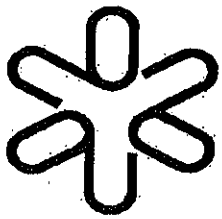

# Instituto de Física
# Universidade de São Paulo

## A new statistical method for transfer coefficient calculations in the framework of the General Multiple-Compartment Model of transport for radionuclides in biological systems

Garcia[3], F.; Arruda-Neto[1,2], J.D.T.; Manso[3], M.V.; Helene[1], O.M.; Vanin[1], V.R.; Likhachev[1], V.P.; Tavares[1], M.V.; Pereira Filho[1], J.W.; Deppman[1], A.; Perez[3], G.; Rodriguez[3], O.; Guzman[3], F.; Camargo[2], S.P. de

[1]*Instituto de Física da Universidade de São Paulo, São Paulo, Brasil*

[2] *Universidade de Santo Amaro, São Paulo, Brasil*

[3]*Instituto Superior de Ciências y Tecnologias Nucleares, Havana, Cuba*

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# A new statistical method for transfer coefficient calculations in the framework of the General Multiple-Compartment Model of transport for radionuclides in biological systems.

F. Garcia, J.D.T. Arruda-Neto, M.V.Manso, O.M. Helene, V.R. Vanin,

V.P. Likhachev, M.V. Tavares, J.W. Pereira Filho, A. Deppman,

*Instituto de Física da Universidade de São Paulo, São Paulo,*

*Brazil*

G. Perez , O Rodriguez, F. Guzman

*Instituto Superior de Ciencias y Tecnologias Nucleares. Havana, Cuba*

S. P. de Camargo

*Universidade de Santo Amaro, São Paulo, Brazil*

It is proposed a new and simple statistical (STATFLUX) procedure for the calculation of transfer coefficients of radionuclides transport to animals and plants. The method is based on the General Multiple-Compartment Model, which uses a system of linear equations involving geometrical volume considerations. By using experimental data for each compartment curve available in the literature, it is estimated the flux parameters with the minimum square procedure. The convergence is tested by comparing the results of the STATFLUX procedure with those from the standard Least Square Method using the Gauss- Marquardt algorithm. Some numerical results are presented, in order to compare the STATFLUX transfer coefficients with those from other works and experimental data.

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# I. INTRODUCTION

The technological, biological and medical applications of radiation and radioactivity have become so much a part of our everyday life that it is easy to lose sight of the fact that, viewed historically, all radiation science is recent. We are now in the verge of a new cycle of significant discoveries related to the effect of ionizing radiation. The progress in the molecular biology of DNA is providing new tools, almost daily, for the examination of damage and repair processes in these important molecules. In this problem we have two types of situation : the external exposition to radiation and internal intake of radionuclide, which lead us unavoidably to the evaluation of local harm in organs. In the last case, the first step of any study necessarily goes through the investigation of biokinetics and metabolism of the intaken radionuclides.

The investigation of transport mechanisms for radioactive substances, through environmental pathways, is very important in radiological protection of the public. One of such pathway, associated with the food chain, is the grass -animal-man sequence. The distribution of trace elements in humans and laboratory animals has been intensively studied over the past 60 years (Pendlenton et al 1963 and Mays 1966). In addition, investigations on the incidence of cancer in humans, and possible causal relationship to radioactive fallout were undertaken (Weiss et al 1971, Rallison et al 1974 and Lyon et al 1979); however, few and not systematic biokinetics data exist in the literature.

The particularities on the physical and chemical nature of contaminants, their life times, as well as properties as radiation emitters ( gamma, beta or alpha and, in some cases, fission fragments), make the study of the metabolism of such contaminants in a biological system much more complex. The proper consideration of all these characteristics, and the need of taking into account them in experimental detection methods, make the issue discussed in this work quite interesting, and a current research line at the interface between nuclear physics and biophysics. All of these facts point to the necessity of developing ever more complex and reliable models, which are able for the analysis and prediction of harms, originated from

the spread of radioactive contaminants in all links of the alimentary chain. In this sense, there are in the literature many open questions.

Due to the wide range of questions concerning e.g. interpretation, reliability or relevance of many of the results so far obtained, it has been difficult to determine the most appropriate biokinetics or dosimetric model to be used in deriving exposure guidelines.

The need of mathematical models to quantify the penetration of a trace substance in animals, and their products, has often been stressed in the literature (Lassey 1980, Assimakopoulos et al 1989 , Skrable et al 1974, Simmonds 1979, Johnson 1981, Birchall 1986, Birchall and James 1989 and Ward et al 1987). A biokinetics (metabolic, retention, pharmacokinetics) model is a mathematical description of the time- dependent distribution, and excretion, of a substance in the body after its absorption or injection into blood. The use of biokinetics models is central to the estimation of organ doses, resulting from internal deposition of radionuclides in humans. The biokinetics models most commonly applied in radiation protection are those recommended in documents of the International Commission on Radiological Protection (ICRP 1987, ICRP 1989 and ICRP 1991).

