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ORIGINAL PAPER

Linear compartmental systems. I. kinetic analysis and derivation of their optimized symbolic equations

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Abstract The study of many biological systems requires the application of a compartmental analysis, together with the use of isotopic tracers, parameter identification and methods to evaluate the mean parameters. For all this, the kinetic equations of the compartmental system as a function of its parameters are needed. In this paper, we present some considerations on the diagrams of connectivity of linear compartmental systems and obtain new properties from the matrix corresponding to the ordinary first-order linear differential equation systems which describe their kinetic behaviour. Using these properties, symbolic equations are obtained in a simplified form. These equations provide the instantaneous amount of substance in any compartment of the system when zero input is injected into one or more of the system compartments,

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solely as a function of those parameters of compartmental systems which really have an influence on the sought expression. This is unlike what happens in the other symbolic equations obtained in a previous contribution that included all the fractional transfer coefficients involved in the compartmental system, regardless of whether or not they had an influence on the instantaneous amount of substance.

Keywords Compartmental system · Linear · Open–closed · Kinectics · Symbolic equations

1 Introduction

A compartmental model originating from the pharmacokinetics field where a deterministic, hypothetical and simplified approximation allows the behaviour of drug concentrations in mathematical terms to be described [1,2]. From this classical perspective, and for model construction purposes, all those structures that take a similar blood flow or affinity by the tracer are considered a compartment; therefore, the drug concentration is the same. Thus, the wide use of these dynamic models extends in parallel with the increasing use of stable isotopes in human systems, together with simulation technologies [3,4].

The majority of known drugs that act on the human organism present an absorption, distribution and elimination first-order linear kinetics, and its specific receipts are joined reversibley and are totally excreted,, therefore behaving like an open system [5,6]. The study of the kinetics behaviour of drugs by means of compartmental models leads, on the one hand, to the evaluation of those parameters related to the absorption, distribution and elimination of drugs and their metabolites, whose measure cannot be taken directly and, on the other hand, to the prediction of behaviour in non accessible places and its time course [7]. Interest in the use of compartment models to define, identify and describe different very important systems in Biology, Medicine, Physiology, Pharmacology, Nutrition, Toxicology, Biochemistry or Kinetic Enzymes has grown in recent years [3,8–24]. Standard and very complete references on compartmental modelling and analyses are those of [25–34]. The kinds of model considered consist in a finite number of compartments related to the transfer rates that control the reaction between them. A compartment may be actually physical or an abstract representation of it [6,7,28,35,36].

The global study of compartmental systems involves the application of determinants and matrix [25], the use of graphic methods [37,38], iterative methods [39] or other methods which require the inversion of matrices. For this reason, systems with a matrix that is not invertible generally have no solution [40,41].

Varon et al. [30] and Garcia-Meseguer et al. [10] developed a kinetic compartmental system analysis of the model parameters (initial amount of substance in each compartment and the fractional transfer coefficients corresponding to the direct connection between compartments).

Such analyses overcome many of the aforementioned difficulties through the introduction of algorithms which facilitate the deduction of kinetic equations (30), while the second analysis mentioned [10] represents a slight improvement over the first one in that it uses symbolic coefficients which are always positive. In these contributions, the symbolic expressions of the coefficients in the kinetic equations were obtained by procedures that do not require the expansion of determinants, operations with matrices or graphic methods. In this way, explicit general equations describing the evolution of any compartment of a linear system, either closed or open, were obtained. Moreover, Garcia-Meseguer et al. [10] implemented a software, COEFICOM, developed in MS Visual BASIC, that provides the expressions of these coefficients as a function of the fractional transfer coefficients.

Nevertheless, the general symbolic equations provided by the above contributions have the disadvantage of not being optimized; they all contain the fractional transfer coefficients involved in the compartmental system' diagram of connectivity, without taking into account whether or not the coefficients influence any variation of the amount of substance in a specific compartment. We believe this limitation is overcome in the present contribution where the derived symbolic equations are given in the most simplified possible form in which only those fractional transfer coefficients and zero inputs with any influence on the instantaneous amount of the desired matter are featured. Thus, the kinetic equations obtained herein are very much improved, and we will refer to them as optimized equations. "Appendix C" includes an example showing the advantage of optimized equations compared with non optimized ones.

The compartmental system model under study in this paper consists of a linear system, open or closed and with or without traps, where the amount of substance is injected at $t = 0$ instantaneously (zero input or bolus) into one or more system compartments. In open systems, the substance is excreted from one or more compartment to enter the environment. Firstly, we will look at closed systems and then, in the Results and Discussion sections, we will show how open systems can be analyzed according to the equations established for closed ones.

The results of this contribution (Paper I of this series) will be the starting point to implement a software program (Paper II of this series) that will provide symbolic equations for the linear compartmental systems.

2 Structure of the linear compartmental systems

Connection diagrams (connectivity diagrams and condensation diagrams) represent a useful instrument for studying the structure of compartmental systems in depth.

2.1 Connectivity diagram

The structure of a compartmental system can be studied from its connectivity diagram. With closed systems, the origin and destination of all the connections (arrows that represent the direct flux of substance between the compartments) lie at one point (identified as a compartment).

2.1.1 Notation and definitions

In each section, the standard definitions and nomenclature that are commonly employed in the literature on closed compartmental systems have been used [8,10,11, 26,28,33,37,42] and will prove useful in the following analysis:

n: Number of compartments in the system.
$\mathbf{X_1, X_2, \ldots, X_n}$: Each n compartment in the system.
$\boldsymbol{\Phi}$: Set of indices of all the inputs in the system: $\Phi = \{X_1, X_2, \ldots, X_n\}$.

The successor and precursor compartments of a given compartment. Let X_i $(i = 1, 2, \ldots, n)$ be one system compartment. We state that compartment X_i is a precursor of compartment $X_j (j = 1, 2, \ldots, n)$ if at least one path that connects compartment X_i with compartment X_j exists. X_i, the precursor of X_j, is denoted by $X_i \prec X_j$ and we state 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 $X_i \not\prec X_j$, we indicate that compartment X_i is not a precursor of compartment X_j.

2.2 Condensation diagrams

The set of points of a connectivity diagram can be partitioned into several subsets, which bring about a new diagram called a condensation diagram.

2.2.1 Notation and definitions

Class or strong component of a directed graph [11,26,28,35]: a set of system compartments; any compartment belonging to this set is both a successor and a precursor of any other compartment belonging the same set. Every system compartment belongs to one, and only one, class. Thus, a directed graph may consist of one or more classes and, 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.

$\boldsymbol{\delta}$: Number of classes of the system
$\boldsymbol{C_1, C_2, \ldots, C_\delta}$: Classes of the directed graph. In the directed graph, each class will be represented by a circle, but we shall mention points of the condensation diagram to refer to them as a whole.
ⓘ: Class to which X_i belongs.

These definitions are illustrated by the example of Fig. 1 in which the overlapping connectivity and condensation diagrams of a compartmental system are indicated.

Connection between classes
The scheme that results from representing a connectivity diagram (directed graph) corresponding to a compartmental system, through their classes and the flow of the substance between them (directed segments), is called a *condensation diagram*. By way of example, Fig. 1 shows a condensation diagram for the classes corresponding to the compartmental system.

The successor and precursor concepts, described above and referring to the connections between compartments, are also applicable to condensation diagrams by classes. In the condensation diagram of Fig. 1, $C_1 \prec C_2 \prec C_3$ and $C_1 \prec C_2 \prec C_4$.

