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General Symbolic Expressions for Statistical Moments in Any Linear Compartmental System

R. Varon[a,*], J. M. Villalba[b], F. García-Sevilla[c], M. Garcia-Moreno[a], M. Molina-Alarcón [d], A. Barbero[e], M.J. García-Meseguer [d] and E. Arribas[f,*].

[a] *Departamento de Quimica-Fisica. Escuela de Ingenieros Industriales. Universidad de Castilla-La Mancha, Albacete, Spain*

[b] *Departamento de Ciencias Médicas. Facultad de Medicina. Universidad de Castilla-la Mancha, Albacete, Spain*

[c] *Departamento de Ingeniería Eléctrica, Electrónica, Automática y Comunicaciones. Escuela de Ingenieros Industriales. Universidad de Castilla-La Mancha, Albacete, Spain*

[d] *Departamento de Enfermería y Fisioterapia. Escuela Universitaria de Enfermería. Universidad de Castilla-La Mancha, Albacete, Spain*

[e] *Departamento de Física Aplicada. Escuela Técnica Superior de Ingenieros Agrónomos. Universidad de Castilla-la Mancha, Albacete, Spain*

[f] *Departamento de Física Aplicada. Escuela Superior de Ingeniería Informática. Universidad de Castilla-La Mancha, Albacete, Spain*

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Abstract

The use of statistical moments in the analysis of linear multicompartmental systems is most important in the forward problem; i.e., to obtain analytical symbolic expressions from a known linear compartmental system, and in the inverse problem; i.e., when estimating the involved fractional transfer constant from fitting experimental data to the symbolic equations. Nowadays, however, the use of these statistical moments is practically limited to the zeroth, or the first ones, and to very simple compartmental systems. In this work, we obtain general symbolic expressions as an explicit function of the fractional transfer constants for the statistical moments of any order and for any linear compartmental system, simple or complex, with zero input, open or closed, with or without traps. We apply the results to four examples. The numerical values of the statistical moments of different orders, together with the corresponding symbolic expressions, enable us to evaluate the different transfer constants involved in the linear compartmental system under study.

* Corresponding author, Departamento de Quimica-Fisica, Escuela de Ingenieros Industriales, Avenida de España s/n, E-02071 Albacete, Spain. Tel.: +34 967599200, ext. 2480, Fax: +34 967599224, e-mail: ramon.varon@uclm.es

The number of statistical moments obtained (of zero-, first-, second-, etc., order) depends on the number of fractional transfer constants to be evaluated. The proposed experimental design depends on the form of the corresponding symbolic equations for the moments. Finally, by using the general expression for the statistical moment, important pharmacokinetic parameters (such as AUC, AUMC and MRT) can be obtained.

1. INTRODUCTION

The inverse problem of linear compartmental systems consists in the parameter estimation from the equations that provide the instantaneous amount of matter or the instantaneous rate in one or more system's compartments. These equations are generally multi-exponential, and estimating the parameters is possible by fitting the experimental data to one or more of these equations. Although different fitting methods exist, they present difficulties. The most important methods are [1]: the curve peeling methods for decay exponential curves and the methods for fitting sums of exponentials. A more recent method is the statistical moments method of a multi-exponential function, which provides the instantaneous amount or rate of substance in a compartment [1-3].

In chemistry, statistical moments have been widely used for more than fifty years to evaluate the mass diffusion phenomenon [4] in chromatography [5, 6], tracer kinetics [7], metabolism and distribution studies [8], and in the estimations of rate constants in several simple and complex chemical kinetic systems [9]. More recently, the use of moment equations to predict the dynamics of systems in stochastic chemical kinetics has increased [10-14]. Statistical moments for the parameter estimations of linear multicompartmental systems and for other applications are also widely used in different fields of pharmacokinetics [15-17], enzyme kinetics [2, 18-20], evaluation of residence times [21, 22], among others [12, 13, 23-27].

The utility of these statistical moments is twofold: they define the fundamental mean kinetic parameters, such as the mean residence time (MRT) [28-30], the Area Under the plasma concentration Curve (AUC) or the Area Under the First Moment Curve (AUMC) [9, 31] to then obtain the corresponding symbolic expressions; as mentioned above, by comparing these symbolic expressions with the numerical values of the same corresponding statistical moments obtained from the experimental data, it is possible to determine all, or some of, the fractional transfer constants involved in the linear compartmental system under study. Obtaining the numerical values of statistical moments generally requires a numerical integration to obtain the area under a certain time course curve depending on the order of the statistical moment to be obtained. Therefore, statistical moments are useful for two main objectives in a compartmental analysis: the forward problem; i.e., obtaining analytical symbolic expressions from a known linear compartmental system; the inverse problem; i.e., acquisition of the fractional transfer coefficients from fitting experimental data to symbolic equations.

In spite of its importance, the study of statistical moments in linear compartmental systems has, in our opinion, important limitations, which we attempt to circumvent with the present contribution. These limitations are: (1) obtaining statistical moments is practically limited to open linear compartmental systems as these are handled in pharmacokinetic models. Only recently have statistical moments been used by our group in the closed compartmental system form by the enzyme forms of three enzyme systems [2, 3, 18]; (2) statistical moments in linear compartmental systems have been almost exclusively applied to determine the mean MRT, AUC and AUMC parameters in the pharmacokinetics field; this is possibly because they involve only zero or first-order statistical moments, which are easy to find. Only recently have second-order statistical moments (in addition to zero and one-order moments) been used [2, 18]; (3) obtaining statistical moments, even those of low orders, in linear compartmental systems of certain complexity prove mathematically laborious [1]; (4) general expressions for statistical moments of any order have been given [1, 32-36]; however, they are not explicit functions of the fractional transfer constants involved in the linear system, but of amplitudes A_i and arguments λ_i involved in a sum of the type $\sum_{i=1}^{m} A_i e^{\lambda_i t}$, and are not an explicit function of all the fractional transfer coefficients involved. Only the symbolic expressions of zero-order statistical moments have been obtained for simple linear compartmental systems and, in some cases, they have been acquired as an explicit function of the fractional transfer involved. (5) Obtaining symbolic expressions for statistical moments of any order as an explicit function of the transfer constants, even for simple compartmental systems, currently implies serious mathematical algebraic problems [1].

The main purposes of this contribution are to obtain general symbolic expressions for the statistical moments of any order and for any linear compartmental system, simple or complex, with zero input, open or closed, with or without traps. The numerical values of the statistical moments of different orders, together with the corresponding symbolic expressions, allow us to evaluate the different transfer constants involved in the linear compartmental system under study. The number of statistical moments to be obtained (of zero-, first-, second-, etc., order) depends on the number of fractional transfers to be evaluated, while the proposed experimental design depends on the form of the corresponding symbolic equations for the moments.

2. PRELIMINARIES

The linear compartmental system model under study in this paper is open or closed, with or without traps, in which the matter is injected at $t = 0$ instantly (zero *input* or *bolus*) into one system compartment, or more. Seeing that the kinetic behaviour of any open system is the equivalent to the corresponding closed one obtained by adding a hypothetical compartment, which collects all the excretions, this contribution treats open systems as the corresponding closed systems. In this section, aspects of the structure *of Closed Linear Systems* (CLS hereafter) and some definitions and notations required to fulfil this contribution's objectives are summarized and have been taken from previous contributions [1, 37-46]. The structure of the compartmental systems can be treated from the points of view of their connection diagrams and the matrix´s set of linear differential equations describing kinetic behaviour. Both aspects of the structure are complementary.

Regarding connection diagrams, both connectivity diagrams (also called directed graphs) and condensation diagrams, by classes, are treated. Regarding the compartmental system structure in accordance with the system matrix, there are interesting properties that also help fulfil the purposes of this work.

2.1. Connection diagrams

The connection diagrams in CLS can be *directed graph* and condensation diagrams. To illustrate the definitions in this section, the directed graph shown in Figure 1 is used.

2.1.1. Directed graphs

One of the characteristics of directed graphs is that the origin and destination of all the connections (arrows that represent the direct flux of substance between compartments) are at one point (identified as a compartment) [1, 37].

This contribution selects the points (black circles) and directed segments, as the connections between them, as a representation form of the compartments.

2.1.1.1. Notation and definitions

n: Number of compartments in the CLS, e.g., $n = 9$ in Fig. 1.

X_1, X_2, ..., X_n: Each n compartment of the CLS. In Fig. 1, the compartments are denoted by X_1, X_2, ..., X_9.

Path connecting X_i with X_j: Set of oriented segments, which are all in the direction from X_i to X_j which connects compartment X_i with X_j but with no repetition of compartments. The number of segments in a path is called the length of the path; i.e., in the CLS of Fig. 1, there are two paths connecting compartments X_2 and X_9; one is $X_2 \to X_3 \to X_4 \to X_7 \to X_8 \to X_9$, of length 5, while the other is $X_2 \to X_3 \to X_4 \to X_9$ of length 3.

$K_{i,j}$ (i,j =1, 2, ..., n; $i \neq j$): the fractional transfer coefficient, or simply the transfer constant, which corresponds to the direct flux of the matter from compartment X_i to compartment X_j. These constants are always non-negative. Figure 1(a) indicates all the transfer constants.

