COMPUTERIZED EVALUATION OF MEAN RESIDENCE TIMES IN MULTICOMPARTMENTAL LINEAR SYSTEM AND PHARMACOKINETICS

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Key Words:	linear compartment, biological system, mean residence time, pharmacokinetics, computer chemistry

COMPUTERIZED EVALUATION OF MEAN RESIDENCE TIMES IN MULTICOMPARTMENTAL LINEAR SYSTEM AND PHARMACOKINETICS.

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Abstract

The deriving of mean residence times is an important task both in pharmacokinetics as well as in linear multicompartmental system. Taking as start point the analysis of the mean residence times in multicompartmental linear systems open or closed ¹, we implement a versatile software, using the VISUAL BASIC 6.0 language for MS-Windows, that is easy to use and with a user-friendly format for the input of data and the output of the results. For any multicompartmental linear system of up to 512 compartments, closed or open, with traps or without traps, with zero input in one or more of the compartments,

this software allows the user to obtain, both the symbolic expressions, in the most simplified form, and/or the numerical values of the mean residence times in any of its compartments, in the entire system or in a part of the system. As far as we known from the literature, such a software has not been implemented before. The advantage of the present software is that it cuts down on the work time needed and minimizes the human errors that are frequent in compartmental and kinetic systems even those that are relatively straightforward.

The software bioCelTer, along with instructions, can be downloaded from <http://oretano.iele-ab.uclm.es/~fgarcia/bioCelTer/>

1. INTRODUCTION

Interest in using compartment models to define, identify and describe biophysical systems, which include many physiological, pharmacological, nutritional, toxicological and biochemical systems has grown in recent years²⁻⁴. Such models consist of a finite number of components related to transfer rates or the reaction between them. A compartment may represent a real physical region or an abstract representation of the same⁵⁻⁹.

The application of compartmental analysis to biological systems^{10,11}, along with the use of isotopic tracers, parameter identification and methods to evaluate mean parameters, involves an overall analysis of the model under consideration, including the deduction of kinetic equations for the system of compartments in terms of its parameters and the evaluation of mean residence time¹². Compartmental model originated in the field of pharmacokinetics and is a commonly used mathematical model for positron emission tomography (PET), which has recently achieved great success in tumor detection and cancer stages¹³.

Most known drugs that act on the human body have an absorption, distribution and elimination kinetics of linear first-order. The drugs bind in a reversible way to their specific receptors and are completely excreted, behaving therefore as an open system. This allows the concentration to be determined in each space and at each time, along with other parameters of pharmacokinetic interest, such as mean residence time (the subject of this contribution) bioavailability, etc.⁸, depending on the rate constants in these compartments where it is possible take samples.

The use of compartmental analysis is increasing among nutritionists^{14,15}. Compartmental analysis can be applied to the kinetic study of models of nutrient digestion, absorption and metabolism and to estimating masses of nutrients and their metabolites; it also allow various parameters that depend on time, such as the fractional catabolic rate and the

mean residence times, to be obtained. Examples we may mention as being among the most representative, are the multicompartmental model proposed for zinc and changes in its metabolism that depend on various parameters such as diet, genetic factors and certain diseases¹⁶, the micronutrient kinetic model¹⁷ and the multicompartmental kinetic model proposed for cholesterol distribution¹⁸. Recently,¹⁹ developed a multicompartmental model consisting of thirteen compartments to describe the kinetics of the postprandial distribution and metabolism of dietary nitrogen in humans.

Compartmental analysis may also be useful in toxicology²⁰: certain toxic or chemical species may accumulate in significant quantities in a given compartmental model and flow very slowly to the bloodstream, i.e. a certain tissue may act as a reservoir for a substance, for example, lead in bone. Another interesting example is the compound benzo[*a*]pyrene, a polycyclic aromatic hydrocarbon, widely recognized as a carcinogen in animals, and suspected of having a neoplastic effect in human. Benzo[*a*]pyrene is found in tar, tobacco smoke and diesel vapor and may be formed by heating certain fats. A multicompartmental distribution has been proposed in experimental animals, establishing a model of eleven compartments²¹.

The study of compartmental systems usually has two main objectives: 1) Obtaining the time variation for the amount of matter in each of the compartments or in one part of the system, in open or closed compartmental systems when there is zero input in any of them, i.e., analysis of the kinetics of the system, and 2) Obtaining, for the same type of compartmental system, the mean residence time in the compartments, in the entire system or in any part of it.

The kinetics of these systems has been widely analyzed^{8,22-29}. The contribution of³⁰ provides symbolic time course equations corresponding to a general model of a linear compartmental system, closed or open, with or without traps and with zero input.

Regarding the determination of mean residence time,¹ performed a complete analysis of the mean residence times in linear compartmental systems, closed or open, with or without traps and with zero input. This analysis allows the derivation of explicit and simple general symbolic formulas to obtain the mean residence time in any compartment of any linear compartmental system, closed or open with or without traps as well as formulas to evaluate the mean residence time in the entire system. The formulas are given as functions of coefficients, which in turn are a function of the fractional transfer coefficients between the compartments and, in the case of open systems, include coefficients for the excretion to the

environment from the different compartments. The relationship between the formulas derived and the particular connection properties of the compartments was discussed. Until this contribution, only the residence times for open compartmental systems in which the matter is completely eliminated had been defined and therefore evaluated and open systems with traps or closed systems had not been studied. However, this contribution¹ has two major limitations: a) The coefficients involved in the symbolic expression of the mean residence times must be obtained either manually or using appropriate software, e.g the computer program COEFICOM³⁰; (b) Once the expressions of the coefficients are inserted in the corresponding symbolic expression for the mean residence times, a subsequent manual simplification may be necessary to eliminate those fractional transfer coefficient not involved in the mean residence time desired; (c) If the numerical value of any mean residence time is wanted, it must be obtained manually from the corresponding symbolic expression and the individual values of the fractional transfer coefficients involved in this expression.