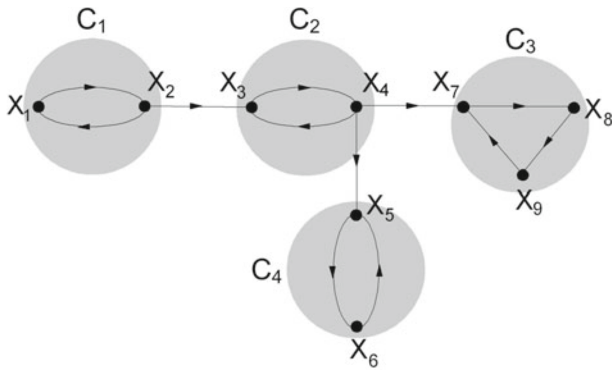

Fig. 1 Connectivity and condensation diagrams corresponding to the same compartmental system where the four classes have been labeled as *gray circles*. In this case $\delta = 4$, $\Phi_c = \{C_1, C_2, C_3, C_4\}$, $C_1 = \{X_1, X_2\}$, $C_2 = \{X_3, X_4\}$, $C_3 = \{X_7, X_8, X_9\}$ and $C_4 = \{X_5, X_6\}$

Types of classes

Initial class: That class which is only the successor of itself; that is, it does not receive any flux of substance from any other class. In the condensation diagram of Fig. 1, C_1 is an initial class.
Final class: Defined as any class of the system that does not transfer substance to any other class. In the condensation diagram of Fig. 1, C_3 and C_4 are final classes. The final class concept coincides with the definition of simple trap [26,28]. When the condensation diagram consists in only one class, this is considered a final class.
Transit Class: By exclusion, any class of the system that does not fulfil the conditions defined for the rest of the classes types. In the condensation graph of Fig. 1, C_2 is a transit class.

3 Matrix of the system and some of its properties

The study of the matrix associated with linear compartmental systems is an indispensable bridge between the structural and the kinetic studies of linear compartmental systems [10,30,43].

3.1 Notation and definitions

Next, we revise the additional definitions and notations on compartmental systems [10,11,30] needed to make progress in the paper. To support this task, we will use the compartmental system shown in Fig. 2.

$\boldsymbol{K_{i,j}}$ $(\mathbf{1}, \mathbf{2}, \ldots, \mathbf{n}; \boldsymbol{i} \neq \boldsymbol{j})$: the fractional transfer coefficients corresponding to the direct flux of substance from compartment X_i to compartment X_j.

K: the matrix of the set of differential equations describing the kinetics of the closed compartmental system under study, given by:

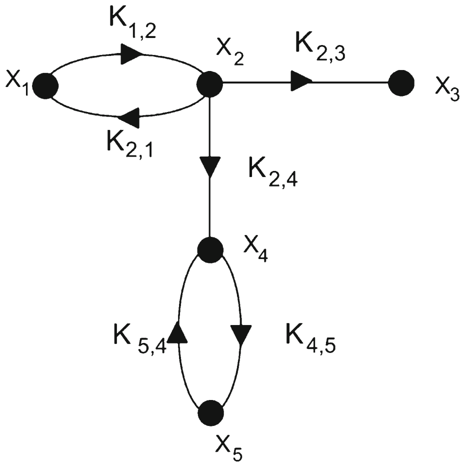

Fig. 2 Directed graph regarding a closed system consisting of five compartments. $X_1, X_{2,\ldots,} X_5$ denote the compartments. *Arrows* indicate the flux of substance among them and $K_{1,2}, K_{2,1}, \ldots, K_{5,4}$ are the fractional transfer coefficients relating to these connections. $C_1 = \{X_1, X_2\}$, $C_2 = \{X_3\}$ and $C_3 = \{X_4, X_5\}$. $n_1 = 2, c_1 = 0, u_1 = 2$; $n_2 = 1, c_2 = 1, u_2 = 0$; $n_3 = 2, c_3 = 1, u_3 = 1$. C_1 is an initial class; C_2 and C_3 are the final classes

$$K = \begin{bmatrix} K_{1,1} & K_{2,1} & \cdots & K_{n,1} \\ K_{1,2} & K_{2,2} & \cdots & K_{n,2} \\ . & . & \cdots & . \\ . & . & \cdots & . \\ . & . & \cdots & . \\ K_{1,n} & K_{2,n} & \cdots & K_{n,n} \end{bmatrix} \tag{1}$$

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

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

A square matrix $n \times n$ in which it is verified that each element in the main diagonal is, in absolute values, greater than or equal to the sum of all other elements of its own column is denominated *dominant diagonal matrix* [44]; therefore, matrix $\boldsymbol{K}$ is a matrix of this type. For the graph in Fig. 2 this matrix is:

$$K = \begin{bmatrix} K_{1,1} & K_{2,1} & 0 & 0 & 0 \\ K_{1,2} & K_{2,2} & 0 & 0 & 0 \\ 0 & K_{2,3} & K_{3,3} & 0 & 0 \\ 0 & K_{2,4} & 0 & K_{4,4} & K_{5,4} \\ 0 & 0 & 0 & K_{4,5} & K_{5,5} \end{bmatrix} \tag{3}$$

where elements $K_{i,i} (i = 1, 2, \ldots, n)$ are:

$$K_{1,1} = -K_{1,2}; \quad K_{2,2} = -(K_{2,1} + K_{2,3} + K_{2,4}); \quad K_{3,3} = 0; \quad K_{4,4} = -K_{4,5}; \quad K_{5,5} = -K_{5,4}$$

$\boldsymbol{D(\lambda)}$: the characteristic polynomial of matrix $\boldsymbol{K}$, *i.e.*:

$$D(\lambda) = \begin{vmatrix} K_{1,1}-\lambda & K_{2,1} & \cdots & K_{n,1} \\ K_{1,2} & K_{2,2}-\lambda & \cdots & K_{n,2} \\ . & . & \cdots & . \\ . & . & \cdots & . \\ . & . & \cdots & . \\ K_{1,n} & K_{2,n} & \cdots & K_{n,n}-\lambda \end{vmatrix} \tag{4}$$

$\boldsymbol{D(0)}$: $D(\lambda)$ where we set $\lambda = 0$.
$\boldsymbol{\lambda_h}(h = 1, 2, \ldots, n)$: the eigenvalues of matrix $\boldsymbol{K}$.
$\boldsymbol{u}$: the number of non null eigenvalues of matrix $\boldsymbol{K}$.
$\boldsymbol{\lambda}_1, \boldsymbol{\lambda}_1, \ldots, \boldsymbol{\lambda_u}$: the non null roots of characteristic polynomial $D(\lambda)$. In this contribution, we assume that the algebraic multiplicity of each non zero eigenvalue of $\boldsymbol{K}$ is one. Hearon [44] showed that the eigenvalues of a diagonally dominant matrix, like matrix $\boldsymbol{K}$, are negative real or complex with a negative real part and are, in no case, purely imaginary.
$\boldsymbol{c}$: the number of the null eigenvalues of matrix $\boldsymbol{K}$, which coincides with the number of the final classes of the compartmental system. As the system is closed, it follows [8,11,28] that:

$$c \geq 1 \tag{5}$$

Given that the number of the eigenvalues of matrix $\boldsymbol{K}$ is n, it is obvious that:

$$n = u + c \tag{6}$$

$\boldsymbol{D_{k,i}(\lambda)}(k, i = 1, 2, \ldots, n)$: the determinant which results after removing the kth row and the ith column from $D(\lambda)$.

3.2 Some properties of $D(\lambda)$

The expansion of $D(\lambda)$, given by Eq. (4), leads to [10,30]:

$$D(\lambda) = (-1)^n \lambda^c \sum_{q=0}^{u} F_q \lambda^{u-q} \quad (F_0 = 1) \tag{7}$$

$D(\lambda)$ can also be expressed as a function of the roots of this polynomial as:

$$D(\lambda) = (-1)^n \lambda^c \prod_{h=1}^{u} (\lambda - \lambda_h) \tag{8}$$

By taking into account Eq. (7), the non null roots of $D(\lambda)$ coincide with the roots of the following polynomial:

$$T(\lambda) = \sum_{q=0}^{u} F_q \lambda^{u-q} \tag{9}$$

By comparing Eqs. (7) and (9), we obtain the following expression, which will prove useful later:

$$D(\lambda) = (-1)^n \lambda^c T(\lambda) \tag{10}$$

3.3 Some properties of $D_{k,i}(\lambda)(k, i = 1, 2, \ldots, n)$

The expansion of $D_{k,i}(\lambda)(k, i = 1, 2, \ldots, n)$ leads to [10,33]:

$$D_{k,i}(\lambda) = (-1)^{n+i+k-1}\lambda^{c-1} \times \sum_{q=0}^{u} (f_{k,i})_q \lambda^{u-q} \quad \left[(f_{k,i})_0 = 0 \text{ if } k \neq i;\ (f_{k,i})_0 = 1 \text{ if } k = i\right] \tag{11}$$

where coefficients $(f_{k,i})_q (k, i = 1, 2, \ldots, n; q = 0, 1, 2, \ldots, u)$, when they are not 1 or 0, consist of a sum of the terms involved in the corresponding coefficient F_q.