$K_{i,o}$ (i= 1, 2, ..., n): the fractional excretion coefficient, or simply the excretion constant, which corresponds to the direct flux of matter in an open linear compartmental system from compartment X_i to the environment. When this system is treated as a closed system by adding a hypothetic compartment X_{n+1}, which collects all the excretions, constant $K_{i,o}$ must be replaced with constant $K_{i,n+1}$. Once the desired results have been obtained, $K_{i,n+1}$ must be replaced with $K_{i,o}$. These constants are always non-negative.

Successor and precursor compartments of a given compartment: let X_i (i=1,2,...,n) be any compartment of a system. We say that compartment X_i is the *precursor* of compartment X_j (j = 1,2,...,n), which is denoted by $X_i \prec X_j$, if there is a path connecting compartment X_i with compartment X_j. If $X_i \prec X_j$ exists, we say that X_j is the *successor* of X_i. Evidently, a compartment is a *successor* and a *precursor* of itself. By means of the notation $X_m \not\prec X_i$, we indicate that compartment X_m is *not a precursor* of compartment X_i. For example, in the CLS of Fig. 1, X_3 is the *precursor* of X_8 and, therefore, X_8 is the *successor* of X_3, as $X_8 \not\prec X_3$.

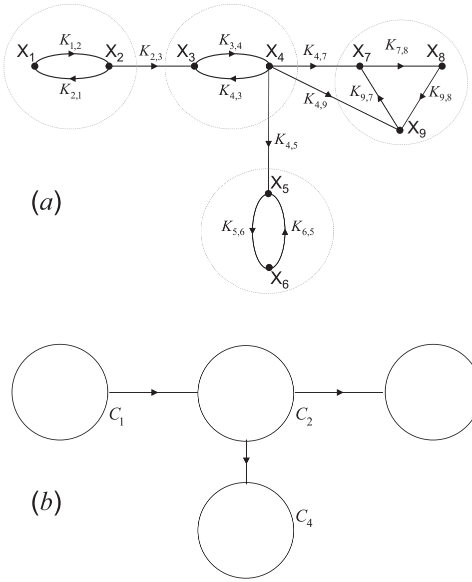


Figure 1. Directed graph and condensation diagram corresponding to the same example of a CLS system of 9-compartments (*a*) Directed graph: X_1, X_2, ..., X_9 denote the compartments, the directed segments represent the flux of substance between compartments, and $K_{1,2}$, $K_{2,1}$, ..., $K_{9,7}$ are the fractional transfer coefficients relating to these fluxes. The compartments inside each dashed circle, which are auxiliaries, are those belonging to the same class. (b) Condensation diagram: there are 4 classes that have been marked with solid-line circles and they correspond to the auxiliary circles from (*a*). Classes are denoted by C_1, C_2, C_3 and C_4 and are: $C_1 = \{X_1, X_2\}$, $C_2 = \{X_3, X_4\}$, $C_3 = \{X_7, X_8, X_9\}$, $C_4 = \{X_5, X_6\}$. C_1 is an initial class, C_2 is a transit class and C_3 and C_4 are final classes. Observe how the connection of two classes is drawn by only one arrow.

$\boldsymbol{\omega}$: a set whose elements are the subindices of the notation from those compartments in which a zero input is made. For example, if in CLS these inputs are made in X_2 and X_5, then $\omega = \{2,5\}$

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

2.1.2. Condensation diagrams

Directed graph elements can be grouped according to certain criteria to obtain representations known as *condensation diagrams.*

2.1.2.1. Notation and definitions

Class or strong component of a directed graph: a set of system's compartments; any of them can be a *precursor* of all the others belonging to this set. If a compartment is a *precursor* of all the other compartments in the class, it is also the *successor* of them all. We can conclude that the compartments belonging to a class are simultaneously *precursors* and *successors* of them all. All the CLS compartments belong to only one class. Thus, a directed graph may consist in one or more classes; in turn, a class may contain one or more compartments. Therefore in a directed graph, we can distinguish several subgraphs, one for each class of the system. The class concept [44] is the equivalent to the strong component [1], and is the second word of equivalence class due to the following relationship between compartments: "to be a successor and a predecessor of" has reflexive, symmetric and transitive properties. Therefore, it creates a partition of the set to which it is applied (the compartmental system) in the subsets that are equivalence classes, and each is formed for the compartments that fulfil the relationship. Figure 1 depicts the four classes and the compartments belonging to each one. The scheme resulting in the representation of a directed graph, corresponding to a compartmental system, through its classes (circles, although points are talk) and the flow of the matter between them (directed segments) is called a condensation diagram by classes. Figure 1 *(b)* shows the condensation diagram of the directed graph of Fig. 1 (a).

ⓘ: a class to which compartment X_i belongs. For example, in the CLS of Fig. 1, ⑥ is the class to which compartment X_6 belongs, e.g., class $C_3=\{X_5, X_6\}$.

Initial class: a class to which compartments are not the *successors* of the compartments belonging to the other classes. In the condensation diagram of Fig. 1(*b*), C_1 is an initial class.

Final class: a class whose compartments are not the *precursors* of the compartments belonging to the other classes. The final class concept coincides with the definition of a simple trap [1, 37]. In the CLS of Fig. 1(*b*), C_3 and C_4 are final classes.

Transit class: any system class that does not fulfil the initial or final class conditions defined. In the condensation diagram of Fig. 1(b), C_2 is a transit class.

In a condensation diagram corresponding to a CLS, there will always be an initial and a final class. There may be no transit classes. If a condensation diagram is formed by only one class, then it is considered a final class [44].

2.2. The system matrix and some of its properties

The knowledge of the properties of this matrix, its eigenvalues, its characteristic polynomial, its minors of the (n-1)-th order, etc., is essential to obtain the kinetic equations of compartmental systems [38, 40, 43-45]. This matrix is an essential connection between the structural and kinetic study of CLS [38, 40, 43-45]. To illustrate this section, we will use the CLS indicated in Fig. 2.

2.2.1. Notations and definitions

In addition to the notations and definitions already used in this section, some additional definitions and notations have been included [38, 40, 43-45] which are useful for the CLS analysis. To support this task, the CLS shown in Fig. 2(a) are also employed.

***K*:** the matrix of the set of differential equations system that describes the kinetics of the CLS under study. This is given by:

$$\boldsymbol{K} = \begin{bmatrix} K_{1,1} & K_{2,1} & \cdots & K_{n,1} \\ K_{1,2} & K_{2,2} & \cdots & K_{n,2} \\ \vdots & \vdots & \cdots & \vdots \\ K_{1,n} & K_{2,n} & \cdots & K_{n,n} \end{bmatrix} \qquad (1)$$

where elements $K_{i,j}$ (i=1,2,...,n; $i \neq j$) are the above-defined fractional transfer coefficients, while the elements of the main diagonal $K_{i,i}$ (i=1,2,...,n) are defined by the expression below:

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

For the example of Fig. 2, this matrix is:

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

where:

$$\left.\begin{aligned} K_{1,1} &= -(K_{1,2}+K_{1,4}) \\ K_{2,2} &= -(K_{2,1}+K_{2,3}) \end{aligned}\right\} \tag{4}$$

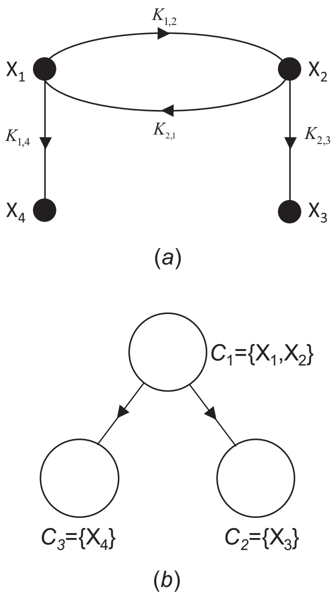


Figure 2 (a) Directed graph of CLS. (b) Condensation diagram where the classes and compartments belonging to each one are shown. C_1 is an initial class and C_2 and C_3 are final classes.

Characteristic polynomial, D (λ)**: the determinant of matrix *K* of the system. This determinant is given by the following expression:**

$$D(\lambda)=\begin{vmatrix} K_{1,1}-\lambda & K_{2,1} & \cdots & K_{n,1} \\ K_{1,2} & K_{2,2}-\lambda & \cdots & K_{n,2} \\ \vdots & \vdots & \cdots & \vdots \\ K_{1,n} & K_{2,n} & \cdots & K_{n,n}-\lambda \end{vmatrix} \tag{5}$$

The expansion of this determinant leads to its polynomial form; i.e., the characteristic polynomial of matrix **K**. By following the example of Fig. 2(a), this determinant is:

$$D(\lambda)=\begin{vmatrix} K_{1,1}-\lambda & K_{2,1} & 0 & 0 \\ K_{1,2} & K_{2,2}-\lambda & 0 & 0 \\ 0 & K_{2,3} & -\lambda & 0 \\ K_{1,4} & 0 & 0 & -\lambda \end{vmatrix} \qquad (6)$$

$\boldsymbol{\lambda_j}$ (j = 1, 2, ..., n): eigenvalues of matrix **K**. They coincide with the roots of the characteristic polynomial $D(\lambda)$.

u: number of non-null eigenvalues of matrix **K**. This number coincides with the number of non-null roots of polynomial $D(\lambda)$.