The models are usually restricted to first-order kinetics, because many of the natural processes responsible for movement in such systems can be described by a single exponential function of time. In cases where the transport mechanism is not fully understood, the use of a more complicated expression cannot be justified, and a more detailed study is recommended. A general algorithm for solving first order compartmental models including recycling systems was developed in (Birchall and James 1989). The general basis of the model for recycling systems is presented in this work; the equations system associated with the model is solved analytically using matrix algebra, which allowed to avoid the singularity problem found in the use of analytical solutions of linear chains, as e.g. when the total removal rate constants of any two compartments are equal (Skrable et al 1974). Recently, Assimakopoulos and collaborators (Assimakopoulos et al 1991) worked out a new approach to the General Multiple-Compartment Model (GMCM), for the transport of trace elements to animals, which takes into account the geometry of individual compartments. In particular, an attempt

was made toward the elucidation of some important aspects associated with systems of linear differential equations used in the GMCM (we refer the reader to reference Assimakopoulos et al 1991 and references therein). This new version of the GMCM, proposed in Assimakopoulos et al 1991, is adequate for the analysis of more general and realistic situations, as e.g. the compartment volume variation in time. It was proposed, in particular, that in a system of compartments with different volumes, the changes of the molecules rate in each compartment depends linearly on the differences in concentration among the various compartments, and not on the differences in population, as noted in previous papers. In the frame of the general ideas of the GMCM, and for calculation purposes, we adopted in this work the particular central-blood scheme used by Assimakopoulos and collaborators in several of their works.(Assimakopoulos et al 1991, Assimakopoulos et al 1993 and Assimakopoulos et al 1995). The results of (Assimakopoulos et al 1995) show the validity of the central-blood scheme for the transport of radiocesium in ruminants, and that it can also be used as one of the possible schemes in any transport study with radionuclides and animals other than cesium and ruminants. These results also indicated that the transfer coefficients, of the various body compartments of animals, may depend strongly on the species, physiological state, or type of food for the animal.

The number of compartments in realistic studies can be very large, and the calculations are performed by means of iterative evaluations of exponential of matrices, which is a numerically difficult problem. Thus, it would be reasonable to work out an alternative, one step, statistical procedure. This is the goal of the present work.

We use the general ideas of the GMCM in the same way as described elsewhere (Assimakopoulos et al 1993). However, we propose additionally a new algorithm to perform calculations of transfer coefficients. We note, on the other hand, that the GMCM has a strong dependence on many parameters, and that the sole knowledge of all flux parameters (associated with species, contaminants and any other conditions ), could not be the best and practical way to deal with transfer coefficients determination. In this regard, we propose the use of the GMCM in the inverse sense, namely: (a) to consider as input the experi-

mentally determined time dependence of the concentrations in each compartment; and (b) to determine, from these data, all the parameters in a statistical approach (as described below).

Also, we suggest in this work some different model assumptions to be used in the calculations. For instance, the possibility to fix a gastrointestinal absorption coefficient, or its inclusion in the statistical fitting, will be implemented in an "ad-hoc " routine. It will be implemented also the different variants of contaminants excretion to the outside world.

We use in this work the system of linear differential equations from the Assimakopoulos modified version of the GMCM (Assimakopoulos et al 1991), in order to develop a new procedure suitable to the determination of flow parameters and, finally, transfer coefficients.

Therefore, the main goal of this paper is to propose an alternative statistical procedure for the calculation of transfer coefficients, as well as the analysis of its applicability in radionuclides transport problems. To reach this goal we also develop a new approach (STATFLUX) to the use of the Least Squares Method (LSM).

## II. DESCRIPTION OF THE STATFLUX METHOD.

The STATFLUX method is implemented in a FORTRAN code (Garcia et al 1999) that simulates the transport of radionuclides from blood to different organs of animals. The central purpose of the STATFLUX fitting code is the determination of the flow parameters (for several compartments) in order to obtain the transfer coefficients for the biological system.

Before applying the General Multiple-Compartment Model to any concrete problem, we have to do some considerations, namely:

(a) it should be selected the pathway to release molecules of contaminants to the outside world;

(b) the model should be properly delineated, by means of a previous choice of the inter-compartment links; and

(c) it should be considered one of the following possibilities: the fractional absorption coefficient $\gamma$ of the daily intake ($\gamma F$ ) as a known input, or the $\gamma$ coefficient added to the set of fitting parameters.

### A. Basic Ideas of the Model

The fundamentals of the GMCM can be easily applied to the case of just one animal, for which the metabolic individualities, as reflected in all flux parameters, can be fixed. The basic ideas of the model implemented in the STATFLUX procedure are the same of the GMCM, plus a simplified version of a system of $n$ interconnected compartments with constant volume $V_i$ fed via blood. In particular, this central compartment (blood) is fed from the outside at a constant rate $\gamma$.F, where $\gamma$ represents the fractional absorption coefficient for the total intake (F). We adopted in the present work the following system of linear equations :

$$\frac{d(V_i X_i(t))}{dt} = \delta_{i1}\gamma F_1 + \sum_{j=1,.j\neq i}^{n} r_{ji}X_j - X_i(\sum_{j=1,.j\neq i}^{n} r_{ij}) - \xi_i X_i \ , \qquad (1)$$

where $X_i$ is the concentration of trace molecules in the compartment i, $F_1$ is a constant rate of feeding from outside world, $r_{ij}$, $r_{ji}$ and $\xi_i$ are the flow parameters (see figure 1), and $\delta_{i1}$ represents the fact that feeding occurs only via blood.

