda_1$, with which vanish all the elements of the first column except the first one, which remains the unit.

2) **Next**, we expand the resulting determinant using the elements of the first column and their corresponding cofactors and so it results a ($n$-1)-th order determinant, the $r_1$-1 first columns of which coincide with the $r_1$-1 first ones of the determinant $\Lambda\left(\lambda_1, r_1; \lambda_2, r_2; ...; \lambda_q, r_q\right)$, without, naturally, their last elements.

3) We take out from each ($s_h$-1)-th ($h$=2,3,…,$q$) column of this new determinant the common factor $\lambda_h - \lambda_1$ and so we have:

$$\Lambda\left(\lambda_1, r_1; \lambda_2, r_2; ...; \lambda_q, r_q\right) = E\prod_{h=2}^{q}\left(\lambda_h - \lambda_1\right) \tag{A1}$$

where E is ($n$-1)-th order determinant resulting in this step.

4) Then we substract from each ($s_h$-1 + $p_h$) –th (h=2, …, $q$, but if $r_h$ = 1, then $h$ must take the next possible value; $p_h$=1,2, …, $r_h$-1) column of determinant E the preceding one and we make out from each new ($s_h$-1 + $p_h$)–th ($h$=2, …, $q$; $p_h$=1,2, …, $r_h$-1) resulting column the factor $\lambda_h - \lambda_1$**.** Thus, it results:

$$E = \Lambda\left(\lambda_1, r_1 - 1; \lambda_2, r_2; ...;_q, r_q\right)\prod_{h=2}^{q}\left(\lambda_h - \lambda_1\right)^{r_h - 1} \tag{A2}$$

and from eqs. (A1) and (A2) it is obtained:

$$\Lambda\left(\lambda_1,r_1;\lambda_2,r_2,...,\lambda_q,r_q\right)=\Lambda\left(\lambda_1,r_1-1;\lambda_2,r_2;...;\lambda_q,r_q\right)\prod_{h=2}^{q}\left(\lambda_h-\lambda_1\right)^{r_h} \qquad \text{(A3)}$$

Obviously, if $r_1 = 1$ then $r_1$-1=0 what means that the column containing $\lambda_1$ is missing and, therefore $\Lambda\left(\lambda_1,r_1-1;\lambda_2,r_2;...;\lambda_q,r_q\right)=\Lambda\left(\lambda_2,r_2;...;\lambda_q,r_q\right)$, i.e. eq. (A3) coincides with eq. (A5) below and one must go to step 6). The same is valid whenever any of the multiplicities $r_h$ ($h$=1,2,...,$q$) is equal to the unity.

5) If we repeat the steps 1), 2), 3) and 4) with $\Lambda\left(\lambda_1,r_1-1;\lambda_2,r_2,...;\lambda_q,r_q\right)$, we obtain:

$$D\left(\lambda_1,r_1-1;\lambda_2,r_2,...,\lambda_q,r_q\right)=D\left(\lambda_1,r_1-2;\lambda_2,r_2,...,\lambda_q,r_q\right)\prod_{h=2}^{q}\left(\lambda_h-\lambda_1\right)^{r_h} \qquad \text{(A4)}$$

and so until a total of $r_1$ times, so that we have:

$$\Lambda\left(\lambda_1,r_1;\lambda_2,r_2,...,\lambda_q,r_q\right)=\Lambda\left(\lambda_2,r_2;...;\lambda_q,r_q\right)\left\{\prod_{h=2}^{q}\left(\lambda_h-\lambda_1\right)^{r_h}\right\}^{r_1} \qquad \text{(A5)}$$

6) Dealing with determinant $\Lambda\left(\lambda_2,r_2;...;\lambda_q,r_q\right)$ in an identical way as with the initial determinant, and so, one obtains, finally:

$$\Lambda\left(\lambda_1,r_1;\lambda_2,r_2,...,\lambda_q,r_q\right)=\Lambda\left(\lambda_q,r_q\right)\prod_{\substack{a,b\\a>b}}^{q}\left(\lambda_a-\lambda_b\right)^{r_a r_b} \qquad \text{(A6)}$$

Determinant $\Lambda\left(\lambda_q,r_q\right)$ is inferior and triangular, being the elements of its main diagonal equal to the unity and, therefore:

$$\Lambda\left(\lambda_q,r_q\right)=1 \qquad \text{(A7)}$$

If eq. (A7) is taking into account in eq. (A6) the result is eq. (17) in the main text.

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