$\boldsymbol{\lambda_1, \lambda_1, \ldots, \lambda_u}$: non-null roots of characteristic polynomial $D(\lambda)$. Therefore, they are the non-null eigenvalues of matrix **K**. In this contribution, we assume that the non-null eigenvalues of matrix **K** are simple, i.e., they are not repeated, which is the most probable and frequent situation. Hearon [47] demonstrated that the non-null eigenvalues of a dominant diagonal matrix, like matrix **K,** are real, negative or complex with the real negative part, and that they are never purely imaginary (i.e., complex with the real part null).

c: number of null eigenvalues of matrix **K**; i.e., number of null roots of polynomial $D(\lambda)$. This value coincides with the number of final classes of CLS. Because the system is closed, then $c \geq 1$ is fulfilled [1, 40, 44]; i.e., at least one null root exists. Because the number of eigenvalues of matrix K is n, it is obvious that:

$$n = u + c \qquad (7)$$

$\boldsymbol{D_{k,i}(\lambda)}$ (k,i = 1, 2, ..., n): is the resulting determinant of order n-1, when the k-th row and the i-th column have been removed from $D(\lambda)$. For example, the determinants $D_{1,2}(\lambda)$, $D_{2,2}(\lambda)$, $D_{1,3}(\lambda)$ and $D_{2,3}(\lambda)$ corresponding to the system of Fig. 2 are:

$$D_{1,2}(\lambda) = \begin{vmatrix} K_{1,2} & 0 & 0 \\ 0 & -\lambda & 0 \\ K_{1,4} & 0 & -\lambda \end{vmatrix} \tag{8}$$

$$D_{2,2}(\lambda) = \begin{vmatrix} K_{1,1}-\lambda & 0 & 0 \\ 0 & -\lambda & 0 \\ K_{1,4} & 0 & -\lambda \end{vmatrix} \tag{9}$$

$$D_{1,3}(\lambda) = \begin{vmatrix} K_{1,2} & K_{2,2}-\lambda & 0 \\ 0 & K_{2,3} & 0 \\ K_{1,4} & 0 & -\lambda \end{vmatrix} \tag{10}$$

$$D_{2,3}(\lambda) = \begin{vmatrix} K_{1,1}-\lambda & K_{2,1} & 0 \\ 0 & K_{2,3} & 0 \\ K_{1,4} & 0 & -\lambda \end{vmatrix} \tag{11}$$

2.2.2. Some properties of the characteristic polynomial *D*(λ)

The expansion of characteristic polynomial, $D(\lambda)$, given by Eq. (5), leads to the following polynomial [38, 43]:

$$D(\lambda) = (-1)^n \lambda^c T(\lambda) \tag{12}$$

Where:

$$T(\lambda) = \sum_{q=0}^{u} F_q \lambda^{u-q} \qquad (F_0 = 1) \tag{13}$$

The coefficients F_q (q=0, 1, ..., n-1) in Eq. (13), where F_0 is always equal to 1, may be obtained by expanding the characteristic polynomial $D(\lambda)$ corresponding to Eq. (5). However, this procedure may prove very tedious and can be prone to possible human error, even when systems are not very complex. Varon *et al*. (1995) [38] proposed an alternative, simple and systematic method to obtain these coefficients, which avoids this problem. More recently, Garcia-Meseguer *et al*. [43] implemented a software called COEFICOM, available at http://oretano.iele-ab.uclm.es/~fgarcia/COEFICOM/), which provides these coefficients in a suitable fashion, as well as the u and c values.

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

$$\left.\begin{array}{l} \lambda_1 + \lambda_2 + \cdots + \lambda_u = -F_1 \\ \lambda_1\lambda_2 + \lambda_1\lambda_3 + \cdots + \lambda_{u-1}\lambda_n = F_2 \\ \vdots \\ \lambda_1\lambda_2\cdots\lambda_u = (-1)^u F_u \end{array}\right\} \quad (14)$$

The sum of all the product q-narys of eigenvalues λ_h (h =1,2,...,u) is denoted by P_q (q= 1,2,...,u). For completeness purposes, $P_0 = F_0 = 1$ is done. The relation between P_q and F_q is:

$$P_q = (-1)^q F_q \qquad (q = 0,1,2,...,u) \quad (15)$$

Then, by way of example, the expressions of the coefficients of the characteristic polynomial $D(\lambda)$ corresponding to Fig. 2(a) are provided. After taking Eq. (6) into account, $D(\lambda)$ for this scheme is:

$$D(\lambda) = -\lambda^2(\lambda^2 + F_1\lambda + F_2) \quad (16)$$

Therefore, determinant $T(\lambda)$ is given by:

$$T(\lambda) = \lambda^2 + F_1\lambda + F_2 \quad (17)$$

where

$$F_1 = K_{1,2} + K_{1,4} + K_{2,1} + K_{2,3} \quad (18)$$

$$F_2 = K_{1,2}K_{2,3} + K_{1,4}K_{2,1} + K_{1,4}K_{2,3} \quad (19)$$

and it is verified that u = 2 and c =2. For this example, polynomial $D(\lambda)$ has four roots; two are null and two are non-null (λ_1 and λ_2), which coincide with the roots of polynomial $T(\lambda)$ given by Eq. (17).

2.2.3. Some properties of determinant $D_{k,i}(\lambda)$ (k,i = 1, 2, …,n)

The expansion of $D_{k,i}(\lambda)$ (k,i = 1, 2, …, n) leads to [38, 39, 43, 48, 49]

$$D_{k,i}(\lambda) = (-1)^{n+i+k-1}\lambda^{c-1}\sum_{q=0}^{u}(f_{k,i})_q\lambda^{u-q} \quad [(f_{k,i})_0 = 0 \text{ si } k \neq i;\ (f_{k,i})_0 = 1 \text{ si } k = i] \tag{20}$$

where coefficients $(f_{k,i})_q$, if not 0 or 1, consist in a sum of terms involved in the corresponding coefficient F_q and they are always non-negative. The coefficients $(f_{k,i})_q$ (q = 1, 2, ..., u) of this minor can be obtained in different ways: 1) expansion of determinant $D_{k,i}(\lambda)$ and using Eq. (20). 2) It is easier to use the corresponding coefficients F_q (q = 1, 2, ..., u) in polynomial $D(\lambda)$ through a systematic procedure, which avoids expanding the minor [43]. 3) The aforementioned COEFICOM software [43] also provides coefficients $(f_{k,i})_q$ (q = 1, 2, ..., u).

Below, we provide an example of how to use the aforementioned (1): the expressions of coefficients $(f_{k,i})_q$ (k=1,2; i=2,3; q=0,1,2) result from expanding determinant $D_{k,i}(\lambda)$ (k=1,2; i=2,3) expressed in Eqs. (8)-(11). Thus for k=1 and i=2, the expansion of the determinant in the Eq. (8) is:

$$D_{1,2}(\lambda) = \lambda^2 K_{1,2} \tag{21}$$

On the other hand, we have general equation (20) which can, in this case be k=1, i=2, n = 4, u = 2 and c = 2, and can be written as so:

$$D_{1,2}(\lambda) = \lambda\left((f_{k,i})_0\lambda^2 + (f_{k,i})_1\lambda + (f_{k,i})_2\right) \tag{22}$$

By comparing Eqs. (21) and (22), the following is immediately obtained:

$$\left.\begin{array}{l} (f_{1,2})_0 = 0 \\ (f_{1,2})_1 = K_{1,2} \\ (f_{1,2})_2 = 0 \end{array}\right\} \tag{23}$$

By reasoning analogously with determinants $D_{2,2}(\lambda)$, $D_{1,3}(\lambda)$ and $D_{2,3}(\lambda)$, we find that:

$$\left.\begin{aligned}(f_{2,2})_0 &= 1\\ (f_{2,2})_1 &= K_{1,2} + K_{1,4}\\ (f_{2,2})_2 &= 0\end{aligned}\right\} \tag{24}$$

$$\left.\begin{aligned}(f_{1,3})_0 &= 0\\ (f_{1,3})_1 &= 0\\ (f_{1,3})_2 &= K_{1,2}K_{2,3}\end{aligned}\right\} \tag{25}$$

$$\left.\begin{aligned}(f_{2,3})_0 &= 0\\ (f_{2,3})_1 &= K_{2,3}\\ (f_{2,3})_2 &= K_{1,2}K_{2,3} + K_{1,4}K_{2,3}\end{aligned}\right\} \tag{26}$$