No computer program has yet been developed, based on theoretical considerations and appropriate algorithms contained in the two above mentioned contributions, that allows the computerized acquisition for any linear compartmental system, closed or open, with traps or without traps, with zero input in one or more of the compartments, of the symbolic expressions, in the most simplified form, and/or the numerical values of the residence times in any of its compartments, in the entire system or in a part of the system. The main subject of this contribution is the implementation of such a software. This software will be useful for any linear compartmental system and may be expected to stimulate scientific development in biophysical and biomedical sciences in general and in nutrition, pharmacokinetics and in toxicology, in particular.

2. MATERIALS AND METHODS

The software is deployed to obtain symbolic expressions as a function of fractional transfer coefficients and in the case of fractional excretion coefficients involved in the system or numerical values of the mean residence times in the compartmental system and in entire system. Symbolic expressions are used in a final and highly simplified form. Those provided by¹ are summarize below. The above symbolic equations involve polynomial coefficients that result from developing the crucial feature of the system of differential equations and minors of this determinant of order one less unit. To obtain these coefficients we applied algorithms developed previously by our working group^{1,24,28-35}. The programming language used was the

Visual Basic 6.0 for Windows included in Microsoft Visual Studio 6.0 Professional Edition package.

The model we study consists of a linear compartmental system, open or closed, with no traps or traps with zero input in one or more compartment over the system, which is the same as analyzed by ¹ to evaluate the symbolic equations of the mean residence times.

To check the software and to apply it to the different examples in this paper we have used a Pentium (R) 4 CPU 2.80 GHz, 1.50 GB of RAM .

3. NOTATION

To provide the reader with the basis for using the software presented in this paper, we summarize a minimal set of definitions and symbolic expressions of the mean residence times taken from previous contributions of our group ¹.

Compartmental systems are considered closed, if there is no interchange of substance between any compartments of the system with the environment. Otherwise, they are named open systems.

3.1. Summary of definitions and symbolic expressions for the mean residence time in closed systems

n : number of compartments of the compartmental system.

X_i ($i=1,2,\dots,n$): each of the compartments of the system.

x_i ($i=1,2,\dots,n$): instantaneous amount of substance in compartment X_i

x_i^0 ($i=1,2,\dots,n$): amount of substance in compartment X_i at $t=0$, i.e. the initial x_i -value

$K_{i,j}$ ($i,j=1,2,\dots,n$; $i \neq j$): fractional transfer coefficient corresponding to the direct connection between the compartments X_i and X_j . $K_{i,j}$ is a positive or null quantity depending upon whether or not a direct connection between the compartments X_i and X_j exists.

$K_{i,i}$ ($i=1,2,\dots,n$): is defined as $-\sum_{\substack{j=1 \\ j \neq i}}^n K_{i,j}$. From the definition it follows that $K_{i,i}$ always is a non-

positive quantity, i.e. it is null or negative.

$D(\lambda)$: The secular determinant associated to the matrix of the compartmental system, i.e.:

$$D(\lambda) = \begin{vmatrix} K_{1,1} - \lambda & K_{2,1} & \cdot & \cdot & \cdot & K_{n,1} \\ K_{1,2} & K_{2,2} - \lambda & \cdot & \cdot & \cdot & K_{n,2} \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ K_{1,n} & K_{2,n} & \cdot & \cdot & \cdot & K_{n,n} - \lambda \end{vmatrix} \quad (1)$$

$D(\lambda)$ is also referred as *the secular polynomial*.

c : number of null roots of $D(\lambda)$. This number coincides with the number of final classes in the compartmental system.

u : number of non-null roots of $D(\lambda)$. Note that $u + c = n$

Coefficients F_q ($q = 0, 1, \dots, u$): When determinant $D(\lambda)$ is expanded:

$$D(\lambda) = (-1)^n \lambda^c T(\lambda) \quad (2)$$

where

$$T(\lambda) = \sum_{q=0}^u F_q \lambda^{u-q} \quad (F_0 = 1) \quad (3)$$

Therefore, the expressions for the coefficients F_q ($q=0, 1, 2, \dots, u$) may be obtained by expanding the secular determinant $D(\lambda)$ and taking equation (2) and equation (3) into account. However, this is not necessary because the expressions for these coefficients may be obtained in an easy, systematic and recurrent way from combinations of the $K_{i,j}$ 's²⁹.

Coefficients $(f_{m,i})_q$ ($m, i=1, 2, \dots, n$; $q=0, 1, 2, \dots, u$): If the m -th row and the i -th column in the determinant $D(\lambda)$ are removed, the resulting determinant is named $D_{m,i}(\lambda)$ ($m, i=1, 2, \dots, n$). The expansion of $D_{m,i}(\lambda)$ leads to:

$$D_{m,i}(\lambda) = (-1)^{n+i+m-1} \lambda^{c-1} \sum_{q=0}^u (f_{m,i})_q \lambda^{u-q} \quad [(f_{m,i})_0 = 0 \text{ if } m \neq i; (f_{m,i})_0 = 1 \text{ if } m=i] \quad (4)$$

where $(f_{m,i})_q$ consists of a subset of the terms involved in the corresponding F_q and is always a non-negative quantity. Thus, the coefficients $(f_{m,i})_q$ could be obtained by expanding $D(\lambda)$ and using equations (2) and (3) or, much easier, by using the systematic and recurrent method to derive these coefficients from the corresponding coefficient F_q .