3.4 Some properties, associated with the structure of a compartmental system, of coefficients $(f_{k,i})_q$

It is possible [45] to apply the following additional characteristics to coefficients $(f_{k,i})_q (k, i = 1, 2, \ldots, n; q = 0, 1, 2, \ldots, u)$, deduced for coefficients $(a_{k,i})_q$ by Galvez and Varon [11]:

$$\text{If } ⓘ\ (i = 1, 2, \ldots, n) \text{ is not a final class, then } (f_{k,i})_u = 0 \tag{12}$$

$$X_k(k = 1, 2, \ldots, n) \not\prec X_i(i = 1, 2, \ldots, n) \Leftrightarrow (f_{k,i})_0 = (f_{k,i})_1 = \cdots = (f_{k,i})_u = 0 \tag{13}$$

$$X_k(k = 1, 2, \ldots, n) \prec X_i(i = 1, 2, \ldots, n) \Leftrightarrow (f_{k,i})_{u-1} \neq 0 \tag{14}$$

$$X_k(k = 1, 2, \ldots, n) \prec X_i(i = 1, 2, \ldots, n) \text{ and } ⓘ \text{ is a final class} \Leftrightarrow (f_{k,i})_u \neq 0 \tag{15}$$

3.5 Additional considerations on matrix K, $D(\lambda)$ and its minors of $n - 1$ order

Matrix $\boldsymbol{K}$, together with $D(\lambda)$ and its minors $D_{k,i}(\lambda)$, have been expressed by implicitly assuming that the differential kinetic equations for each compartment are written in the same order as they are numbered. This way makes it easier to obtain the properties that have already been discussed, without generality loss, and they are all equally valid, regardless of the order chosen for writing the differential equations. However, the choice of another order to write the equations, for the same arbitrary numbering of compartments as X_1, $X_{2,\ldots,}$ X_n, allows us to establish additional properties in relation to the different classes in the condensation diagram. The form that matrix $\boldsymbol{K}$ takes depends on the order chosen for the compartments when writing their differential kinetic equations. For a given numbering of the compartments, there will be $n!$ possible $\boldsymbol{K}$ matrices. Obviously, the aspect of $D(\lambda)$ depends on the order for writing matrix $\boldsymbol{K}$.

For a given arbitrary numbering of the system compartments, all the rows and columns of any $n!$ possible $\boldsymbol{K}$ matrices that we decide to write and their corresponding $D(\lambda)$ are associated with a system compartment. Evidently, the ordinal number of the row associated with a compartment coincides with the ordinal number of the column associated with the same compartment.

A row (or column) of matrix $\boldsymbol{K}$ can be identified by its order; *i.e.*, 1st row, 4th column, etc., or through the compartment associated with the row or the column; for example, the row associated with the compartment X_2, column associated with compartment X_1, etc.

Below we will use the following additional notations:

row$(\mathbf{X}_j)(j = 1, 2, \ldots, n)$: the row associated with compartment $X_j(j = 1, 2, \ldots, n)$ in matrix $\boldsymbol{K}$ and in the corresponding $D(\lambda)$.
column$(\mathbf{X}_j)(j = 1, 2, \ldots, n)$: the column associated with compartment $X_j(j = 1, 2, \ldots, n)$ in matrix $\boldsymbol{K}$ and in the corresponding $D(\lambda)$.
of(j): Ordinal number of $row(X_j)$.
oc(j): Ordinal number of *column*(X_j).

Note that the eigenvalues of matrix $\boldsymbol{K}$ are independent of any of the $n!$ possible written forms.

The minor $D_{k,i}(\lambda)$, that results removing $row(X_k)$ and *column*(X_i) from $D(\lambda)$ is given by:

$$D_{k,i}(\lambda) = (-1)^{n+oc(i)+of(k)-1}\lambda^{c-1} \times \sum_{q=0}^{u} (f_{k,i})_q \lambda^{u-q} \quad [(f_{k,i})_0 = 0, \text{if } k \neq i;\ (f_{k,i})_0 = 1, \text{if } k = i] \tag{16}$$

where coefficients $(f_{k,i})_q(k, i = 1, 2, \ldots, n; q = 0, 1, \ldots, u)$ only depend on compartments X_k and X_i.

3.6 A suggested numbering of compartments and classes

The number of initial, transit and final classes in the condensation diagram is denoted, respectively, by a, b and c and, obviously, by $a + b + c = \delta$. For convenience, we will take:

$$a + b = f \tag{17}$$

The n compartments in the directed graph are numbered arbitrarily and consecutively from X_1 to X_n, and the classes of the condensation diagram are numbered by the following procedure: 1) First, the a initial classes from 1 to a, in any order. 2) The b transit classes, from $a+1$ to f so that if $C_r \prec C_v$ then $r < v$. 3) Then the c final classes, from $f+1$ to δ, in any order.

We will denote the number of compartments belonging to class $C_r\,(r = 1, 2, \ldots, \delta)$ by n_r. Obviously:

$$\sum_{r=1}^{\delta} n_r = n \tag{18}$$

Let $w_{r_1}, w_{r_2}, \ldots, w_{r_n}$ be the compartments that belong to class $C_r\,(r = 1, 2, \ldots, \delta)$ where: $w_{r_1} < w_{r_2} < \cdots < w_{r_{n_r}}$.

$\boldsymbol{c_r}$: the parameter that indicates whether class C_r is a final one or not and which takes the values:

$$c_r = \begin{cases} 1 \text{ if } C_r \text{ it is a final class} \\ \\ 0 \text{ if } C_r \text{ it is not a final class} \end{cases} \tag{19}$$

This parameter coincides with the number of null eigenvalues of submatrix $\boldsymbol{M}_{r,r}$, which is discussed below, and is associated with class C_r. Note that $c_r = 0$ if $r \leq f$, and that $c_r = 1$ if $r > f$.

$\boldsymbol{u_r}$: is defined as:

$$u_r = n_r - c_r \tag{20}$$

Therefore, this parameter coincides with the number of compartments in class C_r if this is not a final, or with the number of compartments minus one if it is a final one.

In the legend of Fig. 2, we have indicated the corresponding suggested numbering of this subsection, as well as the values of n_r, c_r and u_r.

3.7 The expression of matrix K in the submatrices

It is easy to show that, if the differential kinetic equations of the different system compartments are written by beginning with the compartments of class C_1, and then with those corresponding to C_2 and up to C_δ, and for a given class, and by writing the equations in the same order in which the compartments are numbered in the class, matrix $\boldsymbol{K}$ will admit an expression in the submatrices as follows:

$$K=\begin{bmatrix} M_{1,1} & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \\ 0 & M_{2,2} & \cdots & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots \\ 0 & 0 & \cdots & M_{a,a} & 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \\ M_{1,a+1} & M_{2,a+1} & \cdots & M_{a,a+1} & M_{a+1,a+1} & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \\ M_{1,a+2} & M_{2,a+2} & \cdots & M_{a,a+2} & M_{a+1,a+2} & M_{a+2,a+2} & \cdots & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots \\ M_{1,f} & M_{2,f} & \cdots & M_{a,f} & M_{a+1,f} & M_{a+2,f} & \cdots & M_{f,f} & 0 & 0 & \cdots & 0 \\ M_{1,f+1} & M_{2,f+1} & \cdots & M_{a,f+1} & M_{a+1,f+1} & M_{a+2,f+1} & \cdots & M_{f,f+1} & M_{f+1,f+1} & 0 & \cdots & 0 \\ M_{1,f+2} & M_{2,f+2} & \cdots & M_{a,f+2} & M_{a+1,f+2} & M_{a+2,f+2} & \cdots & M_{f,f+2} & 0 & M_{f+2,f+2} & \cdots & 0 \\ \vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots \\ M_{1,\delta} & M_{2,\delta} & \cdots & M_{a,\delta} & M_{a+1,\delta} & M_{a+2,\delta} & \cdots & M_{f,\delta} & 0 & 0 & \cdots & M_{\delta,\delta} \end{bmatrix} \tag{21}$$

where the submatrices indicated as $\boldsymbol{M}_{r,v}(r, v = 1, 2, \ldots, \delta; r \leq v)$ are given by:

$$M_{r,v}=\begin{bmatrix} K_{w_{r_1},w_{v_1}} & K_{w_{r_2},w_{v_1}} & \cdots & K_{w_{r_{n_r}},w_{v_1}} \\ K_{w_{r_1},w_{v_2}} & K_{w_{r_2},w_{v_2}} & \cdots & K_{w_{r_{n_r}},w_{v_2}} \\ \cdot & \cdot & \cdots & \cdot \\ \cdot & \cdot & \cdots & \cdot \\ \cdot & \cdot & \cdots & \cdot \\ K_{w_{r_1},w_{v_{n_v}}} & K_{w_{r_2},w_{v_{n_v}}} & \cdots & K_{w_{r_{n_r}},w_{v_{n_v}}} \end{bmatrix} (r, v = 1, 2, \ldots, \delta; r \leq v) \tag{22}$$

and each submatrix indicated as 0 in Expression (21), which is located in the rth row and vth column of matrix K, has n_v rows and n_r columns, while all its elements are zeros. It may also possible that one or more of the submatrices denoted as $\boldsymbol{M}_{r,v}(r > v$ if $r \leq f)$ may be a matrix $r \times v$, whose elements are all zeros.