2.2.4. Some properties of coefficients $(f_{k,i})_q$ (q=1,2,…,u) relating with the structure of the CLS

It is possible to apply the following additional characteristics, a)-d) [43, 44] to coefficients $(f_{k,i})_q$ as so:

a) If ⓘ (i = 1, 2, ..., n) is not a final class, then

$$(f_{k,i})_u = 0 \tag{27}$$

b) If X_k (k = 1, 2, ..., n) $\nprec$ X_i (i = 1, 2, ..., n), then all the coefficients $(f_{k,i})_q$ (q = 0, 1, ..., u) are null and vice versa, i.e.,:

$$X_k\ (k = 1, 2, ..., n) \nprec X_i\ (i = 1, 2, ..., n) \Leftrightarrow (f_{k,i})_0 = (f_{k,i})_1 = ... = (f_{k,i})_u = 0 \tag{28}$$

c) If X_k (k = 1, 2, ..., n) $\prec$ X_i (i = 1, 2, ..., n) then $(f_{k,i})_{u-1} \neq 0$ and vice versa, i.e.,:

$$X_k\ (k = 1, 2, ..., n) \prec X_i\ (i = 1, 2, ..., n) \Leftrightarrow (f_{k,i})_{u-1} \neq 0 \tag{29}$$

d) If X_k (k = 1, 2, ..., n) $\prec$ X_i (i = 1, 2, ..., n) and ⓘ is a final class, then $(f_{k,i})_u \neq 0$ and vice versa, i.e.,:

$$X_k\ (k = 1, 2, ..., n) \prec X_i\ (i = 1, 2, ..., n) \text{ and ⓘ is a final class} \Leftrightarrow (f_{k,i})_u \neq 0 \tag{30}$$

3. THEORY

3.1. Instantaneous amount of the matter in the compartments of a CLS with a zero input

In the equations corresponding to the instantaneous amount of matter in any compartment X_i a, the CLS with a zero input in one or more of its compartments are [39, 43, 50]:

$$x_i = A_{i,0} + \sum_{h=1}^{u} A_{i,h} e^{\lambda_h t} \tag{31}$$

$$A_{i,0} = \frac{\sum_{k\in\omega} (f_{k,i})_u x_k^0}{F_u} \tag{32}$$

$$A_{i,h} = \frac{(-1)^{u-1} \sum_{k\in\omega} x_k^0 \left(\sum_{q=0}^{u} (f_{k,i})_q \lambda_h^{u-q} \right)}{\lambda_h \prod_{p=1}^{u} \left(\lambda_p - \lambda_h \right)} \tag{33}$$

If there is one non-null eigenvalue, λ_1, then the denominator of Eq. (33) is λ_1, and is equal to $-F_1$. The amplitudes $A_{i,h}$ (h = 1,2,...,u), given by Eq. (33) are explicit functions of the corresponding eigenvalue λ_h (h = 1,2,...,u) and of the remaining u-1 eigenvalues λ_p (p=1,2,...,u; $p \neq h$) of the transfer rate constants involved in the process through coefficients $(f_{k,i})_q$ (q=0,1,2,…,u), and of the initial amount of matter in the different compartments. $A_{i,0}$ is a non-negative quantity that depends on the transfer constants involved in the process through coefficients $(f_{k,i})_u$ **(**$k \in \omega$**)** and F_u, and of the initial amounts of matter in the different compartments, whose meaning is the value of x_i at high t-values, or, mathematically as so:

$$A_{i,0} = \lim_{t\to\infty} x_i \tag{34}$$

If compartment X_i does not belong to a final class, then $A_{i,0}$=0 because, in this case, all the coefficients $(f_{k,i})_u$ **(**$k \in \omega$**)** involved in Eq. (32) are null, as indicated in the previous section. Moreover, Eq. (31) can be written as:

$$x_i = \sum_{h=1}^{u} A_{i,h} e^{\lambda_h t} \tag{35}$$

with $A_{i,h}$ given by:

$$A_{i,h} = \frac{(-1)^{u-1} \sum_{k \in \omega} x_k^0 \left(\sum_{q=0}^{u-1} (f_{k,i})_q \lambda_h^{u-q-1} \right)}{\prod_{p=1}^{u} \left(\lambda_p - \lambda_h \right)} \tag{36}$$

thus $(f_{k,i})_u = 0$ **$(k \in \omega)$** is the numerator of Eq (33); therefore, we can have eigenvalue λ_h as a common factor which is cancelled by the value of its denominator.

If $A_{i,0} \neq 0$, which happens if, and only, if $(f_{k,i})_u \neq 0$ $(k \in \omega)$, then Eqs. (31)-(33) remain unchanged. If, in this case, we take the time derivative in Eq. (31) and we take into account Eq. (33), we obtain:

$$\frac{dx_i}{dt} = (-1)^{u-1} \sum_{h=1}^{u} \frac{\sum_{k \in \omega} x_k^0 \left(\sum_{q=0}^{u} (f_{k,i})_q \lambda_h^{u-q} \right)}{\prod_{p=1}^{u} \left(\lambda_p - \lambda_h \right)} e^{\lambda_h t} \tag{37}$$

3.2. Definition of function $g_i(t)$ associated with function x_i

We define function $g_i(t)$ associated with function x_i as follows:

$$g_i(t) = \begin{cases} x_i & if \ A_{i,0} = 0 \\ \dfrac{dx_i}{dt} & if \ A_{i,0} \neq 0 \end{cases} \tag{38}$$

i.e.,

$$g_i(t) = \sum_{h=1}^{u} \gamma_{i,h} e^{\lambda_h t} \tag{39}$$

where:

$$\gamma_{i,h} = \begin{cases} \dfrac{(-1)^{u-1} \sum_{k \in \omega} x_k^0 \left(\sum_{q=0}^{u-1} (f_{k,i})_q \lambda_h^{u-q-1} \right)}{\prod_{p=1}^{u} \left(\lambda_p - \lambda_h \right)} & \text{if} \quad A_{i,0} = 0 \\ \\ \dfrac{(-1)^{u-1} \sum_{k \in \omega} x_k^0 \left(\sum_{q=0}^{u} (f_{k,i})_q \lambda_h^{u-q} \right)}{\prod_{p=1}^{u} \left(\lambda_p - \lambda_h \right)} & \text{if} \quad A_{i,0} \neq 0 \end{cases} \tag{40}$$

3.3. The statistical moments of function $g_i(t)$

From the well-known definition of the statistical moment of order j of one function [51-54], the j-th (j = 0,1,2,....) statistical moment (which we denote $M_{j,i}$) of any of the above-defined functions $g_i(t)$ is given by:

$$M_{j,i} = \int_0^\infty t^j g_i(t) dt \quad (j = 0,1,2,....) \tag{41}$$

The j-th statistical moment, $M_{j,i}$, can be obtained as either a symbolic expression from the expressions of $g_i(t)$ and the analytical integration indicated in Eq. (41), or numerically from the experimental time course of $g_i(t)$ by considering that the integral on the right-hand side of Eq. (41) coincides with the area below the curve $t^j g_i(t)$ between t = 0 and $t \to \infty$ ($t \to \infty$ must be interpreted as a time, and arbitrarily chosen by the worker, at which it is assumed that $t^j g_i(t) \to 0$).

If in Eq. (41) we insert Eq. (39), we find that:

$$M_{j,i} = \sum_{h=1}^{u} \gamma_{i,h} \left(\int_0^\infty t^j e^{\lambda_h t} dt \right) \qquad (j = 0,1,2,....) \tag{42}$$

The integral in Eq. (42) is the well-known *Gamma Function* [51], given by:

$$\int_0^{\infty} t^j e^{\lambda_h t} dt = \frac{j!}{\left(-\lambda_h\right)^{j+1}} \qquad [\mathrm{Re}(\lambda_h)<0] \tag{43}$$

If we bear in mind that Eq. (43), then Eq. (42) can be written as:

$$M_{j,i} = \left(-1\right)^{j+1} j! \sum_{h=1}^{u} \frac{\gamma_{i,h}}{\lambda_h^{\,j+1}} \qquad (j = 0, 1, 2, ...) \tag{44}$$

The $M_{j,i}$ expression is obtained with Eq. (44) by replacing the expressions of $\gamma_{i,h}$ (h= 1,2,...,u), by subsequently performing the indicated sum and by finally considering the relationships between arguments λ_h (h = 1,2,...u). By proceeding in this way, the general symbolic expressions $M_{j,i}$ for those cases in which $A_{i,0}$ is zero, or not, is obtained

3.2.1. Derivation of expression $M_{j,i}$ for the case of $A_{i,0} = 0$

In this case, $\gamma_{i,h}$ (h = 1,2,...,u) is given by the first of the Eqs. (40). If we replace this expression in Eq.(44), we obtain:

$$M_{j,i} = \left(-1\right)^{j+u} j! \sum_{h=1}^{u} \frac{\sum_{k\in\omega} x_k^0 \left(\sum_{q=0}^{u-1} (f_{k,i})_q \lambda_h^{u-q-1} \right)}{\lambda_h^{\,j+1} \prod_{p=1}^{u} \left(\lambda_p - \lambda_h\right)} \tag{45}$$