The formal resolution of the eqn (1) can be accomplished in the following way:

The system of the linear equations represented in eqn (1) may be expressed on the matrix form as

$$\frac{d}{dt}(\mathbf{VX}) = \mathbf{F} + \mathbf{RX} \quad . \qquad (2)$$

$\mathbf{X}$ and $\mathbf{F}$ are column vectors with elements $X_i$ and $F_i$ , respectively, $\mathbf{V}$ is a diagonal matrix with elements $V_i$ ( volume of $i^{th}$-compartment), always when diagonal elements as

$r_{ii} = -\sum_{\substack{j=1,\\ j\neq i}}^{n} r_{ij} - \xi_i$ are defined. $\mathbf{R}$ is the transpose of the matrix with flux parameters elements $r_{ij}$ .

Since we have considered compartments with constant volumes, eqn (2) could be expressed as :

$$\mathbf{V}\frac{d}{dt}\mathbf{X} = \mathbf{F} + \mathbf{R}\mathbf{X} \quad . \tag{3}$$

This is a non-homogeneous matrix equation. It is shown elsewhere (Assimakopoulos et al 1991) that the solution of eqn (3) is given by:

$$\mathbf{X}(t) = [\exp(\mathbf{V}^{-1}\mathbf{R}.t) - 1].\mathbf{R}^{-1}\mathbf{F} + \exp(\mathbf{V}^{-1}\mathbf{R}.t)\mathbf{X}(0) \quad , \tag{4}$$

where the contaminant concentrations in the compartment at t=0 are given by the vector $\mathbf{X}(0)$.

It is expected that the behavior of a realistic multiple-compartment system reaches asymptotically a steady-state equilibrium. In this case, the most important observable is the transfer coefficient ($q$). This quantity for the $i^{th}$ compartment is defined as a fraction of the total input of the system, $p$, namely:

$$q_i = \frac{X_i(t \longrightarrow \infty)}{p} \quad , \tag{5}$$

which can be written in matrix notation as

$$\mathbf{q} = \frac{1}{p}\mathbf{X}(t \longrightarrow \infty) \quad .$$

By taking into account the formal general solutions ( eqn (4) ), for the model described above, the transfer coefficient vector takes the form (Assimakopoulos et al 1991):

$$\mathbf{q} = -\frac{1}{p}\mathbf{R}^{-1}\mathbf{F} \; , \tag{6}$$

where the total intake of the biological system, the scalar $p$, is given by the general expression

$$p = \sum_{i=1}^{n} F_i ,$$

which in our applied model has the value

$$p = F_1$$

### B. STATFLUX : Statistical procedure

Complete information about all compartments, for just one animal, can't be obtained ( the reasons are presented above). Besides, it is necessary to sacrifice an animal in order to get complete information at a given time. Thus, each experimental point, as a function of time, corresponds to a different animal. In this sense, the statistical treatment we introduced in the GMCM, provides us with mean results (e.g. the transport of trace elements) valid for the whole set of animals.

To the solution of eqn (3) one needs the values for all flux parameters. In a real situation, however, what we know are measured data for the concentrations (in some compartments) as a function of time, while the flux parameters are unknown. In order to overcome this problem, we suggest the use of a statistical fitting on the grounds of the new method, which we call STATFLUX method, where the convergence is tested with the standard procedure based on the Gauss-Marquardt algorithm (Bevinton 1969). This would allow us also to answer some important questions related to the GMCM, as : is the linearity of the equations system able to describe the behaviour of the concentrations as a function of time? Which particular constraint is more adequate in each situation ? How to introduce the problem of fluctuation of flux parameters in the set of animals ?

The STATFLUX statistical procedure starts with a known set of experimentally determined contaminant concentrations, $X_i(t_j)$, for a compartment $i$ with volume $V_i$ and as a function of time $(t_j)$.

The system of linear differential equations (eqn (1) )can be written in matrix form for all experimental point as

$$\mathbf{Y} = \mathbf{Z} * \mathbf{P} \quad , \tag{7}$$

where $\mathbf{Z}$ is the design matrix of the equation system, which contains all the information of the adopted model, as: the multiple-compartment open connections, and intake (release) from (to) the outside world. The elements of column-vector $\mathbf{P}$ are the parameters to be fitted, and the elements of column-vector $\mathbf{Y}$ are the time derivatives of $X_i(t)$, which can be approximated simply as

$$Y_i(t_j) = \frac{\partial X_i(t)}{\partial t} \mid_{t=t_j} \approx \frac{X_i(t_{j+1}) - X_i(t_{j-1})}{t_{j+1} - t_{j-1}}. \tag{8}$$