Below, matrix $\boldsymbol{K}$ in the submatrices will be denoted by $\boldsymbol{K}^{\bullet}$. Matrix $\boldsymbol{K}^{\bullet}$ is a square $\delta \times \delta$ and a lower triangular. Each submatrix $\boldsymbol{M}_{r,r}(r = 1, 2, \ldots, \delta)$ may be considered the associated matrix with class C_r.

3.7.1 Additional notations and definitions

We shall define a number of sets and matrices that will prove useful later:

Ω: a set of the compartments of the compartmental system; that is, a non empty subset of set Φ.

$\boldsymbol{\omega}$: a set whose elements are the subindices used in the notation of the compartments of set Ω.

$\boldsymbol{\Omega(i)}$: a set consisting in those compartments of set Ω which are precursors of compartment X_i.

$\boldsymbol{\omega(i)}$: a set whose elements are the subindices used in the notation of the compartments of set $\Omega(i)$.

$\mathbf{E(\Omega, X_{\mathit{i}})}$: a set of the classes that are, simultaneously, successors of the classes to which the compartments of set Ω and the precursors of class ①. For convenience, in some equations, $E(\Omega, X_i)$ is written as the abbreviated form of E_i.

$\boldsymbol{\alpha}$: the number of classes belonging to set $E(\Omega, X_i)$, thus:

$$E(\Omega, X_i) = \{C_{r_1}, C_{r_2}, \ldots, C_{r_\alpha}\} \tag{23}$$

Obviously in some cases, the set $\mathbf{E}(\Omega, X_i)$ may have no elements; *i.e.* it may be the empty set, thus $\alpha = 0$.
$\mathbf{e}(\boldsymbol{i})$: a set whose elements are the subindices used to denote the classes belonging to $E(\Omega, X_i)$, *i.e.*:

$$e(i) = \{r_1, r_2, \ldots, r_\alpha\} \tag{24}$$

$\mathbf{S}(\boldsymbol{\Omega}, \mathbf{X}_{\boldsymbol{i}})$: a set of compartments belonging to the set of classes $E(\Omega, X_i)$, *i.e.*, the set of the compartments that are simultaneously the successor compartments of set Ω and the precursors of compartment X_i.
$\boldsymbol{n}(\boldsymbol{i})$: the number of compartments belonging to set $S(\Omega, X_i)$.
$\mathbf{s}(\boldsymbol{i})$: a set whose elements are the subindices used to denote the compartments belonging to set $S(\Omega, X_i)$.
$\boldsymbol{c}(\boldsymbol{i})$: a number equal to 1 if ⓘ is a final class, or equal to 0 if ⓘ is not a final class.
$\boldsymbol{u}(\boldsymbol{i})$: a number equal to $n(i)$ if ⓘ is not final, and equal to $n(i) - 1$ if ⓘ is final, *i.e.*:

$$u(i) = n(i) - c(i) \tag{25}$$

3.7.2 Eigenvalues and the characteristic polynomial of matrix K from matrix $K^\bullet$

In matrix $\boldsymbol{K}^\bullet$, the submatrices $\boldsymbol{M}_{r,r}(r = 1, 2, \ldots, \delta)$ of the main diagonal are irreducible; *i.e.*, they cannot be expressed in the following form:

$$M_{r,r} = \begin{bmatrix} M'_{r,r} & 0 \\ M''_{r,r} & M'''_{r,r} \end{bmatrix} \tag{26}$$

where $\mathbf{M}'_{r,r}$ and $\mathbf{M}'''_{r,r}$ are square submatrices. This means that it would be another class within class C_r that is associated with $\mathbf{M}_{r,r}$, which is not possible since we know that all the classes are disjoints.

In addition, if $r \leq f$, in the column of matrix $\boldsymbol{K}^\bullet$ to which $\boldsymbol{M}_{r,r}$ belongs, there will be at least one other non null submatrix. At these conditions $\boldsymbol{M}_{r,r}$ is a matrix in which at least one of the elements on its main diagonal is, in absolute values, greater than the sum of all the other elements in the same column; *i.e.*, is a diagonally dominant matrix. In this case, if the matrix is also irreducible, then it is non singular [46]; *i.e.*, it has no null-eigenvalue. On the other hand, if $r > f$, the sum of the elements of all the columns is zero and $\boldsymbol{M}_{r,r}$ has one, and only one, null eigenvalue [44]. Therefore, the number of the null eigenvalues of matrix $\boldsymbol{K}^\bullet$ coincides with the number of final classes of the corresponding compartmental system.

We will denote the characteristic polynomial associated with submatrix $\boldsymbol{M}_{\boldsymbol{r},\boldsymbol{r}}(r = 1, 2, \ldots, \delta)$ as $\Delta_r(\lambda)\quad(r = 1, 2, \ldots, \delta)$ or, with its equivalent, class $C_r(r = 1, 2, \ldots, \delta)$. The expansion of $\Delta_r(\lambda)\quad(r = 1, 2, \ldots, \delta)$ gives:

$$\Delta_r(\lambda) = (-1)^{n_r}\lambda^{c_r}\left\{\lambda^{u_r} + F_1(r)\lambda^{u_r-1} + F_2(r)\lambda^{u_r-2} + \cdots + F_{u_r-1}(r)\lambda + F_{u_r}(r)\right\}$$
$$[F_0(r) = 1] \tag{27}$$

If class C_r is final $(r > f)$, then polynomial $\Delta_r(\lambda)$ has one, and only one, null root.

For further arguments, it is convenient to define polynomial $T_r(\lambda) \quad (r = 1, 2, \ldots, \delta)$ as:

$$T_r(\lambda) = \sum_{q=0}^{u_r} F_q(r)\lambda^{u_r-q} \tag{28}$$

Now polynomial $\Delta_r(\lambda)$ in Eq. (27) can be written as:

$$\Delta_r(\lambda) = (-1)^{n_r}\lambda^{c_r}T_r(\lambda) \tag{29}$$

and, therefore, the non null roots of $\Delta_r(\lambda)$ are the roots of $T_r(\lambda)$. In those cases where $u_r = 0$, which happens when class C_r is final and has only one compartment, $n_r = c_r = 1$, Eqs. (28) and (29) are reduced to:

$$T_r(\lambda) = 1 \qquad (n_r = c_r = 1) \tag{30}$$

$$\Delta_r(\lambda) = -\lambda \qquad (n_r = c_r = 1) \tag{31}$$

By now applying the Laplace rule for the development of a determinant by the complementary minors, we obtain:

$$D(\lambda) = \prod_{r=1}^{\delta}\Delta_r(\lambda) \tag{32}$$

The eigenvalues of matrix $\boldsymbol{K}^{\bullet}$ are the set of eigenvalues of all the submatrices $\mathbf{M}_{r,r}$ $(r = 1, 2, \ldots, \delta)$; *i.e.*, the roots of polynomials $\Delta_r(\lambda)(r = 1, 2, \ldots, \delta)$. As follows, we will number the n eigenvalues of matrix $\boldsymbol{K}^{\bullet}$ in a such way that they are the eigenvalues of submatrix $\boldsymbol{M}_{r,r}$, and if C_r is a final class $(r > f)$, we will assign the same subindex to the corresponding null root as that corresponding to the compartment denoted with the higher subindex in the class; *i.e.*, if $C_r = \{X_{w_{r_1}}, X_{w_{r_2}}, \ldots, X_{w_{r n_r}}\}$ is a final class, then the null root is denoted by $\lambda_{w_{r n_r}}$.