$r_{i,m}$ ($i, m=1, 2, \dots, n$): The mean residence time in the compartment X_i , when the matter is initially injected in the compartment X_m .

$r_{i,m_1,m_2,\dots,m_w}$ ($i=1,2,\dots,n$; $w \leq n$): The mean residence time in compartment X_i , when more than one zero input entered simultaneously in different compartments, e.g. $x_{m_1}^0, x_{m_2}^0, \dots, x_{m_w}^0$ in the corresponding compartments $X_{m_1}, X_{m_2}, \dots, X_{m_w}$. Obviously if $w=1$, then $m_1=m$

x_T^0 : Sum of the zero input in an arbitrary set of compartments $X_{m_1}, X_{m_2}, \dots, X_{m_w}$, i.e.,

$$x_T^0 = x_{m_1}^0 + \dots + x_{m_w}^0 \quad (5)$$

r_m ($m=1,2,\dots,n$): The mean residence time in the entire compartmental system of the substance, when it is injected at $t=0$ in to compartment X_m . It is defined as the sum of the mean residence times of the substance in each of the compartments of the system, when it is injected in compartment X_m at $t=0$, i.e. the mean time that the substance spends in the system.

This is given by:

$$r_m = \sum_{i=1}^n r_{i,m} \quad (m=1,2,\dots,n) \quad (6)$$

In a closed system:

$$r_m = \infty \quad (m = 1, 2, \dots, n) \quad (7)$$

This result is to be expected, because in a closed compartmental system there is no excretion to the environment from any compartment. Therefore, the mean residence time in the entire compartment must be infinite regardless of the X_m compartment in which the matter is injected.

$r_{m_1,m_2,\dots,m_w}$ ($w \leq n$): The mean residence time in the entire compartmental system when more than one zero input are made simultaneously in different compartments, e.g. $x_{m_1}^0, x_{m_2}^0, \dots, x_{m_w}^0$ in the corresponding compartments $X_{m_1}, X_{m_2}, \dots, X_{m_w}$.

Ω : A subset of the system formed by certain compartments $X_{g_1}, X_{g_2}, \dots, X_{g_h}$ ($h \leq n$).

$r_{\Omega,m_1,m_2,\dots,m_w}$: The mean residence time in Ω when more than one zero input, e.g.

$x_{m_1}^0, x_{m_2}^0, \dots, x_{m_w}^0$, are simultaneously made in the different corresponding compartments

$X_{m_1}, X_{m_2}, \dots, X_{m_w}$.

3.2. Summary of definitions and symbolic expressions for the mean residence time in open systems

Open systems can be treated formally as an hypothetical equivalent closed system from the kinetic point of view, where the environment is replaced by one compartment which receives all the excretions⁵.

Next, we give a general notation for open systems.

N : number of compartments of open systems.

$K_{i,o}$ ($i=1, 2, \dots, N$): Fractional transfer coefficient describing the excretion of material from compartment X_i to the environment. Evidently, if no excretion from any compartment of the system to the environment occurs, all these coefficients are null and it would be a closed system. Therefore, an open system has to be, at least a non-null fractional excretion coefficient.

The closed linear compartmental system which is kinetically equivalent to an open system under study consists of n compartments, $X_1, X_2, \dots, X_N, X_{N+1}$ ($X_n \equiv X_{N+1}$) where X_n is the added hypothetical compartment to the open system that receives all the excretions. Thus, the application of this formalism yields:

$$K_{i,o} \equiv K_{i,n} \quad (i=1, 2, \dots, N) \quad (8)$$

Evidently, we have:

$$n=N+1 \quad (9)$$

3.3. General expressions for the mean residence time.

Fig. 1 presents a simple diagram¹ to obtain the expressions of $r_{i,m}$ ($i, m=1, 2, \dots, n$), which depend on whether $(f_{m,i})_u$ and $(f_{m,i})_{u-1}$ are zero or not.

In Fig. 2, another diagram to obtain the expressions of r_m in open systems is presented.

4. IMPLEMENTATION

The coefficients appearing in the symbolic expressions of the mean residence times in Figs. 1 and 2 can be obtained manually as they are coefficients of the polynomials indicated in the previous section. However, we have developed subroutines using algorithms previously developed by our group (COEFICOM^{30,36}). These subroutines allow the computer to carry out this task easily and quickly, for any compartmental linear system irrespective of its complexity, thus avoiding possible human error and saving time. From the symbolic expressions, it is possible to obtain the numerical values of the wanted mean residence times by merely replacing the symbol for the fractional transfer coefficients by the corresponding numerical value. This task also can be carried out by our software.