The matrices in eqn (7) have a form which encompasses the details of our adopted model. For example, if the cases of both simple central blood compartment, and a constant volume with the fitting parameter $\gamma$, are considered, these matrices can be written as:

$$
\mathbf{Z}=\begin{pmatrix}
\left(\frac{F_1}{V_1}\right) & \left(\frac{X_2(t_2)}{V_1}\right) & \cdots & \left(\frac{X_n(t_2)}{V_1}\right) & -\left(\frac{X_1(t_2)}{V_1}\right) & \cdots & -\left(\frac{X_1(t_2)}{V_1}\right) & -\left(\frac{X_1(t_2)}{V_1}\right) & 0 & 0 \cdots & 0 \\
\left(\frac{F_1}{V_1}\right) & \left(\frac{X_2(t_3)}{V_1}\right) & \cdots & \left(\frac{X_n(t_3)}{V_1}\right) & -\left(\frac{X_1(t_3)}{V_1}\right) & \cdots & -\left(\frac{X_1(t_3)}{V_1}\right) & -\left(\frac{X_1(t_3)}{V_1}\right) & 0 & 0 \cdots & 0 \\
\cdot & \cdot & \cdots & \cdot & \cdot & \cdots & \cdot & \cdot & 0 & \cdots & 0 \\
\cdot & \cdot & \cdots & \cdot & \cdot & \cdots & \cdot & \cdot & \cdot & \cdots & \cdot \\
\left(\frac{F_1}{V_1}\right) & \left(\frac{X_2(t_k)}{V_1}\right) & \cdots & \left(\frac{X_n(t_k)}{V_1}\right) & -\left(\frac{X_1(t_k)}{V_1}\right) & \cdots & -\left(\frac{X_1(t_k)}{V_1}\right) & -\left(\frac{X_1(t_k)}{V_1}\right) & 0 & 0 \cdots & 0 \\
0 & -\left(\frac{X_2(t_2)}{V_2}\right) & 0 \cdots & 0 & \left(\frac{X_1(t_2)}{V_2}\right) & \cdots & 0 & 0 & -\left(\frac{X_2(t_2)}{V_2}\right) & 0 \cdots & 0 \\
0 & -\left(\frac{X_2(t_3)}{V_2}\right) & 0 \cdots & 0 & \left(\frac{X_1(t_3)}{V_2}\right) & \cdots & 0 & 0 & -\left(\frac{X_2(t_3)}{V_2}\right) & 0 \cdots & 0 \\
\cdot & \cdot & \cdots & \cdot & \cdot & \cdots & \cdot & \cdot & \cdot & \cdots & \cdot \\
\cdot & \cdot & \cdots & \cdot & \cdot & \cdots & \cdot & \cdot & \cdot & \cdots & \cdot \\
0 & -\left(\frac{X_2(t_k)}{V_2}\right) & 0 \cdots & 0 & \left(\frac{X_1(t_k)}{V_2}\right) & \cdots & 0 & 0 & -\left(\frac{X_2(t_k)}{V_2}\right) & 0 \cdots & 0 \\
0 & 0 & \cdots & 0 & 0 & \cdots & \cdot & \cdot & \cdot & \cdots & \cdot \\
\cdot & \cdot & \cdots & \cdot & \cdot & \cdots & \cdot & \cdot & \cdot & \cdots & \cdot \\
0 & 0 & & 0 & 0 & & 0 & 0 & 0 & & 0 \\
0 & 0 & \cdots 0 & -\left(\frac{X_n(t_2)}{V_n}\right) & 0 & \cdots 0 & \left(\frac{X_1(t_2)}{V_n}\right) & 0 & 0 & \cdots 0 & -\left(\frac{X_n(t_2)}{V_n}\right) \\
0 & 0 & \cdots 0 & -\left(\frac{X_n(t_3)}{V_n}\right) & 0 & \cdots 0 & \left(\frac{X_1(t_3)}{V_n}\right) & 0 & 0 & \cdots 0 & -\left(\frac{X_n(t_3)}{V_n}\right) \\
\cdot & \cdot & \cdots & \cdot & \cdot & \cdots & \cdot & \cdot & \cdot & \cdots & \cdot \\
\cdot & \cdot & \cdots & \cdot & \cdot & \cdots & \cdot & \cdot & \cdot & \cdots & \cdot \\
0 & 0 & \cdots 0 & -\left(\frac{X_n(t_k)}{V_n}\right) & 0 & \cdots 0 & \left(\frac{X_1(t_k)}{V_n}\right) & 0 & 0 & \cdots 0 & -\left(\frac{X_n(t_k)}{V_n}\right)
\end{pmatrix}
$$

where $t_k$ is penultimate point of time

$$\mathbf{Y}= \begin{pmatrix} \dot{X}_1\,(t_2) \\ \dot{X}_1\,(t_3) \\ . \\ . \\ \dot{X}_1\,(t_k) \\ \dot{X}_2\,(t_2) \\ \dot{X}_2\,(t_3) \\ . \\ . \\ \dot{X}_2\,(t_k) \\ . \\ . \\ \dot{X}_n\,(t_2) \\ \dot{X}_n\,(t_3) \\ . \\ . \\ \dot{X}_n\,(t_k) \end{pmatrix}, \qquad \text{and} \qquad \mathbf{P}= \begin{pmatrix} \gamma \\ r_{21} \\ r_{31} \\ . \\ . \\ r_{n1} \\ r_{12} \\ r_{13} \\ . \\ . \\ r_{1n} \\ \xi_1 \\ \xi_2 \\ . \\ . \\ . \\ \xi_n \end{pmatrix}$$

The linear matrix equation 7 is the master equation, from which the vector $\mathbf{P}$ can be obtained by the LSM. The parameters vector is obtained, in the framework of our approach, when both the square function is minimized and the variance matrix of the experimental data is known (see, for example, the appendix of Ref. Vanin et al 1997 ). The estimated value of the matrix $\mathbf{P}$ is thus given by

$$\tilde{\mathbf{P}} = (\mathbf{Z}^t\mathbf{V}_y^{-1}\mathbf{Z})^{-1}\mathbf{Z}^t\mathbf{V}_y^{-1}\mathbf{Y}, \tag{9}$$

and the covariance matrix of parameters by

$$\mathbf{V}_p = (\mathbf{Z}^t\mathbf{V}_y^{-1}\mathbf{Z})^{-1} \quad , \tag{10}$$

where $\mathbf{Z}^t$ is the transpose of the design matrix defined above, $\mathbf{Y}$ is the vector of derivatives, and $\mathbf{V}_y$ is the covariance matrix of $\mathbf{Y}$.