3.7.3 Expressions of $D(\lambda)$, $D_{k,i}(\lambda)$ and $T(\lambda)$ corresponding to set $E(\boldsymbol{\Omega}, X_i)$

We will denote the matrix obtained from matrix $\boldsymbol{K}^{\bullet}$ by $K^{\bullet}_{E_i}$ by eliminating the submatrices in the rows and columns whose number of order does not belong to set $e(i)$. We will denote the corresponding matrix by K_{E_i} whose elements are the fractional transfer coefficients.

By taking into account the form of matrix $\boldsymbol{K}^{\bullet}$ and by applying the Laplace rule again for the expansion of a determinant by the complementary minors, polynomial $D(\lambda)$ can also be written as:

$$D(\lambda) = \left[\prod_{\substack{r=1 \\ r \notin e(i)}}^{\delta} \Delta(\lambda) \right] D_{E_i}(\lambda) \tag{33}$$

where $D_{E_i}(\lambda)$ is the characteristic polynomial corresponding to matrix $K^{\bullet}_{E_i}$; *i.e.*:

$$D_{E_i}(\lambda) = (-1)^{n(i)} \lambda^{c(i)} T_{E_i}(\lambda) \tag{34}$$

in which:

$$T_{E_i}(\lambda) = \sum_{q=0}^{u(i)} F_q(E_i) \lambda^{u(i)-q} \quad [F_0(E_i) = 1] \tag{35}$$

We will name the set of the subindices corresponding to the non null roots of the characteristic polynomial $D_{E_i}(\lambda)$ $\mathbf{z}(i)$. These non null roots coincide with the roots of the corresponding polynomials $T_{E_i}(\lambda)$.

If in $D_{E_i}(\lambda)$, *row*(X_k) $(k \in \omega)$ and *column*(X_i) (the subindex of X_i involved in $\mathbf{E}(\Omega, X_i)$) are removed, then:

$$D_{k,i}(\lambda) = 0 \qquad \text{if } X_k \nprec X_i \tag{36}$$

$$D_{k,i}(\lambda) = \left[\prod_{\substack{r=1 \\ r \notin e(i)}}^{\delta} \Delta_r(\lambda) \right] D_{E_i;k,i}(\lambda) \qquad \text{if } X_k \prec X_i \tag{37}$$

where $D_{E_i;k,i}(\lambda) \quad [k, i = 1, 2, \ldots, n(i)]$ can be expressed in a polynomial form as:

$$D_{E_i;k,i}(\lambda) = (-1)^{n(i)+oc(i)+of(k)-1} \lambda^{c(i)-1} \times \sum_{q=0}^{u(i)} (f_{k,i})_q (E_i) \lambda^{u(i)-q} \quad [k, i = 1, 2, \ldots, n(i)] \tag{38}$$

3.7.4 The relation among $T(\lambda)$, $T_r(\lambda)(r = 1, 2, \ldots, \delta)$ and $T_{E_i}(\lambda)$

If Eqs. (29) and (34) are replaced in Eq. (33), then:

$$D(\lambda) = \left[\prod_{\substack{r=1 \\ r \notin e(i)}}^{\delta} (-1)^{n_r} \lambda^{c_r} T_r(\lambda) \right] (-1)^{n(i)} \lambda^{c(i)} T_{E_i}(\lambda) \tag{39}$$

By bearing in mind Eq. (21) and c, the number of total null roots can be written as so:

$$D(\lambda) = (-1)^n \lambda^c \left[\prod_{\substack{r=1 \\ r \notin e(i)}}^{\delta} T_r(\lambda) \right] T_{E_i}(\lambda) \tag{40}$$

On the other hand, if in Eq. (32) we replace the expression of $\Delta_r(\lambda)$ with that given in Eq. (29), we find that:

$$D(\lambda) = (-1)^n \lambda^c \prod_{r=1}^{\delta} T_r(\lambda) \tag{41}$$

Once again, if we consider Eq. (21) and the total number of null roots c by comparing Eq. (40) with Eq. (41), we obtain:

$$\prod_{r=1}^{\delta} T_r(\lambda) = \left[\prod_{\substack{r=1 \\ r \notin e(i)}}^{\delta} T_r(\lambda) \right] T_{E_i}(\lambda) \tag{42}$$

Then from both members of equality, we will finally obtain:

$$T_{E_i}(\lambda) = \prod_{\substack{r=1 \\ r \in e(i)}}^{\delta} T_r(\lambda) \tag{43}$$

4 Kinetic analysis

The kinetic behaviour of the linear compartmental system with a zero input is described by a homogeneous system of first-order ordinary differential equations with constant coefficients. We will assume that the eigenvalues of matrix $\boldsymbol{K}$ of the differential equations system are simple (i.e., they are not repeated) which, in practice, is the most likely situation.

4.1 Notation and additional definitions

In this section, the standard definitions and the nomenclature which usually appears in the literature on compartmental systems will be used, along with some notations and additional definitions which, together with the previous ones, will be required to obtain the corresponding symbolic equations. To help, the closed compartmental system of Fig. 3 will be used.

$x_i (i = 1, 2, \ldots, n)$: Instantaneous amount of substance in compartment X_i.
$x_i^0 (i{=}1, 2, \ldots, n)$: Instantaneous amount of substance in compartment X_i at $t{=}0$.
$G(\Omega, X_i)$: A brief form of designating the compartmental system of Graph G for which the instantaneous amount of substance in compartment X_i is required to be

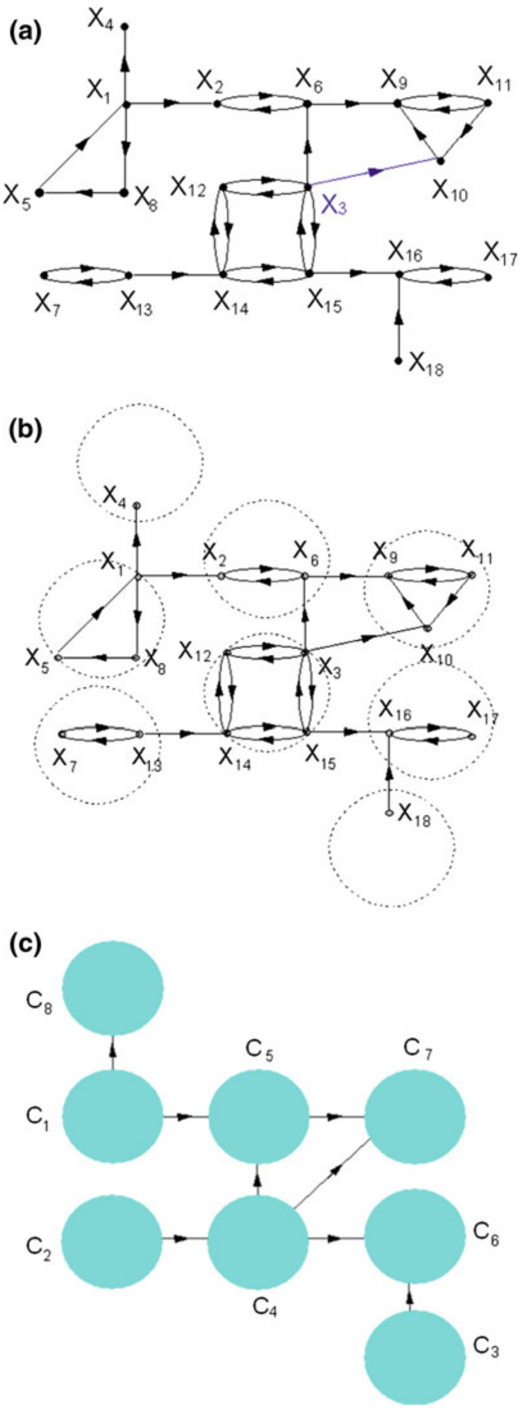

Fig. 3 Example of a compartmental system: **a** Directed graph with the numbering (arbitrary but correlative) of compartments. **b** *Circles* of *discontinuous lines* corresponding to different classes which involve the compartments belonging to them. **c** Condensation diagram that shows the eight classes of the system. Classes C_1, C_2 and C_3 are the initial ones; classes C_4 and C_5 are transit classes; C_6, C_7 and C_8 are the final classes