Eq. (45) can also be written as:

$$M_{j,i} = \left(-1\right)^{j+u} j! \sum_{k\in\omega} x_k^0 \left\{ \sum_{q=0}^{u-1} (f_{k,i})_q \left(\sum_{h=1}^{u} \frac{1}{\lambda_h^{\,j+1-(u-1)+q} \prod_{p=1}^{u} \left(\lambda_p - \lambda_h\right)} \right) \right\} \tag{46}$$

Eq. (25) shows the expression:

$$\sum_{h=1}^{u}\frac{1}{\lambda_h^{\,j+1-(u-1)+q}\prod_{p=1}^{u}\left(\lambda_p-\lambda_h\right)} \tag{47}$$

Which is of this type:

$$\sum_{h=1}^{u}\frac{1}{\lambda_h^{r}\prod_{\substack{p=1\\p\neq h}}^{u}(\lambda_p-\lambda_h)} \qquad (u = 1,2,3,\ \ldots;\ r \text{ is an integer number}) \tag{48}$$

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

$$r_q = j+1-(u-1)+q \tag{49}$$

Our work group has developed an algorithm [55-57], which is summarized in the Appendix, that allows us to easily obtain the sum indicated in Eq. (48). We slightly adapt the expressions in the Appendix by replacing n with u, r with r_q and v with q. As seen in the next section, this algorithm allows us to obtain this sum expressed as a function of the coefficients F_1, F_2,…, F_u involved in polynomial $T(\lambda)$. The result of the sum depends on the relative values of u and r_q, and on r_q being negative, positive or null.

Should we replace the expression given by Eq. (47) in Eq. (46) in accordance with Eq. (A1) in the Appendix, then we obtain:

$$M_{j,i} = \left(-1\right)^{j+u} j!\sum_{k\in\omega} x_k^0 \left\{\sum_{q=0}^{u-1}(f_{k,i})_q Q(u,r_q)\right\} \qquad (A_{i,0}=0) \tag{50}$$

3.2.2. Derivation of expression $M_{j,i}$ for the case $A_{i,0} \neq 0$

In this case, γ_h ($h = 1,2,...,u$) is given by the second of the Eqs. (40). If we replace this expression in Eq. (44), we obtain:

$$M_{j,i} = (-1)^{j+u}\ j!\sum_{h=1}^{u}\frac{\sum_{k\in\omega} x_k^0\left(\sum_{q=0}^{u}(f_{k,i})_q\,\lambda_h^{u-q}\right)}{\lambda_h^{\ j+1}\prod_{p=1}^{u}\left(\lambda_p-\lambda_h\right)} \tag{51}$$

Eq. (51) can also be written as:

$$M_{j,i} = (-1)^{j+u}\ j!\sum_{k\in\omega} x_k^0\left\{\sum_{q=0}^{u}(f_{k,i})_q\left(\sum_{h=1}^{u}\frac{1}{\lambda_h^{\ j+1-u+q}\prod_{p=1}^{u}\left(\lambda_p-\lambda_h\right)}\right)\right\} \tag{52}$$

Eq. (52) shows the expression:

$$\sum_{h=1}^{u}\frac{1}{\lambda_h^{\ j+1-u+q}\prod_{p=1}^{u}\left(\lambda_p-\lambda_h\right)} \tag{53}$$

which is of the same type as Eq. (48) where:

$$r = j+1-u+q \tag{54}$$

As in the case before, we can write r_q instead of r to indicate that r depends on q; i.e.:

$$r_q = j+1-u+q \tag{55}$$

If in Eq. (52) we replace the expression given by Eq. (51) with the corresponding one in accordance with Eq. (A1) in the Appendix, then we obtain:

$$M_{j,i} = (-1)^{j+u}\ j!\sum_{k\in\omega} x_k^0\left\{\sum_{q=0}^{u}(f_{k,i})_q Q(u,r_q)\right\} \qquad (A_{i,0}\neq 0) \tag{56}$$

4. RESULTS AND DISCUSSION

In this contribution, we obtain the general equations to determine the moments of any order j (j=0,1,2,…) corresponding to function, $g_i(t)$, which gives either the instantaneous amount of matter, x_i, in compartment X_i (i=1,2,…,n), when $A_{i,0}$ =0 [Eq. (50)], or the time derivative of this instantaneous amount, in which case, $A_{i,0} \neq 0$ [Eq. (56)]. The reason to choose function $g_i(t)$ as dx_i/dt when $A_{i,0} \neq 0$ is that the j-th moment (j=0,1,2,…) defined by Eq. (41) is finite. However, if we use x_i instead of dx_i/dt, then the integral of Eq. (41) is infinite.

Both Eqs. (50) and (56) are involved in the initial amount of matter x_k^0 $(k \in \omega)$ in compartments X_k $(k \in \omega)$, where a zero input is made with the u parameter, the coefficients $(f_{k,i})_q$ [q=0,1,…,u-1 in Eq. (50); q=0,1,…,u in Eq. (56)], and quantities Q(u,r_q). Quantities x_k^0 $(k \in \omega)$ are either known or arbitrarily fixed. There are several strategies to obtain u values and $(f_{k,i})_q$ expressions, which are explained in the previous section. Hence, the expressions of sums $Q(u,r_q)$ are given by Eqs. (A2)-(A8) in the Appendix by replacing n with u and r with r_q, and they depend on u and r_q. Apart from the cases in which r_q = 0, and $-r_q < u$-1 (where $r_q < 0$) and $-r_q = u$-1 (where $r_q < 0$), in which $Q(u,r_q)$ is equal to 0, 0 and $(-1)^{u-1}$, respectively, in the remaining cases, $Q(u,r_q)$ depends on one or more quantities P_q (q=1,2,…,u), and on the sum of all the different combinations of the u null eigenvalues taken from p to p. For instance, if u = 4; then:

$$P_1 = \lambda_1 + \lambda_2 + \lambda_3 + \lambda_4 \tag{57}$$

$$P_2 = \lambda_1\lambda_2 + \lambda_1\lambda_3 + \lambda_1\lambda_4 + \lambda_2\lambda_3 + \lambda_2\lambda_4 + \lambda_3\lambda_4 \tag{58}$$

$$P_3 = \lambda_1\lambda_2\lambda_3 + \lambda_1\lambda_2\lambda_4 + \lambda_1\lambda_3\lambda_4 + \lambda_2\lambda_3\lambda_4 \tag{59}$$

$$P_4 = \lambda_1\lambda_2\lambda_3\lambda_4 . \tag{60}$$

Either of these sums of products P_q (q = 1,2,…,u) and P_0 may relate to the coefficients F_q (q=0,1,2,…; u; F_0 = 1) of polynomial $T(\lambda)$ given by the equation shown below:

$$P_q = (-1)^u F_q \qquad (q=0,1,\ldots,u;\ P_0 = F_0 = 1) \tag{61}$$

If we take into account Eq. (61), determinants $R(u,r_q)$ and $R'(u,r_q)$ which are featured in Eqs. (A5) and (A8) of the Appendix, can be expressed as:

$$R(u,r_q)=\begin{vmatrix} (-1)^{u-1}F_{u-1} & (-1)^{u-2}F_{u-2} & \cdot\ \cdot\ \cdot & (-1)^{u-r_q+1}F_{u-r_q+1} \\ (-1)^{u}F_{u} & (-1)^{u-1}F_{u-1} & \cdot\ \cdot\ \cdot & (-1)^{u-r_q+2}F_{u-r_q+2} \\ 0 & (-1)^{u}F_{u} & \cdot\ \cdot\ \cdot & (-1)^{u-r_q+3}F_{u-r_q+3} \\ \cdot & \cdot & \cdot\ \cdot\ \cdot & \cdot \\ \cdot & \cdot & \cdot\ \cdot\ \cdot & \cdot \\ \cdot & \cdot & \cdot\ \cdot\ \cdot & \cdot \\ 0 & 0 & \cdot\ \cdot\ \cdot & (-1)^{u-1}F_{u-1} \end{vmatrix} \qquad if\ r_q>1 \qquad (62)$$

$$R'(u,r_q)=\begin{vmatrix} -F_1 & 1 & 0 & \cdot\ \cdot\ \cdot & 0 \\ F_2 & -F_1 & 1 & \cdot\ \cdot\ \cdot & 0 \\ -F_3 & F_2 & -F_1 & \cdot\ \cdot\ \cdot & 0 \\ \cdot & \cdot & \cdot & \cdot\ \cdot\ \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot\ \cdot\ \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot\ \cdot\ \cdot & \cdot \\ (-1)^{-(u+r_q-1)}F_{-(u+r_q+1)} & (-1)^{-(u+r_q)}F_{-(u+r_q)} & (-1)^{-(u+r_q-1)}F_{-(u+r_q-1)} & \cdot\ \cdot\ \cdot & -F_1 \end{vmatrix} \qquad if\ -r_q>u-1$$

(63)

Thus by knowing coefficients F_q (q=0,1,2,…u), we can establish the determinants of Eqs. (62) and (63). Therefore, by considering the results of the Appendix and by then adapting the notation, the expressions of sums $Q(u,r_q)$, for the different possibilities of the r_q values are given by:

$$Q(u,r_q)=\begin{cases} 0 & \text{si } r_q=0 \\ \dfrac{1}{(-1)^u F_u} & \text{si } r_q=1 \\ \dfrac{R(u,r_q)}{(-1)^{ur_q}F_u^{r_q}} & \text{si } r_q>1 \\ 0 & \text{si } r_q<0 \text{ y } -r_q<u-1 \\ (-1)^{u-1} & \text{si } r_q<0 \text{ y } -r_q=u-1 \\ (-1)^{u-1}R'(u,r_q) & \text{si } r_q<0 \text{ y } -r_q>u-1 \end{cases} \qquad (64)$$

Should $A_{i,0} = 0$, then moment $M_{j,i}$ is always positive, unless none of the compartments X_k $(k \in \omega)$ is a precursor of X_i. If this is the case, then $M_{j,i}$ is zero because all the coefficients $(f_{k,i})_q$ $(q = 0,1,2,\ldots,u)$ are zero and, therefore $g_i(t)=0$ [see Eqs. (28) and (29)]. If conversely $A_{i,0} \neq 0$, then moment $M_{j,i}$ can be positive, negative or zero since function $g_i(t)$ is the time derivative of the amount of matter in compartment X_i; so it can take positive, negative or zero values.