The covariance matrix of $\mathbf{Y}$ can be calculated from the variances on the concentrations, note that

$$\mathbf{Y} = \mathbf{D} \cdot \mathbf{X} \,, \tag{11}$$

where $\mathbf{D}$ is the derivative matrix operator (defined in terms of the approximation given in eqn (8)), and such that $\mathbf{X}$ is formed by the concentration of each organ (compartment) at a time t.

As a consequence, the $\mathbf{V}_y$ matrix can be calculated as

$$\mathbf{V}_y = \mathbf{D} \cdot \mathbf{V_x} \cdot \mathbf{D}^t, \tag{12}$$

where $\mathbf{V}_x$ is the variance matrix of the concentrations for each compartment. For the determination of $\mathbf{V}_x$ we considered the measurement uncertainties of the concentrations in each compartment, at different times, independent. This fact led us to the diagonal matrix

$$V_x(i,j) = \sigma_i^2.\delta_{ij} \quad . \tag{13}$$

The $\chi^2$ function is calculated from the expression

$$\chi^2 = (\mathbf{Y} - \mathbf{Z}.\tilde{\mathbf{P}})^t.\mathbf{V}_y^{-1}.(\mathbf{Y} - \mathbf{Z}.\tilde{\mathbf{P}}) \quad , \tag{14}$$

where $\mathbf{Z}$ must be calculated with the concentration values evaluated with the fitted parameters.

If the initial hypothesis of the model (linearity, constant flux parameters, etc.) are fulfilled, it is expected then to get a good set of resulting parameters, which satisfactorily describes the experimental transfer coefficients. In general, this simple procedure could be considered a " first-run " parameters evaluation, and also as a good starting point for the more sophisticate $\chi^2$-standard iterative procedure.

In order to test the efficiency of our proposed STATFLUX method, we used the Gauss-Marquardt algorithm, described in (Bevinton 1969), to the non linear problem corresponding to fit $\mathbf{R}$ in equation (4), and whose application to a concrete problem is summarized below.

### C. Application of the Gauss-Marquardt algorithm

Assuming that $X_i^{eval}(t_k)$ is a sufficiently good approximation of the concentration at time $(t_k)$, we can start with the following equations system :

$$X_i^{\exp}(t_k) \cong X_i^{eval}(r_{ij}, \xi_i, t_k) + \sum_{j \neq i}^{n} [\frac{\partial}{\partial r_{ij}} X_i^{eval}(t_k).\Delta r_{ij}] + \sum_{j}^{n} \frac{\partial}{\partial \xi_j} X_i^{eval}(t_k).\Delta \xi_j, \qquad (15)$$

where

$X_i^{\exp}(t_k)$ is the experimental concentration function for each compartment at a time $t_k$;

$X_i^{eval}(t_k)$ is the concentration function evaluated from equation (4) at a time $t_k$, using an iterative set of flux parameter, which started with the results of the STATFLUX procedure;

$\Delta r_{ij}, \Delta r_{ji}$, and $\Delta \xi_i$ are the flux parameters variations.

Then,

$$X_i^{\exp}(t_k) - X_i^{eval}(t_k) \cong \sum_{j} \frac{\partial}{\partial P_j} X_i^{eval}(t_k).\Delta P_j \quad . \qquad (16)$$

Let 's assign $\mathbf{R}$ as the matrix of the differences $X_i^{\exp} - X_i^{eval}$, $\mathbf{S}$ as the matrix of the derivative of the evaluated concentrations in each compartment by all fitting parameters, and $\mathbf{Q}$ as the matrix of parameters variation $\Delta P_j$. In this sense, we obtain a new linear equation similar to eqn. (7), but now for the parameters variation, namely

$$\mathbf{R} = \mathbf{S}.\mathbf{Q} \quad , \qquad (17)$$

where $\mathbf{Q}$ can be estimated by the LSM as

$$\mathbf{Q} = \left(\mathbf{S}^t.\mathbf{V}_R^{-1}.\mathbf{S}\right)^{-1} \mathbf{S}^t \mathbf{V}_R^{-1} \mathbf{R} \quad , \qquad (18)$$

and $\mathbf{V}_R^{-1}$ is the inverse of the covariance matrix of differences $X_i^{\exp} - X_i^{eval}$, that have the same $\mathbf{V}_x^{-1}$ value, with the consideration of null error in $X_i^{eval}$.