A simplified flow diagram of the implemented software is shown in Fig. 3

The computer program, we have named bioCelTer, is written using VISUAL BASIC for Windows v.6.0 included in MICROSOFT VISUAL STUDIO 6.0 PROFESSIONAL EDITION package. The main characteristics of this software are:

- i) The program evaluates the symbolic expressions and/or numerical values of mean residence times in compartment systems of up to 512 compartments (a number subject to the limitations imposed by the memory and disk space available). The maximum number of compartments could easily be increased if necessary.
- ii) The input and output data are easy to introduce, due to the graphical interface and versatility of Visual Basic 6.0. As data is entered, options will turn on and off in a very intuitive way.
- iii) The entire program is conducted in a single window, which greatly facilitates the task use.
- iv) The results can be saved in a text file, which can be opened and manipulated with most word processor programs.
- v) The symbolic expressions and/or the numerical values of the fractional transfer coefficient, K_{ij} can be saved and later imported for any purpose.
- vi) The compartmental system under study, whether a new or imported, can be modified at any time by the use, i.e. the symbolic expressions of the transfer fractional coefficients and/or its numerical values can be changed.
- vii) In the output file, the symbolic expressions and/or the numerical values of the mean residence times wanted are written, together with the time the computer has elapsed in the process.

4.1. Hardware requirements.

The main requirement is for a 32-bit Windows operating system such as Windows 2000, XP, Vista or Windows 7 with enough free memory. In addition, to facilitate viewing of all the screens it is recommended that a graphical resolution of at least 800x600 pixels (with small fonts) displaying 256 colours or more be used.

4.2. Input syntax and structure.

To run the program we must select whether it is an open or closed compartmental system and the number of compartments, n , which the system under study contains. A grid is automatically displayed where we select the cells corresponding to values of i and j so that K_{ij}

is not null, i.e. we select those cells for which compartment X_i is directly connected with compartment X_j . Another option is that all cells in the grid are displayed as selected and then the user can delete the marks in the cells corresponding to the null $K_{i,j}$'s. This option is useful when the numbers of non-null $K_{i,j}$'s is considerably higher than that of null $K_{i,j}$'s. To select this option "All" must be pressed. When a cell is selected, the grey colour of the cells in the grill containing the corresponding i - and j -values turns green as long as the left hand button of the mouse remains pressed. This facilitates the correct selection of the cells and thus avoids possible errors. If you desire to remove a marked connection, simply re-press on the corresponding cell. Once these steps have been carried out, click on "Save" in the "Compartment Connections" box.

When another symbolic expression for $K_{i,j}$ (and $K_{i,o}$'s for open systems) is required, e.g. " $k_1[S]_0$ " instead of $K_{1,2}$, etc, the corresponding cell must be selected and then a window is displayed to write the alternative symbolic expression (see Fig. 4). If the user does not assign a symbolic expression for some particular $K_{i,j}$, the program assumes it to be $K_{i,j}$ as soon as the "Save" is pressed in the "Symbolic Expression" box.

From now on numerical values can be entering by clicking in the selected cell. A window is displayed to write the numerical value and later pressing "Save" in the "Numerical Values" box.

Obviously, when one is interested only in the numerical values of the mean residence time no symbolic expression other than $K_{i,j}$ is needed, and only to press "Save" in the "Symbolic Expressions" box needs to be pressed and the corresponding numerical values entered.

Once the connections have been saved, we can also remove or add new connections pressing "Modify" and later "Save" in the "Compartment connections" box so that new symbolic expressions and/or numerical values can now be added. If you modify this compartmental system, the software also allows you to import the values saved in the last grid, by pressing the "Import last symbolic expressions" or "Import last values", and to save by pressing "Save" in the corresponding box (symbolic or numerical), see Fig. 5. Note that you save the items that appear in the grid.

The software also permits us to save the system under study, import saved systems and create new ones, clicking the appropriate button,

From here on, there are three different options: (1) To obtain only the symbolic expressions for the mean residence times; (2) To obtain only the numerical value for the mean residence times; (3) To obtain both the symbolic expressions with their numerical values for the mean residence times.

(1) To obtain only the symbolic expressions for the mean residence times

In this option there are two possibilities: (1a) To obtain the mean residence time in compartment X_i due to zero input in one compartment, X_m , i.e, to obtain $r_{i,m}$ and (1b) To obtain the residence time in the entire system when an zero input is made in only one compartment X_m , i.e, to obtain r_m . The way to determine the residence time, in any compartment X_i and in the entire system when different and simultaneous inputs zero are made in more than one compartment X_m , is discussed in the 6.RESULTS AND DISCUSSION section. Next we see the different steps corresponding to cases 1a and 1b above.

1(a) Mean residence time in a compartment X_i due to an zero input in only one compartment X_m

Step 1

Choose the indexes m ($m=1,2,...,n$) of the compartments, X_m , in which the inputs zero are made by clicking on the desired numbered cells in the second columns in the grid “Select compartments”. Then choose those indexes i ($i=1,2,...,n$) of compartments X_i in which the mean residence time is wanted by clicking on the desired numbered cells on the first column in the same grid above. If desired, we can mark or unmark all the compartments in a given column by clicking “pencil icon” on the top box. (If none of the cells in the grid is selected, a warning message appears to indicate that at least one of them must be chosen).

Step 2

Once the wanted $r_{i,m}$ has been selected click on “Mean residence time in compartments” in the “Symbolic expression” box in the windows and then a window appears in which the symbolic expressions of the residence times are displayed (see example 1 below).

Step 3

The above residence times can be saved as a text file by pressing the icon at the bottom of the window showing the results.

1(b) Residence time in the entire system when an zero input is made in only one compartment X_m , i.e, to obtain r_m .

Step 1

Choose the index m ($m=1,2,\dots,n$) of compartment, X_m , in which the zero input is made by clicking the desired numbered cells in the second columns in the grid “Select compartments”. If more than one residence time r_m is desired, then all of the corresponding indexes m must be selected.