In some cases, we find that there are parts of CLS that have no influence on the moment that has to be determined; hence, the corresponding transfer constants and, in which case, the initial amount of the matter in the compartments, should not influence and, therefore, should not be included, in the expression of the statistical moment under study. There are two procedures to ensure that this is so: (1) simplify the resulting equations by cancelling the corresponding transfer constants and initial amount of the matter in the numerator and denominator; (2) annul all the transfer constants $K_{m,n}$ in the moment expression so that X_m and X_n do not belong to the intersection set of successor compartments X_k $(k \in \omega)$ and precursors X_i. For example, if we wish to determine any moment $M_{j,5}$ $(j = 0,1,2,\ldots)$, that is, the j-th moment of function g_5(t) [in this case $g_5(t)$ is dx_5/dt because X_5 belongs to a final class], when considering that a zero input is made in compartments X_1 and X_3, because the intersection of successors X_1 and X_3 and precursors X_5 is the set $\{X_1, X_2, X_3, X_4, X_5, X_6\}$, it is necessary to eliminate the transfer constants $K_{7,8}$, $K_{8,9}$ and $K_{9,7}$ from the $M_{j,5}$ moment expression $(j = 0,1,2,\ldots)$. As this procedure may lead to uncertainties of type 0/0, these are solved by making each null constant equal to ε and by then performing $\varepsilon \to 0$, as done in some enzyme kinetics cases to obtain some equations from each other [58]. Obviously, tracks (1) and (2) lead to the same result.

It is also noteworthy that, given the superposition principle, the moment expressions given by Eqs. (50) and (56) are the exactly the same as if they had been obtained by determining the *j*-th statistical moment of $g_i(t)$, when a zero input is made in all the compartments X_k $(k \in \omega)$, and by then adding these expressions.

4.1. Simplifications of the general equations (50) and (56) when a zero input is made in only one compartment X_k.

The advantage of having a zero input in more than one compartment is that the symbolic equations obtained actually depend on the initial amount of matter in these compartments. Therefore, when fitting experimental data to the obtained equation, we obtain several variables x_k^0 $(k \in \omega)$. This means that when varying each of them for the fixed values of the others, we obtain more equations to be fitted to the experimental data obtained under the same conditions. However, the most commonplace practice involves making a zero input in only one compartment X_k ; for example, in a blood vessel. Here the advantage gained is that Eqs. (50) and (56) are considerably simpler because, in this case, $\omega = \{k\}$. However, there is one disadvantage as there is only one variable x_k^0 available for proposing an experimental design of the experimental data.

If we consider that $\omega = \{k\}$ in Eqs. (50) and (56), they can be simplified, respectively, in the following Eqs. (65) and (66):

$$M_{j,i} = (-1)^{j+u}\ j!\,x_k^0 \sum_{q=0}^{u-1} (f_{k,i})_q Q(u, r_q) \qquad (A_{i,0} = 0) \tag{65}$$

$$M_{j,i} = (-1)^{j+u}\ j!\,x_k^0 \left\{ \sum_{q=0}^{u} (f_{k,i})_q Q(u, r_q) \right\} \qquad (A_{i,0} \neq 0) \tag{66}$$

4.2.1. Applicability of Eqs. (50) and (56)

Equations (50) and (56) are valid for any linear compartmental system, irrespectively of it being open or closed, because, as mentioned above, an open system is treated as a closed one by adding a hypothetical compartment, X_{n+1}, which collects all the excretions. The addition of this compartment does not affect any of the original open system's kinetic properties of the n compartments; therefore, none of the statistical moments is affected. A linear compartmental system has some general compartments for which $A_{i,0} = 0$, and others for which $A_{i,0} \neq 0$. There are two ways to determine if $A_{i,0} = 0$ or $A_{i,0} \neq 0$: (1) if compartment X_i does not belong to a final class, then $A_{i,0}=0$; otherwise, if any of the compartments X_k $(k \in \omega)$ is a precursor of X_i, then $A_{i,0}=0$; (2) to determine u and coefficients $(f_{k,i})_u$ $(k \in \omega)$ (which is very easy using the COEFICOM software). If all coefficients $(f_{k,i})_u$ $(k \in \omega)$ are null, then $A_{i,0}=0$, otherwise $A_{i,0} \neq 0$.

As previously mentioned, Eqs. (50) and (56), apart from being valid for any system with open or closed compartments, are also valid regardless of whether compartments have a zero input, or if their amount of matter or their time derivative is to be determined. In addition, moments are independent of the u-value; i.e., the number of non-null roots of the characteristic polynomial. The only condition for the validity of these equations is that the u non-zero eigenvalues are simple which, in practice, is most likely.

For a zero input in one compartment, X_k, Eqs. (50) and (56) are simplified to Eqs. (65) and (66), respectively, as indicated above. Moreover, when applying any of the Eqs. (50), (56), (65) or (66) to a particular CLS, depending on the i, k and u, q and j values, it is possible that one or more of the coefficients $(f_{k,i})_q$ ($k \in \omega$; k,i=1,2,…,n; q=0,1,2,…,u;), or one or more of the quantities $Q(u,r_q)$, can be null. This implies that when applying these equations, they can considerably reduce, thus making it easier to obtain the desired moments. In Section 4.3 below, general equations are applied to different examples to illustrate these situations.

4.3. Calculus examples of the symbolic expressions of the statistical moments in CLS

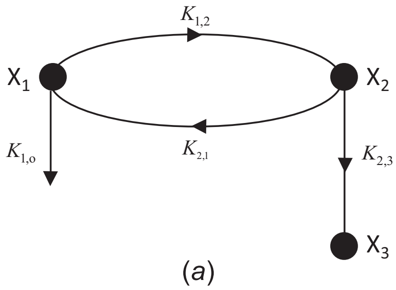
We now go on to apply the previous results to four examples. The power and advantages of the analysis in this contribution are evidenced when applied to complex CLS or when considering higher-order moments. However, and in order to not make this contribution lengthy, we limit these examples to simple systems to avoid loss in generality and to illustrate the procedure properly. The examples cover all possible casuistry; i.e., closed or open systems, $A_{i,0}$ equals to zero or not, and with different j values. Examples 1 and 2 correspond to a closed system, as indicated in Figure 2 (a), while Examples 3 and 4 correspond to an open system, as seen in Figure 3 (a). Examples 1 and 3 correspond to cases in which $A_{i,0}$ = 0, whereas Examples 2 and 4 are cases in which $A_{i,0} \neq 0$.

4.3.1. Example 1

Determination of the moments of the order 0, 1 and 2 corresponding to function x_2 when a zero input in compartments X_1 and X_2 of the closed system, as indicated in Fig. 2(a) is made

In this case, $\omega = \{1,2\}$ and $A_{2,0}$=0 (because X_2 does not belong to a final class). So we can apply Eq. (50). The u parameter, equal to 2, and the coefficients F_1, F_2, $(f_{1,2})_0$, $(f_{1,2})_1$,

$(f_{1,2})_2$, $(f_{2,2})_0$, $(f_{2,2})_1$, $(f_{2,2})_2$, obtained by any of the methods explained below, are indicated in Eqs. (18), (19), (23) and (24).



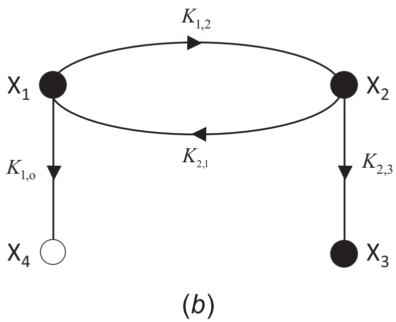


Figure 3. (a) Connectivity diagram of the open linear compartmental system corresponding to Examples 3 and 4. There is an excretion to the environment from compartment X_1 and the excretion constant is $K_{1,o}$ (b) A directed graph of the closed linear compartmental system, which is kinetically equivalent to the open one indicated in (a). This closed linear system is obtained by adding a hypothetical compartment, X_4, indicated by the unfilled circle, which collects the excretion in the environment. Note that the closed system is the same as that indicated in Fig. 1(a) after replacing $K_{1,4}$ with $K_{1,o}$.