known when the substance is initially injected into the compartments of set Ω. For example, if in the compartmental system of Fig. 3 X_{17} is chosen as compartment X_i and the set $\{X_3, X_6, X_{13}\}$ as Ω, then $\mathrm{G}(\Omega, X_i)$ could be briefly denoted by $G(\{X_3, X_6, X_{13}\}, X_{17})$, where G is the directed graph of Fig. 3a.
$Index \in set$: The index which takes each and every one of the values that indicate the elements of the set, and which is always a set of numbers. For example, if $k \in \omega$ is written, where ω is the set $\{3, 6, 13\}$, this indicates that k takes, in any order and successively, the values of 3, 6 and 13.
$\sum_{h\in z(i)}$ expression that depends on h: a sum extended to all the elements of set $z(i)$; $i.e.$, h takes each and every one of the values of the elements of set $z(i)$.
$\sum_{k\in\omega}$ expression that depends on k: a sum extended to all the elements of set ω; $i.e.$, k takes each and every one of the values of the elements of set ω.
$\sum_{k\in\omega(i)}$ expression that depends on k: a sum extended to all the elements of set $\omega(i)$; $i.e.$, k takes each and every one of the values of the elements of set $\omega(i)$.
$\prod_{\substack{p\in z(i)\\ p\neq h}}(\lambda_p - \lambda_h)$: the product of the $u(i) - 1$ factors as indicated so that index p takes each and every one of the values of the elements of set $\boldsymbol{z}(i)$, except value h.

4.2 Optimized general kinetic equations

In “Appendix A”, the following expression is obtained for the variation of substance with time in a compartment $X_i (i = 1, 2, \ldots, n)$ when the substance is injected, at $t = 0$, into one or more of the system compartments (set Ω as defined above):

$$x_i = A_{i,0} + \sum_{h\in z(i)} A_{i,h} e^{\lambda_h t} \qquad (i = 1, 2, \ldots, n) \tag{44}$$

where the expressions of coefficients $A_{i,0}$ and $A_{i,h}$ are:

$$A_{i,0} = \frac{\sum_{k\in\omega(i)} (f_{k,i})_{u(i)}(E_i) x_k^0}{F_{u(i)}(E_i)} \qquad (i = 1, 2, \ldots, n) \tag{45}$$

$$A_{i,h} = \frac{(-1)^{u(i)-1} \sum_{k\in\omega(i)} x_k^0 \left\{ \sum_{q=0}^{u(i)} (f_{k,i})_q (E_i) \lambda_h^{u(i)-q} \right\}}{\lambda_h \prod_{\substack{p\in z(i)\\ p\neq h}} (\lambda_p - \lambda_h)}$$
$$[i = 1, 2, \ldots, n;\ h \in z(i)] \tag{46}$$

If only there is one non null root, $i.e.\ u(i) = 1$, then the denominator of the previous equation is equal to λ_1 and, in this case, its value is $-F_1(E_i)$.

We will design Eqs. (44)–(46) as “*optimized general kinetic equations*” for $\mathbf{G}(\Omega, X_i)$. “Appendix C” includes an example of these optimized general kinetic equations applied to compartmental system $\boldsymbol{G}(\{X_2, X_5\}, X_3)$, where $\boldsymbol{G}$ is the connectivity diagram indicated in Fig. 2. Even in this non complex system, the Expressions (C.26), (C.36)–(C.39) obtained using the non optimized equations are much more complex than those obtained from the optimized kinetic equations (C.9), (C.19)–(C.21).

5 Results

When obtaining the general symbolic kinetic equations for linear compartmental systems, like those analyzed herein, and as described in previous contributions [10,30], neither the properties of matrix $\boldsymbol{K}$ nor its characteristic polynomial $D(\lambda)$ relating to the distribution of system compartments into classes, as described in this paper, have been considered. These equations involve all the initial amounts of substance and all the fractional transfer coefficients in the compartmental system, regardless of the compartment for which we need to know the temporal evolution of the amount of substance and the compartments where the material is injected at $t = 0$. In most cases however, there are zero inputs and fractional transfer coefficients which have no effect on the desired kinetic behavior. When this occurs, much additional work is necessary to apply the equations to a specific case of compartmental systems to obtain both the equations and the subsequent simplification. Indeed, these general equations are not optimized. Below in Sect. 6.3, we emphasize the point of view from the equations presented herein being optimized and we illustrate it with an example.

In the analysis of any linear compartmental system, involving compartments X_1, $X_2, \ldots, X_n$, there are two problems to be solved: 1) the direct problem; i.e., determining the system's kinetic behavior for certain entries by assuming both the connectivity diagram and the values of the fractional non null transfer coefficients $K_{i,j}(i, j = 1, 2, \ldots, n; i \neq j)$ between compartments X_i and X_j. 2) The inverse problem; i.e. determining the structure of the system's connectivity diagram and estimating the values of the fractional transfer coefficients [26,35,47]. Some contributions illustrate the direct problem described in the references [6,10,25,26,30,31,38,39,44]. A recent contribution to the inverse problem was by Juillet et al. [48]. Therefore, applications of compartmental models are very extensive and can be descriptive or predictive, but they may also be theoretical or applied.

The structure of a compartmental system can be approached from two different and complementary points of view: the connection diagrams and the system matrix. In this contribution, we have provided a thorough review of all the compartmental systems which fit the model proposed from both perspectives, and we also provide concepts, definitions and additional properties which, together with those already presented in the literature, have formed the basis for obtaining the expressions that describe the overall kinetic behavior of any compartmental system that fits our model (see "Appendix A").

The importance of these kinetic equations is more readily understood if we take into account that it is necessary to include analytical kinetic equations in the inverse problem of compartmental systems that contain the parameters of the model as variables so that an experimental design can be proposed and an analysis of the experimental data can evaluate these parameters.

6 Discussion

The literature includes contributions covering the derivation of this kind of equations. Nonetheless, in our opinion, they present one or more of the following limitations:

1. They refer to specific compartmental systems in that they consist of a fixed number of compartments and connections [49–51].
2. They deal with only specific compartmental systems such as catenary [52] and mammillary systems [53].
3. They include only those systems where input is performed in only one compartment [25].
4. In those cases in which the expressions are applicable to any compartment model, these are given in a very generic and slightly elaborated form so that implementation requires the manipulation of matrices and symbolic determinants [8,11,26,28], which differ from one particular case to another. As it is known, this task is laborious, tedious and, therefore, prone to human errors. This problem cannot be avoided in systems with a few compartments, and not even when computer resolution packages are being used.
5. Even in the general kinetic equations, in which the development of determinants is facilitated through the systematic use of certain algorithms, Eqs. (44)–(46) are not provided in an optimized form because they involve all the kinetic parameters of the system, regardless of whether or not they have any influence on the instant amount of substance being sought [8,11,30,33].

6.1 Open systems

Open systems involve the release of a substance from one or more of the system compartments (even all of them) to the environment. To determine the kinetic expressions of a linear open system of N compartments with or without traps, it is sufficient to obtain the kinetic equations of the closed system. These equations are obtained by adding to the studied open one, of a single hypothetical compartment, X_n, so that n, equal to $N+1$, is now the number of compartments of the closed system obtained from the open system studied. The additional compartment, X_n, behaves as a collector of all the substance excreted to the environment from any compartment of the real initial open system [28,35]. In order to also determine the kinetics of the elimination of substance from the open system to the environment, it is necessary to simply determine the instant accumulation of substance in compartment X_n.

The open linear compartmental systems with a zero *input* can be formally treated as a hypothetical closed compartmental system from the kinetics point of view, where the environment is replaced with a single compartment that receives all the excretions. Therefore, all the results obtained in this work for closed systems are applicable to open systems after making the slight changes required by the formal addition of the aforementioned compartment; for example, the fractional excretion coefficients, non zero, $K_{i,o}$ $(i = 1, 2, \ldots, N)$ corresponding to the excretion of substance from compartment $X_i (i = 1, 2, \ldots, N)$ to the environment are replaced with the corresponding fractional transfer coefficient $K_{i,n}(i = 1, 2, \ldots, N; n = N + 1)$. Once the kinetic equations of the closed system have been obtained, the fractional transfer coefficients $K_{i,n}(i = 1, 2, \ldots, N; n = N + 1)$ involved in them must be replaced with the corresponding fractional excretion coefficients $K_{i,o}(i = 1, 2, \ldots, N)$. An entire and systematic analysis that treats these open systems through the corresponding kinetically equivalent closed system was carried out by Garcia-Meseguer et al. [10,33].