Step 2

Once the r_m has been selected, click on “Mean residence time in the system” in the “Symbolic expression” box in the screen. A window appears in which the symbolic expression(s) of the mean residence time(s) in the entire system, r_m ($m=1,2,\dots,n$) is/are displayed (see example 1 below).

Step 3

The above residence time(s) can be saved as a text file by pressing the icon at the bottom of the windows showing the results.

(2) To obtain only the numerical value for the mean residence times

In this option there are also two possibilities: 2(a) To obtain the numerical mean residence time in a compartment X_i due to an zero input in only one compartment, X_m , i.e, to obtain $r_{i,m}$ and 2(b) To obtain the numerical mean residence time in the entire system when an zero input is made in only one compartment X_m , i.e, to obtain r_m . The way to determine the numerical mean residence time in any compartment X_i and in the entire system when different and simultaneous inputs zero are made in more than one compartment X_m is discussed in the 6. RESULTS AND DISCUSSION section.

The numerical values of all of the the $K_{i,j}$'s (and $K_{i,o}$'s for open systems) on the grid must be entered. Prior to entering these numerical values, the units for all of them must be selected in the window “Unit of the $K_{i,j}$'s”. Likewise, the units in which the results are desired must be selected on the window “Unit of the Results” on the screen. Once the units have been selected, the corresponding cells containing the $K_{i,j}$ (or any other symbolic expression) must be selected. Then a window appears on which the numerical value must be written and entered by pressing Accept.

Once all the numerical values have been entered, they must be saved by pressing “Save” in the “Numerical Values” box of the screen. Below we enumerate the different steps corresponding to cases 2a and 2b above

2(a) Numerical mean residence time in a compartment X_i due to an zero input in only one compartment, X_m

Step 1

The same as Step 1 in 1(a) above

Step 2

Once the desired $r_{i,m}$ has been selected click on “Mean residence time in compartments” in the “Numerical Values” box and then a window appears in which the numerical values of the residence times are displayed (see example 1 below).

Step 3

As in Step 3 in 1(a) above.

2(b) To obtain the numerical residence time in the entire system when an zero input is made in only one compartment, X_m , i.e, to obtain r_m .

Step 1

The same as Step 1 in 1(b) above

Step 2

Once the r_m 's have been selected, click on “Mean residence time in the system” in the “Numerical Values” box in the screen, and a window appears in which the numerical values of the mean residence times in the entire system, r_m ($m=1,2,\dots,n$) are displayed (see examples below).

Step 3

As in Step 3 in 1(b) above.

(3) To obtain both the symbolic expressions and their numerical values for the mean residence times.

In this last option there are also two possibilities: 3(a) To obtain the symbolic and numerical mean residence time in a compartment X_i due to an zero input in only one compartment, X_m , i.e, to obtain $r_{i,m}$ and 3(b) To obtain the symbolic and numerical mean residence time in the entire system when an zero input is made in only one compartment X_m , i.e, to obtain r_m .

The symbolic expressions and numerical values of the $K_{i,j}$'s (and $K_{i,o}$'s for open systems) are entered and saved as explained in options 1 and 2 above.

3(a) Symbolic and Numerical mean residence times in a compartment X_i due to an zero input in only one compartment, X_m

Step 1

As in Step 1 of 1(a) or 2(a).

Step 2

Once the wanted $r_{i,m}$ has been selected click on “Mean residence time in compartments” in the “Symbolic and Numerical Values” box in the screen and a window appears in which the symbolic expressions with the numerical values of the residence times are displayed (see examples below).

Step 3

To save the result, one proceeds as in Step 3 in 1(a) or 2(a) above.

3(b) To obtain the symbolic and numerical residence time in the entire system when an zero input is made in only one compartment X_m , i.e, to obtain r_m .

Step 1

First, all the steps included in the options (1b) and (2b) above must be carried out.

Step 2

Once the r_m 's have been selected click on “Mean residence time in the system” in “Symbolic and Numerical Values” box in the screen and a window appears in which the symbolic expressions with the numerical values of the residence times in the entire system, r_m ($m=1,2,\dots,n$) are displayed (see examples below).

Step 3

To save the result, one proceeds as in Step 3 in 1(b) or 2(b) above.

In Fig. 6 the three above options 1, 2 and 3 and their corresponding steps are summarized.

5. EXAMPLES

In this section the software will be applied to three examples of linear compartmental systems: examples 1, 2 and 3. Example 1 corresponds to a closed system¹, example 2 to an open system¹ and example 3 to an open system of physiological interest²¹. In each of these examples we will choose one or more of the options (1, 2 and 3 above) and in each option one or both possibilities (a) and (b). For each of the steps 1,2 and 3 of the corresponding possibility (a) or (b) we restrict ourselves to show the screen and windows corresponding to each of the three steps.

5.1. Example 1

The connectivity diagram of this example is shown in Scheme 1 and corresponds to a closed 7-compartment system. We will consider only option 1 indicated in Section 3. IMPLEMENTATION above.

5.1.1. Option 1: To obtain only the symbolic expressions for the mean residence times

For easy and simplicity we maintain the symbolic expressions $K_{2,1}$, $K_{2,3}$, $K_{3,4}$, $K_{4,3}$, $K_{4,5}$, $K_{4,7}$, $K_{5,6}$ and $K_{6,5}$ for the fractional transfer coefficients in Scheme 1 as they are, although any other symbolic expressions are also valid, e.g. $k_{-1}+k_2$ instead of $K_{2,1}$, etc. Now let us assume that we are interested only in the particular possibility (a) below of option 1 above.