The $\chi^2$ is calculated by

$$\chi^2 = \mathbf{d}^t \cdot \mathbf{V}_R^{-1} \cdot \mathbf{d} \quad , \qquad (19)$$

where $\mathbf{d}$ is defined by

$$d_i = X_i^{\exp} - X_i^{eval} \ .$$

This Gauss-Marquardt technique is a powerful standard procedure, which has a fast convergence to solve the linearized least square equations. The cycle starts with the flux parameters obtained with the STATFLUX method, and reaches convergence in about six iterations.

## III. EVALUATION RESULTS

Efforts to evaluate the prediction accuracy and uncertainties associated with the STATFLUX method have been made, and such efforts are to be continued for forthcoming studies. To this purpose, it was firstly simulated a set of experiments with a different number of compartments, taking place in a period of 30 days, covered by both the contamination and decontamination phase (of 15 day each one) . The simulation was performed using the 4th order Runge-Kutta method (Abramowitz and Stegun 1964 and Press et al 1992), including 15 % of fluctuation. The results returned by the STATFLUX procedure were always in good agreement with the set of simulation parameters. As can be appraised in Table 1, the values of flux parameters used in the simulation are in statistical agreement with the set of parameters obtained by both the STATFLUX and the Gauss-Marquardt procedure. The observed relative difference is larger for the set of mean flux parameters than for the transfer coefficients, because the structure of the system of equations leads to strong statistical correlations between the output parameters of each compartment ($r_{12}$ and $r_{12}$ , for example ). We must remember that the marginal uncertainty of a parameters, that is , its uncertainty independent of values assumed by other parameters, is given by the square root of the corresponding element on the diagonal of the covariance matrix. However, the conditional uncertainty, that is, the uncertainty of a parameter if the other parameters would assume fixed element at the inverse of the covariance matrix. In the case of two parameters, the independent and conditional uncertainties are related by $\sigma_{conditional} = \sigma_{independent} \cdot \sqrt{1-\rho^2}$, where $\rho$ is the correlation between the two parameters. If $\rho^2 \approx 1$, as in the case for $r_{12}$ and

$r_{21}$ in the above two compartments simulation ($\rho = 0.997$) the conditional uncertainty is significantly lesser than the independent uncertainty. The large correlation explains also the good $\chi^2$ obtained in the fitting in despite of the large difference between the fitted and simulation parameters. The worst reduced $\chi^2$ value was 1.22 with 53 degrees of freedom. The situation for transfer coefficients is more favorable, because they are a linear combination of the flux parameters and depend mainly on the asymptotic values of the concentration on the corresponding compartment.

Also, in figure 2-3 is shown the two phase concentration function for a two-compartment system. As can be seen, the curves obtained with the parameters calculated with the STATFLUX procedure are in good agreement with the final concentration functions obtained with the standard iterative Gauss-Marquardt algorithm. For many purposes, then, it would be sufficient the simpler and faster STATFLUX procedure

Next, STATFLUX was applied in real experiments. It was studied the set of experimental data published by Assimakopoulos (Assimakopoulos et al 1993), related to the investigation of $^{137}Cs$ contamination and decontamination in sheeps, subjected to a diet of wheat harvested in Northwestern Greece, shortly after the Chernobyl accident. The measurement was made for 11 compartments (blood, muscle, lung, liver, kidney, spleen, heart, brain, rumen, intestine and fat), during 120 days. In the 60 first days the animals were fed with a constant intake of 3500Bq/day, and they were subsequently returned to a contamination free diet. The experiment started with 60 animals, and each sacrificed animal defined one experimental point. The application of the STATFLUX method for this set of data was successfully performed with the inclusion of two metabolic assumptions, namely: (1) excretion takes place only through the central-blood compartment (model No.1), and (2) excretion is also released by the kidney compartment (model No.2). Results from the use of any other possible combination are in total disagreement with the experimental data. Obviously, the analyzed experimental data is the final product of the biokinetics links of the realistic system. In this sense, the set of differential equations associated with a given model could be inconsistent with the experimental data. The final results are shown in Table 2 , where the transfer

coefficients calculated in this work, using two models for excretion of contaminants to the outside world, are compared with those from the multiple compartment sheep model and experimental data from Ref.Assimakopoulos et al 1991 and Assimakopoulos et al 1993.

The good results obtained using the STATFLUX procedure, in this real and large system , led us to propose this procedure as a simpler alternative method with sufficient accuracy for the evaluation of transfer coefficients Also, the results point to the fact that it is possible to suggest the best model in each concrete situation. Only biokinetics schemes, which encompasses excretion from blood and kidney, lead us to realistic results for transfer coefficients; these are the more realistic schemes for animals investigation. Since the numerical results from other biokinetics excretion schemes provided transfer coefficients values in a total disagreement with experiment, we can conclude that in the framework of our first-order linear approximation, it is possible to select the mathematically coherent biokinetics model.

## IV. CONCLUSION AND FINAL REMARKS

One of the distinct features of the STATFLUX code is its applicability in the extraction of flux parameters mean values, directly from data obtained in animal laboratory experiments and, from them (flux parameters), the calculation of transfer coefficients. This code was written with the following assumptions and considerations:

(1) linearity of the parameters entering the system of differential equations (see equation 1 ), in order to use the linear model of the Least Squares Method (LSM);

(2)the time derivatives of the experimental concentrations should be calculated by the approximation defined in equation (8), since these derivatives are needed for the use of the LSM; and

(3)it is possible, in our approach, to impose "a priori " different excretion mechanisms and, from the final results, one is able to select the most appropriate excretion mechanism.