Derivation of $M_{0,2}$

If we use Eq. (50) and bear in mind that u=2 and j=0 and that Eq. (49) gives r_q, we accomplish the following:

$$M_{0,2} = x_1^0 \left\{ (f_{1,2})_0 Q(2,0) + (f_{1,2})_1 Q(2,1) \right\} + x_2^0 \left\{ (f_{2,2})_0 Q(2,0) + (f_{2,2})_1 Q(2,1) \right\} \tag{67}$$

If we take into account the two first Eqs. (64) in Eq. (67) and the expressions of $(f_{1,2})_0$, $(f_{1,2})_1$, $(f_{2,2})_0$, and $(f_{2,2})_1$, we obtain:

$$M_{0,2} = \frac{K_{1,2}}{F_2} x_1^0 + \frac{K_{1,2} + K_{1,4}}{F_2} x_2^0 \tag{68}$$

with F_2 given by Eq. (19).

Derivation of $M_{1,2}$

If we use Eq. (50) and take into account that u =2 and j =1, as well as the Eq. (49) which gives r_q, it is fulfilled that:

$$M_{1,2} = -\left[x_1^0 \left\{ (f_{1,2})_0 Q(2,1) + (f_{1,2})_1 Q(2,2) \right\} + x_2^0 \left\{ (f_{2,2})_0 Q(2,1) + (f_{2,2})_1 Q(2,2) \right\} \right] \tag{69}$$

If we take into account the second and third of the Eqs. (64) in Eq. (69) and the expressions of $(f_{1,2})_0$ $(f_{1,2})_1$, $(f_{2,2})_0$ and $(f_{2,2})_1$, we obtain:

$$M_{1,2} = K_{1,2} \frac{F_1}{F_2^2} x_1^0 + \frac{1}{F_2} \left\{ (K_{1,2} + K_{1,4}) \frac{F_1}{F_2} - 1 \right\} x_2^0 \tag{70}$$

with F_1 and F_2 given by Eqs. (18) and (19).

Derivation of $M_{2,2}$

In this case, when we bear in mind that $u = j = 2$ and that Eq. (49) gives r_q, from Eq. (50), we obtain:

$$M_{2,2} = 2\left[x_1^0 \left\{ (f_{1,2})_0 Q(2,2) + (f_{1,2})_1 Q(2,3) \right\} + x_2^0 \left\{ (f_{2,2})_0 Q(2,2) + (f_{2,2})_1 Q(2,3) \right\} \right] \tag{71}$$

If we take into account the third of the Eqs. (64) in Eq. (71) and the expressions of $(f_{1,2})_0$ $(f_{1,2})_1$, $(f_{2,2})_0$ and $(f_{2,2})_1$, given by Eqs. (23-24), the result is:

$$M_{2,2} = 2\left[K_{1,2} \frac{F_1^2 - F_2}{F_2^3} x_1^0 + \left\{ -\frac{F_1}{F_2^2} + (K_{1,2} + K_{1,4}) \frac{F_1^2 - F_2}{F_2^3} \right\} x_2^0 \right] \qquad (72)$$

where we bear in mind that $Q(2,3)$, according to the third of the Eqs. (64), is:

$$Q(2,3) = \frac{\begin{vmatrix} -F_1 & 1 \\ F_2 & -F_1 \end{vmatrix}}{F_2^3} = \frac{F_1^2 - F_2}{F_2^3} \qquad (73)$$

4.3.2. **Example 2**

Determination of the moment of order 2 corresponding to function dx_3/dt; i.e., $M_{2,3}$, when a zero input in compartments X_1 *and* X_2 *of the closed system indicated in Figure 2(a) is made.*

In this case as $A_{3,0} \neq 0$ (because X_3 does not belong to any final class), we have to necessarily apply Eq. (56), with $u = 2$, $j = 3$ and $\omega = \{1,2\}$, to obtain, and as a result, that Eq. (55) gives r_q, the following:

$$M_{2,3} = 2\left[x_1^0 \left\{ (f_{1,3})_0 Q(2,1) + (f_{1,3})_1 Q(2,2) + (f_{1,3})_2 Q(2,3) \right\} + x_2^0 \left\{ (f_{2,3})_0 Q(2,1) + (f_{2,3})_1 Q(2,2) + (f_{2,3})_2 Q(2,3) \right\} \right] \qquad (74)$$

Moreover, if in Eq. (74) the second and third expressions of Equations (64) and the expressions of $(f_{1,3})_0$, $(f_{1,3})_1$, $(f_{1,3})_2$, $(f_{2,3})_0$, $(f_{2,3})_1$ given by Eqs. (25) and (26) are all considered, after reordering, we obtain:

$$M_{2,3} = 2\left[K_{1,2} K_{2,3} \frac{F_1^2 - F_2}{F_2^3} x_1^0 + K_{2,3} \left\{ -\frac{F_1}{F_2^2} + (K_{1,2} + K_{1,4}) \frac{F_1^2 - F_2}{F_2^3} \right\} x_2^0 \right] \qquad (75)$$

4.3.3. Example 3

Determining the moment of order 2 for function x_2, i.e., $M_{2,2}$, when zero input X_1 *and* X_2 *in the compartmental open system, as indicated in Fig. 3(a), is made.*

The open compartments system shown in Fig. 3(a) is kinetically equivalent to the closed system in Fig. 3(b), which coincides with that of Fig. 2(a) by substituting $K_{1,4}$ with $K_{1,o}$. In this way, the moment $M_{2,2}$ in the open system in Figure 3(a) is exactly the same as that given in the system of Fig. 2(a) when only replacing transfer constant $K_{1,4}$ with excretion $K_{1,o}$ in the result [Eqs. (72), (18) and (19)].

4.3.4. Example 4

Determination of the moment of order 2 corresponding to function dx_3/dt; i.e., $M_{2,3}$, when a zero input in compartments X_1 and X_2 of the open system as indicated in Fig. 3(b) is made.

The open compartmental system shown in Fig. 3(*a*) is kinetically equivalent to the closed system in Fig. 3(*b*) which matches that in Fig. 2(*a*) when replacing $K_{1,4}$ with $K_{1,o}$. The moment $M_{2,3}$ in the open system in Fig. 3(*a*) is exactly the same as that determined for the system in Fig. 2(*a*), and it is only necessary to replace fractional transfer constant $K_{1,4}$ with excretion $K_{1,o}$ in the results [Eqs. (75), (18) and (19)].

4.4. General symbolic expressions of AUC, AUMC and MRT.

The general symbolic expressions obtained in this contribution can be widely applied, as discussed above. In this section, we apply them to obtain the symbolic expressions of the mean kinetic and widely used parameters AUC, AUMC, particularly in pharmacokinetics [9, 31, 59-61], in relation to a compartment, X_i (usually a blood vessel, for which $A_{i,0} = 0$), and to obtain the symbolic expression of MRT. In addition, and for convenience purposes, we only consider the case that a zero input is made in only one compartment, X_k, which should be used to determine the moments; see Eq. (65). The symbolic expressions obtained for these kinetic parameters are valid for any open linear compartmental system (which we study as the equivalent closed one). As far as we know, the literature offers no similar expressions that provide these parameters for any type of system, regardless of its complexity, as explicit functions of the transfer constants of the excretion constants. To date, only analytical expressions of these parameters have been obtained as a function of the transfer and excretion constants for very specific simple systems [62-64].

4.4.1. AUC, Area Under the Curve

AUC is the zeroth moment [9, 59, 60] and, therefore, if in Eq. (65) it is set as $j = 0$, we obtain:

$$AUC = \left(-1\right)^{u} x_k^0 \sum_{q=0}^{u-1} (f_{k,i})_q Q(u, r_q) \tag{76}$$

The general equation shown above can be simplified considerably if we bear in mind the values of Q(u,r_q) for the different values of r_q (q=0,1,2….u-1) indicated in Table 1. Table 1 is general for any u value; however, the results it provides are also the number of rows in it. The values in each cell vary depending on the particular u value. For example, if $u = 1$, there will only be a single row of values of q, r_q and $Q(1,r_q)$, which will be 0, 1 and -1/F_1, respectively.

Table 1

Values of q (q=0,1,…u-1), the corresponding values of r_q [obtained from Eq. (49) with j=0] and the expressions of the corresponding quantities $Q(u,r_q)$ [obtained according to Eqs. (64)]. In gray, the q values that give a negative value of r_q, such as - r_q<u-1, are indicated. In these cases, and according to the fourth of the Eqs. (64), then $Q(u,r_q)$=0. In black, we see the q value that gives a null value of r_q. In this case, and according to the first of the Eqs. (64), then $Q(u,r_q) = 0$

q	r_q	$-r_q$	$Q(u,r_q)$
0	2-u	u-2 (<u-1)	0
1	3-u	u-3 (<u-1)	0
⋮	⋮	⋮	⋮
u-3	-1 (=u-1-u)	1 (<u-1)	0
u-2	0		0
u-1	1		$(-1)^u / F_u$

Eq. (76) for AUMC can be simplified to the following Eq. (77) if we consider the values of $Q(u,r_q)$ for the possible different values of r_q (q=0,1,2.,u-1) indicated in Table 1.

$$AUC = \frac{(f_{k,i})_{u-1}}{F_u} x_k^0 \tag{77}$$

That is, the expression of AUMC relates to compartment X$_i$ when the matter is injected into X$_k$. Note that the expression given for AUC in Eq. (77) is an explicit function of the fractional transfer and excretion constants, just as $(f_{k,i})_{u-1}$ and F_u are.