1(a) *Mean residence time in compartments X_2 and X_4 due to an zero input in only one compartment, X_1 or X_2 .*

Step 1 (See Fig. 7)

Step 2 (See Fig. 8)

Step 3 (See Fig. 9)

5.2. Example 2

The connectivity diagram of this example is shown in Scheme 2 and corresponds to an open 4-compartment system with excretions from two of its compartments. We will consider options 1, 2 and 3 below and in each option the two particular possibilities (a) and (b) indicated in Section 3. IMPLEMENTATION above.

5.2.1. Option 1: To obtain only the symbolic expressions for the mean residence times

For ease and simplicity we maintain the symbolic expressions $K_{1,2}$, $K_{2,3}$, $K_{3,2}$, $K_{3,4}$ and $K_{4,1}$ for the fractional transfer coefficients and the symbolic expressions $K_{1,0}$ and $K_{3,0}$ for the fractional excretion coefficients in Scheme 2 as they are, although any other symbolic expressions are also valid for these coefficients. Now let us assume that we are interested only in possibility 1(a) below.

1(a) *Mean residence time in the compartments X_1 and X_3 when an zero input is made in compartment X_1 , X_3 or X_4*

Step 1 (See Fig. 10)

Step 2 (See Fig 11)

Step 3 (as in Fig 9)

1(b) *Mean residence time in the entire system when one zero input is made in compartment X_1 , X_3 or X_4 .*

Step 1 (See Fig 12)

Step 2 (See Fig 13)

Step 3 (as in Fig 9)

5.2.2. Option 2: To obtain only the numerical values for the mean residence times.

In this option, an arbitrary set of numerical values has to be assigned to the symbolic expressions $K_{1,2}$, $K_{2,3}$, $K_{3,2}$, $K_{3,4}$ and $K_{4,1}$, as seen in Fig.14.

1(a) *Numerical value of the mean residence time in compartments X_1 and X_3 when one zero input is made in compartment X_1 , X_3 or X_4 .*

Step 1 (See Fig 14)

Step 2 (See Fig 15)

Step 3 (as in Fig 9)

1(b) *Numerical value of the mean residence time in the entire system when one zero input is made in compartment X_1 , X_3 or X_4 .*

Step 1 (See Fig 16)

Step 2 (See Fig 17)

Step 3 (as in Fig. 9)

5.2.3. Option 3: To obtain both the symbolic expressions and numerical values of the mean residence times

(a) *Symbolic expressions and numerical values of the mean residence times in compartments X_1 and X_3 when one zero input is made in compartment X_1 , X_3 or X_4*

Step 1 (See Fig 14)

Step 2 (See Fig 18)

Step 3 (as in Fig. 9)

(b) *Symbolic expressions and numerical values of the mean residence time in the entire system when one zero input is made in compartment X_1 , X_3 or X_4 .*

Step 1 (See Fig 16)

Step 2 (See Fig 19)

Step 3 (as in Fig. 9)

5.3. Example 3

The connectivity diagram of this example is shown in Fig. 20 and corresponds to an open 11-compartment system of physiological interest suggested by ²¹ for the disposition of

benzo[*a*]pyrene (B[*a*]P), a widely recognized carcinogen, in rats from which all of the numerical values of the rate constants were evaluated by these authors (Table I) although the evaluation of the mean residence times is not the object of this contribution. In this example we will use option 2, possibilities (a) and (b), to evaluate the mean residence times indicated below.

5.3.1. Option 2: To obtain only the numerical values of the mean residence times

(a) *Mean residence time of the radioactivity in compartments X_1 (Lungs), X_2 (blood) and X_8 (Liver) after intratracheal administration of [^3H]B[*a*]P, radioactive, i.e. after a zero input of radioactivity in compartment X_1 (see Fig. 20)*

Step 1 (See Fig. 21)

Step 2 (See Fig. 22)

Step 3 (as in Fig. 9)

The results for the evaluated mean residence times in the compartments of this physiologically interesting real example are summarized in Table II.

(b) *Numerical value of the mean residence time in the entire system when a zero input is made in compartment X_1 .*

Step 1 (See Fig. 23)

Step 2 (See Fig. 24)

Step 3 (as in Fig. 9)

Note that the mean residence time of the radioactivity in the entire system after intratracheal administration of the radioactive substance [^3H]B[*a*]P is 28.95 days, regardless of the amount of administered radioactivity.

6. RESULTS AND DISCUSSION

In this paper we present a software based on previous mathematical algorithms developed by our group³⁰ for linear compartmental systems, open or closed. To our knowledge, this is the first software in the scientific literature which enables the user to obtain: (1) the symbolic expression and/or the numerical value of the mean residence time in any compartment, X_i ($i = 1, 2, \dots, n$; n = number of compartments of the system), of the chosen system when matter is injected in any compartment, X_m ($m = 1, 2, \dots, n$), which might coincide with the X_i (i.e. $m = i$); (2) The symbolic expression and/or the numerical value of the mean residence time in the entire system when matter is injected in any compartment, X_m ($m=1,2,\dots,n$). Evaluation of the mean residence times is crucial in many aspects of Physics

^{37,38}, Biophysics ³⁹⁻⁴², Biomedicine ^{19,43-45}, Nutrition ^{46,47}, Toxicology ^{48,49} and Pharmacokinetics ⁵⁰⁻⁵².

Example 3 is only one of the several different compartmental models suggested in Nutritional Biology or Biomedicine ^{4,45,53,54} to all of which this software could be applied to increase our knowledge of the same. We hope that the tool we present here encourages the searchers in these fields to use compartmental systems to model their physiological systems in order to evaluate mean kinetic parameters which will complete their kinetic analyses.