The most noticeable characteristics of the STATFLUX code are:

(a) it is simple and fast, and

(b)the parameters are evaluated with a single iteration.

We note, additionally, that the numerical results from STATFLUX are in reasonable agreement with those from the Gauss-Maquardt standard iterative procedure. Also, results obtained with this code could be used, eventually, as a starting point for a more sophisticate iterative $\chi^2$ -test method.

The results (flux parameters and transfer coefficients) allowed us to analyze the consistency of links included in a given model. In this sense, our approach was applied in the reanalysis of data from $^{137}Cs$ contamination and decontamination in sheeps (Assimakopoulos et al 1993). From the several excretion mechanisms that can be assumed, only two of them provided results in agreement with the experimental data (see models **1** and **2** described above). This finding points to both the importance of the assumed excretion mechanism, and to the high sensitivity of the model to the links associated with the biokinetics model used for the data analysis.

It is worth mentioning that the statistical procedure worked out in this paper, opens nice possibilities for the investigation of some questions related to the identification of metabolic originated data fluctuations. This issue can be appraised, for example, in the work reported in reference (Assimakopoulos et al 1993) where each experimental point (e.g. transfer coefficients as a function of time) corresponds to a particular animal sacrificed in a specific date. Thus, the following question is posed: how to interpret correctly the standard deviations estimated for each experimental point ? Such estimations take into account, usually, the counting rate statistics, detectors efficiency, etc. On the other hand, the metabolic responses of animals from a same species could be significantly different, giving rise to strong fluctuations in the experimental points ( see the data sets for several compartments presented in reference Assimakopoulos et al 1993) indicating, thus, that the standard deviations are underestimated. This kind of drawback introduces many difficulties to perform reliable numerical calculations and data analysis. This and other issues (as e.g. the limits of the linearity hypothesis ) are being currently investigated at this Laboratory, where an experiment with Beagles (fed with uranium contamination at different intake levels) is in progress.

The accurate predictions, and the study of localized deposition on each organ, including explicitly systems with a large number of compartments, for a determined period of time, is the by-product of the present improvement in the model calculations.