6.2 Applicability of the equations

The optimized general kinetic equations obtained in this work, Eqs. (44)–(46), can be applied to any linear compartmental system; *i.e.*, open or closed, with one or more zero inputs, with or without traps.

These equations are very elaborate and, at the same time, provide the greatest possible degree of simplification because they provide the instant amount of substance in any system compartment explicitly in terms of only those fractional transfer coefficients and zero inputs that have any influence on the instantaneous amount of substance desired.

The optimized kinetic equations (44)–(46) are valid for the distribution process of substance between system compartments in both the transition phase and the steady state. In the latter, in the steady state ($t \to \infty$), the general expression, this being Eq. (44), it is simplified to:

$$x_i = A_{i,0} \quad (i = 1, 2, \ldots, n) \tag{47}$$

and, in some cases, to $A_{i,0} = 0$.

The analysis used here for those compartmental linear systems with a zero input is also applicable to the solution of systems with inputs other than zero because this analysis firstly requires the solution by assuming a zero input [26,28,35].

6.3 Non optimized kinetic equations

There are other contributions [10,30] that also cover kinetic equations, but these equations have an important limitation which have been circumvented in this work. One of these limitations is that the symbolic equations include all the fractional transfer or excretion coefficients and zero inputs involved in the compartmental system under study, independently of whether these coefficients and inputs have or not any influence on the desired results; *i.e.* there are superfluous quantities involved in the symbolic equations which, therefore, will require ulterior simplification, which is generally difficult. “Appendix B” shows the non optimized equations [Eqs. (B.1)–(B.3)] together with the optimized ones [Eqs. (44)–(46)] so they can be compared.

To emphasize the advantages of the optimized equations obtained herein over the non optimized ones, the advanced but not the optimized Eqs. (B.1)–(B.3) in “Appendix B”, we have obtained the results of applying them to the same example, which are presented in “Appendix C”.

7 Conclusion

In this work we have obtained, for the first time, the kinetic equations corresponding to the linear system of n compartments in their optimized general form; Eqs. (44)–(46). To do this, we have used the structure of these systems, their connectivity and condensation diagrams, as well as the properties of matrix $\boldsymbol{K}$, its characteristic polynomial and minors of order $n - 1$.

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Appendix A

Derivation of the general optimized Eqs. (44)–(46)

In closed linear compartmental systems with a zero input, the differential equations system that describes the progress of substance in each system compartment is given by the following expression:

$$\frac{dx_i}{dt} = K_{1,i}x_1 + K_{2,i}x_2 + \cdots + K_{n,i}x_n \quad (i = 1, 2, \ldots, n) \tag{A.1}$$

The set of Eq. (A.1) corresponds to a homogeneous linear system of ordinary differential equations with constant coefficients.

The Laplace transform, $L\{x_i\}$ $(i = 1, 2 \ldots, n)$, of any of the equations included in Eq. (A.1) is:

$$L\{x_i\} = \frac{(-1)^{oc(i)+1}\sum_{k\in\omega}(-1)^{of(k)}D_{k,i}(\lambda)x_k^0}{D(\lambda)} \tag{A.2}$$

where the meanings of *oc(i)*, *of(k),* $D(\lambda)$, $D_{k,i}(\lambda)$ and $k \in \omega$ have been given in Sects. 3.2 and 3.3.

If Eqs. (7) and (11) are applied to Eq. (9), for $D(\lambda)$ and $D_{k,i}(\lambda)$, then:

$$L\{x_i\} = \frac{(-1)^{oc(i)+1}\sum_{k\in w}(-1)^{of(k)}D_{E_i,k,i}(\lambda)x_k^0}{D_{E_i}(\lambda)} \tag{A.3}$$

If Eq. (37) is now introduced into Eq. (A.3) and the polynomial expression given by Eq. (38) is taken into account, then:

$$L\{x_i\} = \frac{\sum_{k\in\omega} x_k^o \sum_{q=0}^{u(i)} \left(f_{k,i}\right)_q (E_i)\lambda^{u(i)-q}}{\lambda\prod_{h\in z(i)}(\lambda-\lambda_h)}(i = 1, 2, \ldots, n) \tag{A.4}$$

By considering that we have assumed that the $u(i)$ non null roots of $D_{E_i}(\lambda)$ are simple, the second member of Eq. (A.4) may be decomposed into the following sum of simple fractions:

$$L\{x_i\} = \frac{A_{i,0}}{\lambda} + \sum_{h\in z(i)} \frac{A_{i,h}}{\lambda-\lambda_h} \quad (i = 1, 2, \ldots, n) \tag{A.5}$$

By taking the inverse Laplace transform in Eq. (A.5), Eq. (44) from the main text is obtained, where the expressions of coefficients $A_{i.0}$ and $A_{i,h}$ are easily obtained from Eqs. (A.4) and (A.5):

$$A_{i,0} = \frac{\sum_{k\in\omega}(f_{k,i})_u(E_i)x_k^0}{F_{u(i)}(E_i)} \quad (i = 1, 2, \ldots, n) \tag{A.6}$$

$$A_{i,h} = \frac{(-1)^{u(i)-1}\sum_{k\in\omega}x_k^o\left(\sum_{q=0}^{u(i)}(f_{k,i})_q(E_i)\lambda^{u(i)-q}\right)}{\lambda_h\prod_{\substack{p\in z(i)\\ p\neq h}}(\lambda_p-\lambda_h)} \quad [i = 1,2, \ldots, n;\, h \in z(i)] \tag{A.7}$$

If set $z(i)$ consists of only one element or, in other words, if $u(i) = 1$ (*i.e.*, the polynomial has only one non null root), then the denominator of the previous equation is equal to λ_1 which, in this case, coincides with $-F_1(E_i)$.

Index k, which does not belong to set $\omega(i)$ will provide the null coefficients values $(f_{k,i})_q$. Therefore, the above Eqs. (A.6) and (A.7) can be simplified even more to obtain Eqs. (45) and (46) of the main text, where set ω has been replaced with set $\omega(i)$. Obviously, these two sets could coincide.

If there is only one non null root, *i.e.*, $u(i) = 1$, then the denominator of the previous equation is equal to λ_1 which, in this case, would coincide with $-F_1(E_i)$.

Appendix B

Comparison of the symbolic expressions for the optimized and non optimized equations

The meanings of the different magnitudes contained in them are defined in the main text. The numbers of the optimized equations coincide with the equations in the main text.

Optimized equations		**Non optimized equations**	
$x_i=A_{i,0}+\sum_{h\in z(i)}A_{i,h}e^{\lambda_h t} \quad (i=1, 2, \ldots, n)$	(44)	$x_i=A_{i,0}+\sum_{h=1}^{u}A_{i,h}e^{\lambda_h t} \quad (i=1, 2, \ldots, n)$	(B.1)
$A_{i,0}=\frac{\sum_{k\in\omega(i)}(f_{k,i})_{u(i)}(E_i)x_k^0}{F_{u(i)}(E_i)} \quad (i=1, 2, \ldots, n)$	(45)	$A_{i,0}=\frac{\sum_{k\in\omega}(f_{k,i})_u x_k^0}{F_u} \quad (i=1, 2, \ldots, n)$	(B.2)
$A_{i,h}=\frac{(-1)^{u(i)-1}\sum_{k\in\omega(i)}x_k^o\left(\sum_{q=0}^{u(i)}(f_{k,i})_q(E_i)\lambda^{u(i)-q}\right)}{\lambda_h\prod_{\substack{p\in z(i)\\ p\neq h}}(\lambda_p-\lambda_h)}$ $[i=1, 2, \ldots, n;\, h\in z(i)]$	(46)	$A_{i,h}=\frac{(-1)^{u-1}\sum_{k\in\omega}x_k^o\left(\sum_{q=0}^{u}(f_{k,i})_q\lambda^{u-q}\right)}{\lambda_h\prod_{\substack{p=1\\ p\neq h}}^{u}(\lambda_p-\lambda_h)}$ $(i=1, 2, \ldots, n;\, h=1, 2, \ldots, u)$	(B.3)

Note: If there is only one non null root, *i.e.* $u(i) = 1$ (in the optimized equations), or $u = 1$ (in the non optimized ones), then the denominators of Eqs. (46) and (B.3) are equal to λ_1 which, in this case, coincide with $-F_1(E_i)$ in the optimized equations and with $-F_1$ in the non optimized equations.