The software here presented demonstrates its power by handling complex compartmental systems. But the examples suggested in the previous section (5.EXAMPLES) are simple multicompartmental systems so as not to excessively increase the length of the paper. Obviously, the ultimate aim of this software is to apply it to any multicompartmental system irrespective of its complexity.

6.1. Mean Residence Times in one compartment or in the entire system when matter is injected in one compartment, X_m .

The information that the software provides directly is the mean residence time in one compartment or the entire system when matter is injected in only one compartment, although the software makes it possible, for convenience, to simultaneously solve the symbolic expression and/or numerical values of the mean residence time in one or more of the compartments when it is assumed that matter is injected in one or more of the compartments. For example, when values of m are chosen as 1 and 3 and values of i as 2 and 3, and symbolic expressions and/or numerical values of $r_{2,1}$, $r_{3,1}$, $r_{2,3}$ y $r_{3,3}$ are required. Thus, mean residence time in compartment X_2 when only matter is injected in the compartment X_1 is evaluated as $r_{2,1}$, the residence time in compartment X_3 when matter is only injected in the compartment X_1 as $r_{3,1}$ etc. Also, this program provides, simultaneously, the mean residence time in the compartmental system when matter is injected in a single compartment, which we can choose, X_m ($m = 1, 2, \dots, n$). For example, when m values are chosen as 1 and 3 and the symbolic expressions and/or numerical values of r_1 and r_3 are required, the software provides the mean residence time in the entire system when only matter is injected in compartment X_1 (r_1) or only in compartment X_3 (r_3).

6.2. Mean residence time in one compartment or in the entire system when matter is injected, simultaneously, in more than one compartment.

If only one zero input, x_m^0 , is made in compartment X_m , then the mean residence time, $r_{i,m}$, in any compartment, X_i , as well as in the entire system, r_m , is given by the software here presented.

When more than one zero input are made simultaneously in different compartments, e.g. $x_{m_1}^0, x_{m_2}^0, \dots, x_{m_w}^0$ in the corresponding compartments $X_{m_1}, X_{m_2}, \dots, X_{m_w}$, then the mean residence time, $r_{i,m_1,m_2,\dots,m_w}$ in any compartment, X_i , as well as in the entire system under study, $r_{m_1,m_2,\dots,m_w}$, are given by eqs. (10) and (11), respectively, according to⁵⁵, after adaptation of the notation:

$$r_{i,m_1,m_2,\dots,m_w} = \frac{1}{x_T^0} \left(x_{m_1}^0 r_{i,m_1} + x_{m_2}^0 r_{i,m_2} + \dots + x_{m_w}^0 r_{i,m_w} \right) \quad (10)$$

$$r_{m_1,m_2,\dots,m_w} = r_{1,m_1,m_2,\dots,m_w} + r_{2,m_1,m_2,\dots,m_w} + \dots + r_{n,m_1,m_2,\dots,m_w} \quad (11)$$

Thus, in this case, eq. (10), we define the *mean residence time*, $r_{i,m_1,m_2,\dots,m_w}$, in compartment X_i as the sum of the products of each zero input, $x_{m_j}^0$ ($j=1,2,\dots,w$) by the corresponding mean residence time in compartment X_i due exclusively to the zero input, $x_{m_j}^0$ ($j=1,2,\dots,w$). Likewise, the mean residence time in the entire compartment, $r_{m_1,m_2,\dots,m_w}$, is the sum of the mean residence times in each of the n compartments of the system.. Note that in this case both $r_{i,m_1,m_2,\dots,m_w}$ and $r_{m_1,m_2,\dots,m_w}$ are dependent on the w zero inputs in the corresponding w compartments made simultaneously.

According to eq. (10), when only one input is made in compartment $X_{m_1} = X_m$ then $x_{m_1}^0 = x_m^0 = x_T^0$ and the mean residence time in any compartment X_i , $r_{i,m}$, is independent of the zero input and is given by the software. Moreover, in this case, eq. (11) becomes:

$$r_m = r_{1,m} + r_{2,m} + \dots + r_{n,m} \quad (12)$$

Therefore, in this case, the mean residence time in the entire system, r_m , given by eq. (12), is independent of the zero input made in compartment X_m and is furnished by the software.

6.3. Mean residence times in one part of the compartmental system under study.

Sometimes it may be interesting to consider a subset, Ω , to know the mean residence times, $r_{\Omega, m_1, m_2, \dots, m_w}$. In this case, eq. (11) is valid but extending the sum only to this subset of compartments, i.e.:

$$r_{\Omega, m_1, m_2, \dots, m_w} = r_{g_1, m_1, m_2, \dots, m_w} + r_{g_2, m_1, m_2, \dots, m_w} + \dots + r_{g_h, m_1, m_2, \dots, m_w} \quad (13)$$

According to eq. (13), when only one input is made in compartment $X_{m_1} = X_m$ then $x_{m_1}^0 = x_m^0 = x_T^0$ and the mean residence time in Ω is given by:

$$r_{\Omega, m} = r_{g_1, m} + r_{g_2, m} + \dots + r_{g_h, m} \quad (14)$$

Therefore, in this case the mean residence time in Ω , $r_{\Omega, m}$, given by eq. (14), is independent of the zero input made in compartment X_m .

The results for $r_{i, m}$ furnished by the software allow, if necessary using eqs. (10-14), the evaluation of $r_{i, m_1, m_2, \dots, m_w}$, $r_{m_1, m_2, \dots, m_w}$, $r_{\Omega, m_1, m_2, \dots, m_w}$ and $r_{\Omega, m}$, respectively, in either their symbolic expressions or their numerical values.