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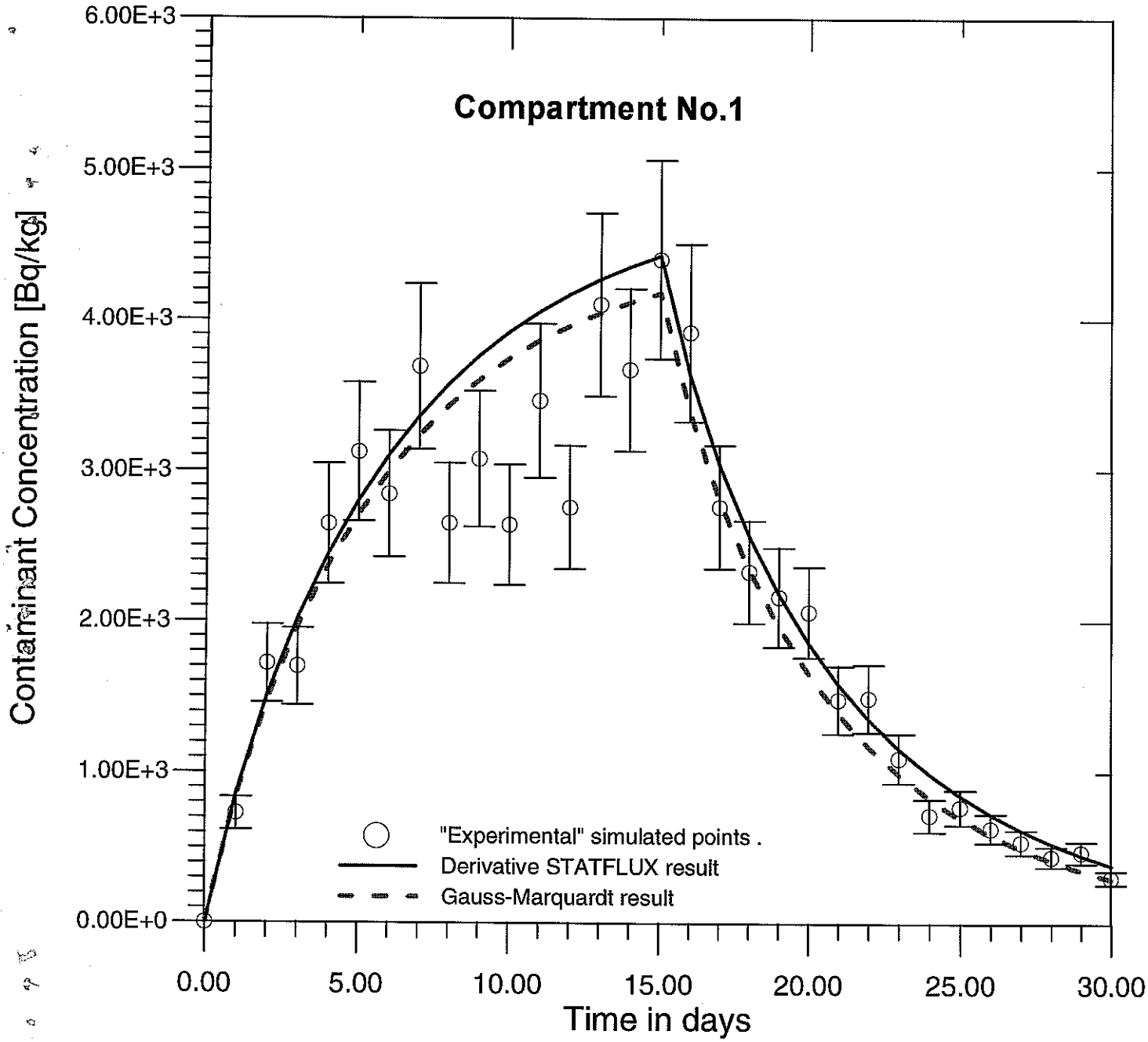
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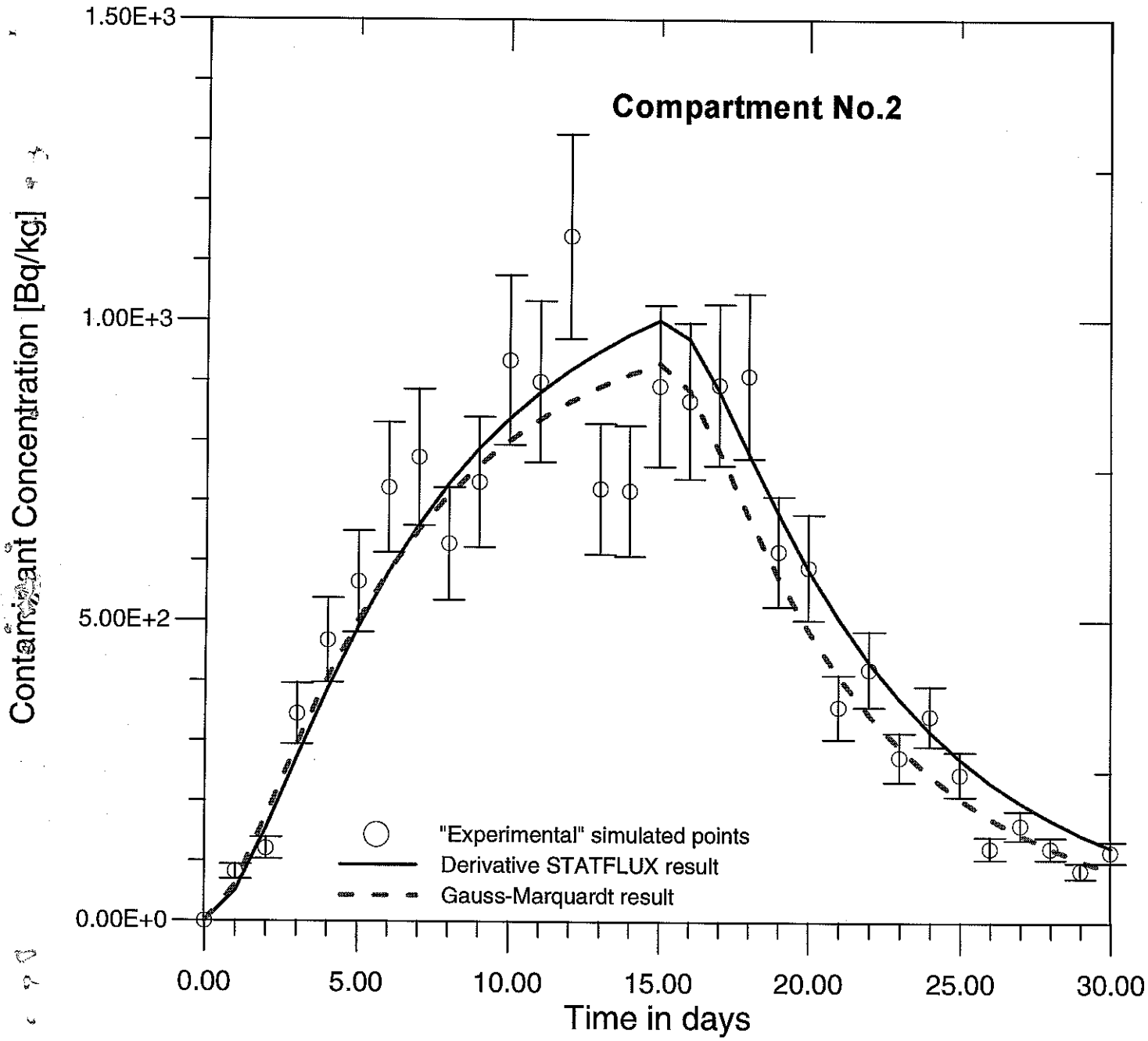
5.00E+3
4.00E+3
3.00E+3
2.00E+3
1.00E+3
0.00E+0
0.00
5.00
10.00
15.00
20.00
25.00
30.00
Time in days
"Experimental" simulated points .
Derivative STATFLUX result
Gauss-Marquardt result

Fig. 2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5.00E+2
0.00E+0
Contaminant Concentration [Bq/kg]
0.00
5.00
10.00
15.00
20.00
25.00
30.00
Time in days
"Experimental" simulated points
Derivative STATFLUX result
Gauss-Marquardt result

Fig. 3