Appendix C

Example 1: Applying the optimized general kinetic equations

In this section, and by way of example, the optimized general kinetic equations $\boldsymbol{G}(\Omega, X_i)$ (44)–(46), will be applied to compartmental system $\boldsymbol{G}(\{X_2, X_5\}, X_3)$ where $\boldsymbol{G}$ is the connectivity diagram indicated in Fig. 2 and $C_1 = \{X_1, X_2\}, C_2 = \{X_3\}$, $C_3 = \{X_4, X_5\}$, where C_1 is an initial class, and C_2 and C_3 are final classes. In this case:

$$\Omega = \{X_2, X_5\} \tag{C.1}$$
$$X_i \equiv X_3 \tag{C.2}$$

This election leads to the following results:

$$E_3(\Omega, X_3) = \{C_1, C_2\} \tag{C.3}$$
$$\omega(3) = \{2\} \tag{C.4}$$
$$z(3) = \{1, 2\} \tag{C.5}$$
$$n(3) = 3 \tag{C.6}$$
$$u(3) = 2 \tag{C.7}$$

The application of Eq. (44) to this case gives:

$$x_3 = A_{3,0} + \sum_{h \in z(3)} A_{3,h} e^{\lambda_h t} \tag{C.8}$$

or, in its expanded form:

$$x_3 = A_{3,0} + A_{3,1} e^{\lambda_1 t} + A_{3,2} e^{\lambda_2 t} \tag{C.9}$$

where, according to Eqs. (45) and (46), and by taking into account values (C.1)–(C.7), we obtain:

$$A_{3,0} = \frac{(f_{2,3})_2 (E_3) x_2^0}{F_2(E_3)} \tag{C.10}$$

$$A_{3,h} = -\frac{x_2^0 \left(\sum_{q=0}^{2} (f_{2,3})_q (E_3) \lambda_h^{2-q} \right)}{\lambda_h \prod_{\substack{p \in z(3) \\ p \neq h}} (\lambda_p - \lambda_h)} \quad (h = 1, 2) \tag{C.11}$$

The roots λ_1 and λ_2 involved in Eqs. (C.9) and (C.11) are the roots of polynomial $T_1(\lambda)$:

$$T_1(\lambda) = \lambda^2 + F_1(1)\lambda + F_2(1) \tag{C.12}$$

where:

$$F_1(1) = K_{1,2} + K_{2,1} + K_{2,3} + K_{2,4} \tag{C.13}$$
$$F_2(1) = K_{1,2}K_{2,3} + K_{1,2}K_{2,4} \tag{C.14}$$

On the other hand, coefficients $F_2(E_3)$ and $(f_{2,3})_q(E_3)(q = 0, 1, 2)$, determined as explained in the main text, are:

$$F_2(E_3) = K_{1,2}(K_{2,3} + K_{2,4}) \tag{C.15}$$
$$(f_{2,3})_0(E_3) = 0 \tag{C.16}$$
$$(f_{2,3})_1(E_3) = K_{2,3} \tag{C.17}$$
$$(f_{2,3})_2(E_3) = K_{1,2}K_{2,3} \tag{C.18}$$

Finally, if in Eqs. (C.10) and (C.11) we substitute Expressions (C.15)–(C.18), then:

$$A_{3,0} = \frac{K_{2,3}}{K_{2,3} + K_{2,4}} x_2^0 \tag{C.19}$$
$$A_{3,1} = -\frac{K_{2,3}\lambda_1 + K_{1,2}K_{2,3}}{\lambda_1(\lambda_2 - \lambda_1)} x_2^0 \tag{C.20}$$
$$A_{3,2} = -\frac{K_{2,3}\lambda_2 + K_{1,2}K_{2,3}}{\lambda_2(\lambda_1 - \lambda_2)} x_2^0 \tag{C.21}$$

Example 2: Applying the non optimized equations

In order to compare the expressions obtained from both equations sets, here we will apply the non optimized Eqs. (B.1)–(B.3) to the same compartmental system $\boldsymbol{G}(\{X_2, X_5\}, X_3)$ used before in Example 1.

In this case:

$$\omega = \{2, 5\} \tag{C.22}$$
$$n = 5 \tag{C.23}$$
$$u = 3 \tag{C.24}$$

The application of Eq. (B.1) to this case gives:

$$x_3 = A_{3,0} + \sum_{h=1}^{3} A_{3,h} e^{\lambda_h t} \tag{C.25}$$

or, in its expanded form:

$$x_3 = A_{3,0} + A_{3,1}e^{\lambda_1 t} + A_{3,2}e^{\lambda_2 t} + A_{3,3}e^{\lambda_3 t} \tag{C.26}$$

where, according to Eqs. (B.2) and (B.3), and by taking into account values (C.22)–(C.24), we obtain:

$$A_{3,0} = \frac{(f_{2,3})_3 x_2^0 + (f_{5,3})_3 x_5^0}{F_3} \tag{C.27}$$

$$A_{3,h} = \frac{x_2^0 \left(\sum_{q=0}^{3} (f_{2,3})_q \lambda_h^{3-q}\right) + x_5^0 \left(\sum_{q=0}^{3} (f_{5,3})_q \lambda_h^{3-q}\right)}{\lambda_h \prod_{\substack{p=1 \\ p \neq h}}^{3} (\lambda_p - \lambda_h)} \quad (h = 1, 2, 3) \tag{C.28}$$

The roots λ_1, λ_2 and λ_3 involved in Eqs. (C.26) and (C.28) are the roots of polynomial $T(\lambda)$:

$$T(\lambda) = \lambda^3 + F_1\lambda^2 + F_2\lambda + F_3 \tag{C.29}$$

where:

$$F_1 = K_{1,2} + K_{2,1} + K_{2,3} + K_{2,4} + K_{4,5} + K_{5,4} \tag{C.30}$$

$$F_2 = K_{1,2}(K_{2,3} + K_{2,4} + K_{4,5} + K_{5,4}) + (K_{2,1} + K_{2,3} + K_{2,4})(K_{4,5} + K_{5,4}) \tag{C.31}$$

$$F_3 = K_{1,2}(K_{2,3} + K_{2,4})(K_{4,5} + K_{5,4}) \tag{C.32}$$

On the other hand, the non zero coefficients $(f_{2,3})_q$ and $(f_{5,3})_q (q = 0, 1, 2, 3)$ are:

$$(f_{2,3})_1 = K_{2,3} \tag{C.33}$$

$$(f_{2,3})_2 = K_{2,3}(K_{1,2} + K_{4,5} + K_{5,4}) \tag{C.34}$$

$$(f_{2,3})_3 = K_{1,2}K_{2,3}(K_{4,5} + K_{5,4}) \tag{C.35}$$

Finally, if in Eqs. (C.27) and (C.28) we substitute the Expressions (C.32)–(C.35), by taking into account the zero-value coefficients $(f_{k,i})_q$, then:

$$A_{3,0} = \frac{K_{2,3}}{K_{2,3} + K_{2,4}} x_2^0 \tag{C.36}$$

$$A_{3,1} = \frac{K_{2,3}\lambda_1^2 + K_{2,3}(K_{1,2} + K_{4,5} + K_{5,4})\lambda_1 + K_{1,2}K_{2,3}(K_{4,5} + K_{5,4})}{\lambda_1(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} x_2^0 \tag{C.37}$$

$$A_{3,2} = \frac{K_{2,3}\lambda_2^2 + K_{2,3}(K_{1,2} + K_{4,5} + K_{5,4})\lambda_2 + K_{1,2}K_{2,3}(K_{4,5} + K_{5,4})}{\lambda_2(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} x_2^0 \tag{C.38}$$

$$A_{3,3} = \frac{K_{2,3}\lambda_3^2 + K_{2,3}(K_{1,2} + K_{4,5} + K_{5,4})\lambda_3 + K_{1,2}K_{2,3}(K_{4,5} + K_{5,4})}{\lambda_3(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} x_2^0 \tag{C.39}$$

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