4.4.2. AUMC, Area Under the First Moment Curve

AUMC is defined as the first moment [6, 9, 15, 65] and, therefore, if in Eq. (50) we set $j = 1$, we obtain:

$$AUMC = (-1)^{u+1} x_k^0 \sum_{q=0}^{u-1} (f_{k,i})_q Q(u, r_q) \tag{78}$$

By reasoning similarly to the case of AUC, and by taking into account that we now find that j=1, we obtain the results shown in Table 2.

Table 2

The values of q (q=0,1,…u-1), the corresponding values of r_q [obtained from Eq. (55) where j=1] and the expressions of the corresponding quantities $Q(u,r_q)$ [obtained according to the Eqs. (64)]. In gray, the q values that give a negative value of $r_{q,}$ such as - r_q<u-1, are indicated. In these cases, and according to the fourth of the Eqs. (64), then $Q(u,r_q)$=0. In black, the q value that gives a null value of r_q is indicated. In this case, and according to the first of the Eqs. (64), then $Q(u,r_q)$ = 0

q	r_q	- r_q	$Q(u,r_q)$
0	3-u	u-3 (<u-1)	0
1	3-u	u-3 (<u-1)	0
⋮	⋮	⋮	⋮
u-4	-1 (=u-1-u)	1 (<u-1)	0
u-3	0		0
u-2	1		$(-1)^u / F_u$
u-1	2		$(-1)^{u-1} F_{u-1} / F_u^2$

Eq. (78) for AUMC can be simplified to the following Eq. (79) if we consider the values of $Q(u,r_q)$ for the possible different values of r_q (q=0,1,2.,u-1), as indicated in Table 2.

$$AUMC = \left[f_{k,i})_{u-1} \frac{F_{u-1}}{F_u^2} - \frac{f_{k,i})_{u-2}}{F_u} \right] x_k^0 \tag{79}$$

That is, the expression of AUMC relates to compartment X_i when matter is injected into X_k. Note that the expression given for AUC in Eq. (79) is an explicit function of the fractional transfer and excretion constants, just as $(f_{k,i})_{u-1}$ and F_u are.

4.4.3. AMUC/AUC

This ratio, according to Eqs. (77) and (79), is given by:

$$\frac{AUMC}{AUC} = \frac{F_{u-1}}{F_u} - \frac{f_{k,i})_{u-2}}{(f_{k,i})_{u-1}} \tag{80}$$

which is the expression of AUMC/AUC in relation to compartment X$_i$ when the matter is injected into X$_k$.

In open systems without traps in which the matter is injected into only one compartment X$_k$ and the matter is eliminated from this same compartment (i = k), parameter AUMC/AUC, denoted in these cases by MRT, matches the mean matter residence time in the whole system [39, 66, 67] and, according to Eq. (80) and k=i, is given by:

$$MRT = \frac{F_{u-1}}{F_u} - \frac{(f_{k,k})_{u-2}}{(f_{k,k})_{u-1}} \tag{81}$$

Note that, as expected, MRT depends on what compartment X$_k$ is. Note also that the expression given for MRT in Eq. (81) is an explicit function of the fractional transfer and the excretion constants, just as $(f_{k,k})_{u-1}$, $(f_{k,k})_{u-2}$, F_u and F_{u-1} are.

4.5. Final remarks

The statistical moments and their expressions offer very interesting applications in chemistry to estimate the kinetic rate constant in enzyme kinetics, to determine the time of enzyme activity in unstable systems [2] and the important pharmacokinetic parameters AUC, AUMC, MRT [31, 59-61] and, in general, to establish the kinetic parameters involved in a compartment by adjusting the statistical moments corresponding to the symbolic expressions obtained experimentally from AUC $t^j g_i(t)$ to between 0 and infinity. Experimentally, infinite is a long time chosen with certain criteria; this has been recently done in an enzyme system under experimental conditions in such a way that the enzyme forms involved are treated as compartments of a linear compartmental system [2, 3].

In this contribution, we provide general symbolic expressions for the statistical moments in compartmental systems in terms of the fractional transfer constants and initial quantities of matter in the compartments. However, the utility of these symbolic expressions is complete if we fit them to the corresponding statistical moments obtained numerically from the area under the experimental or the simulated progress curves, $t^j g_i(t)$ to between 0 and a long time, t, which is arbitrarily chosen, in such a way that $t \to \infty$

The use of statistical moments implies the inherent error of the numerical determination of an AUC which has a discrete set of points; however, this number is very large. Obviously, the larger the number of points, the more minimal the numerical error when determining the area numerically. Currently in measuring devices or in numerical simulation methods, the number of points (t, $g_i(t)$) of curve $g_i(t)$, from which we obtain curve, $t^j g_i(t)$ can be very high. Therefore, the error due to the numerical determination of the AUC can be negligible. Another source of error [1] is that, evidently in practice, a $t \to \infty$ time in experimental curves is not reached, rather some finite time, which we denote as t_{final}. This error can be minimized by using the correction method suggested by Isenberg and Dyson (1969) [33, 36].

Apart from their intrinsic values to define mean kinetic parameters (i.e., AUC, AUMC, MRT and others), as symbolic expressions of statistical moments are useful for determining kinetic parameters from the experimental data of statistical moments, our group plans to submit a contribution to this journal which implements a software that provides the numerical values of the statistical moments of any order from experimental or simulated data (t, $g_i(t)$) [from which the data collection (t, $t^j g_i(t)$) is immediate], which are entered as either a text file or manually.

Appendix

This Appendix summarizes the results obtained [56] for the sums, like those indicated in Eq. (41) in the main text, that appear in our dynamic linear time-invariant systems analysis.

In the sum type indicated in Eq. (41), n is an integer number higher than the unity (i.e., n =2,3…), r is any positive, negative or null integer number, while λ_h and λ_p (h, p = 1,2,3, …,n) are different, complex numbers, and none is null. For simplification, we denote expressions type, like those in Eq. (41), to be Q(n,r); i.e.:

$$Q(n,r) \equiv \sum_{h=1}^{n} \frac{1}{s_h^r \prod_{\substack{p=1 \\ p\neq h}}^{n} (\lambda_p - \lambda_h)} \tag{A1}$$

We provide (derivation not provided) the following summarized results:

$$Q(n,r) = \begin{cases} \dfrac{R(n,r)}{P_n^r} & \text{if r} \geq 0 \\ \\ (-1)^{n-1} R'(n,r) & \text{if r} < 0 \end{cases} \tag{A2}$$

where:

$$R(n,0) = 0 \tag{A3}$$

$$R(n,1) = 1 \tag{A4}$$

$$R(n,r) = \begin{vmatrix} P_{n-1} & P_{n-2} & \cdot & \cdot & \cdot & P_{n-r+1} \\ P_n & P_{n-1} & \cdot & \cdot & \cdot & P_{n-r+2} \\ 0 & P_n & \cdot & \cdot & \cdot & P_{n-r+3} \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & \cdot & \cdot & \cdot & P_{n-1} \end{vmatrix} \quad \text{if } r > 1 \tag{A5}$$

$$R'(n,r) = 0 \quad \text{if } -r < n-1 \tag{A6}$$

$$R'(n,r)=1 \quad \text{if } -r=n-1 \tag{A7}$$

$$R'(n,r)=\begin{vmatrix} P_1 & 1 & 0 & \cdot & \cdot & \cdot & 0 \\ P_2 & P_1 & 1 & \cdot & \cdot & \cdot & 0 \\ P_3 & P_2 & P_1 & \cdot & \cdot & \cdot & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ P_{-(n+r+1)} & P_{-(n+r)} & P_{-(n+r-1)} & \cdot & \cdot & \cdot & P_1 \end{vmatrix} \quad \text{if } -r>n-1 \tag{A8}$$

In Eqs. (A5) and (A8), P_v (v= 1,2,…,n) is equal to the sum of all the v-nary $(v \le n)$ products that differ from λ_1, λ_2,…, λ_n. P_0 always appears and is observed as P_0= 1.

From the definition of P_v (v = 1,2,…,n) and Eq. (4), we find that:

$$P_v=(-1)^v F_v \tag{A9}$$

Therefore, $R(n,r)$ (for $r > 1$) and $R'(n,r)$ (for $-r > n$-1) can be expressed in terms of the coefficients F_1, F_2,…,F_n in Eq. (2) rather than in terms of their roots λ_1, λ_2, …, λ_n.

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