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Figure 1. Flow diagram showing the general expression for the mean residence times in the compartments of any linear system closed or open. Taken from ¹

Figure 2. Flow diagram showing the expressions for the mean residence times in the entire, open, linear compartmental systems. Taken from ¹.

Figure 3. Simplified flow diagram of the implemented software.

Figure 4. Aspect of the screen when the window is displayed to write the alternative symbolic expression.

Figure 5. Aspect of the screen showing how to remove or add new connections as explained in the main text.

Figure 6. Flow diagram showing the three options offered by the software and the corresponding three steps of each option.

Figure 7. Aspect of the screen after carrying out Step 1 in possibility (a) of option 1 of Example 1.

Figure 8. Aspect of the screen after carrying out Step 2 in possibility (a) of option 1 of Example 1

Figure 9. Aspect of the screen after carrying out Step 3 in possibility (a) of option 1 of Example 1

Figure 10. Aspect of the screen after carrying out Step 1 in possibility (a) of option 1 of Example 2

Figure 11. Aspect of the screen after carrying out Step 2 in possibility (a) of option 1 of Example 2

Figure 12. Aspect of the screen after carrying out Step 1 in possibility (b) of option 1 of Example 2

Figure 13. Aspect of the screen after carrying out Step 2 in possibility (b) of option 1 of Example 2

Figure 14. Aspect of the screen after carrying out Step 1 in possibility (a) of option 2 of Example 2

Figure 15. Aspect of the screen after carrying out Step 2 in possibility (a) of option 2 of Example 2

Figure 16. Aspect of the screen after carrying out Step 1 in possibility (b) of option 2 of Example 2

Figure 17. Aspect of the screen after carrying out Step 2 in possibility (b) of option 2 of Example 2

Figure 18. Aspect of the screen after carrying out Step 2 in possibility (a) of option 3 of Example 2

Figure 19. Aspect of the screen after carrying out Step 2 in possibility (b) of option 3 of Example 2

Figure 20. Compartmental model of the disposition of benzo[a]pyrene (B[a]P) in rats according to ²¹ and adapted to our notation. This model corresponds to an open 11-compartment system of physiological interest. Compartments are represented by circles. The compartment named as T represents the sum of radioactivity in kidneys, stomach, testes, spleen and heart/thymus. P indicates lungs, PL plasma, H liver, I+C intestine and its content. TN compartments consist primarily of skin, fat, bone, muscle and associated blood. OR represents the elimination of urine. $K_{i,j}$ are fractional transfer coefficient between compartments and $k_{11,o}$ is the excretion coefficient.

Figure 21. Aspect of the screen after carrying out Step 1 in possibility (a) of option 2 of Example 3

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Figure 22. Aspect of the screen after carrying out Step 2 in possibility (a) of option 2 of Example 3

Figure 23. Aspect of the screen after carrying out Step 1 in possibility (b) of option 2 of Example 3

Figure 24. Aspect of the screen after carrying out Step 2 in possibility (b) of option 2 of Example 3

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$K_{i,j}$	Value (min^{-1})	$K_{i,j}$	Value (min^{-1})
$K_{1,2}$	0.142	$K_{2,1}$	0.873
$K_{2,3}$	0.0726	$K_{2,5}$	0.942
$K_{2,6}$	0.158	$K_{2,8}$	1.08
$K_{2,10}$	0.00379	$K_{3,2}$	0.00925
$K_{4,5}$	0.00180	$K_{5,2}$	0.0881
$K_{5,4}$	0.00372	$K_{6,2}$	0.136
$K_{6,7}$	0.0932	$K_{6,9}$	0.00329
$K_{7,6}$	0.00289	$K_{8,2}$	0.111
$K_{8,9}$	0.0496	$K_{9,6}$	0.0447
$K_{9,8}$	0.0247	$K_{10,11}$	0.09
$K_{11,0}$	0.09		

Table I. Values of the fractional transfer coefficient (rate constants) corresponding to Figure 20.

Compartment (Organ)	Mean Residence Time (h)
X ₁ (Lungs)	27.15
X ₂ (Blood)	4.40
X ₈ (Liver)	33.33

Table II. Values of the mean residence times in lungs, blood and liver corresponding to the compartmental system in Fig. 20 obtained by the software using the fractional transfer coefficient summarised in Table I.

$K_{i,j}$	Value (min^{-1})
$K_{1,2}$	0.142
$K_{2,3}$	0.0726
$K_{2,6}$	0.158
$K_{2,10}$	0.00379
$K_{4,5}$	0.00180
$K_{5,4}$	0.00372
$K_{6,7}$	0.0932
$K_{7,6}$	0.00289
$K_{8,9}$	0.0496
$K_{9,8}$	0.0247
$K_{11,0}$	0.09

$K_{i,j}$	Value (min^{-1})
$K_{2,1}$	0.873
$K_{2,5}$	0.942
$K_{2,8}$	1.08
$K_{3,2}$	0.00925
$K_{5,2}$	0.0881
$K_{6,2}$	0.136
$K_{6,9}$	0.00329
$K_{8,2}$	0.111
$K_{9,6}$	0.0447
$K_{10,11}$	0.09

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Compartment (Organ)	Mean Residence Time (h)
X_1 (Lungs)	27.15
X_2 (Blood)	4.40
X_8 (Liver)	33.33

For Peer Review