SCIENTIFIC PAPER

OPTIMAL DESIGN AND MATHEMATICAL MODEL APPLIED TO ESTABLISH BIOASSAY PROGRAMS

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Bioassays can be used to estimate the initial intake I for the case of an acute intake exposure for an individual worker. To evaluate the effective dose, apart from I, we need to know other parameters such as activity median aerodynamic diameter (AMAD) or the fraction absorption (f_1) in the blood from the GI tract, but in an accident situation these parameters are often unknown. The bioassay measurement values can be used to estimate by fitting the parameters unknown. In this paper, optimal designs for the estimation of the unknown parameters are developed. The efficiency of the design will depend on the number of samples and the measurement accuracy. The method described applies D-optimality that maximises the determinant of the Fisher information matrix to find the best moments where the bioassay measurements should be taken. It requires obtaining the analytical solution of the biokinetic model as a function of the parameters to be fitted. The method has been implemented in a computer program.

INTRODUCTION

The internal doses for workers or members of the public exposed to the intake of radioactive particulates can be estimated using bioassay data such as lung and body counter measurements, urine or faecal radioisotope concentration, etc. The International Commission on Radiological Protection (ICRP) biokinetic models are applied to establish a relationship between the individual intake and the bioassay measurements, and then to infer the internal dose.

According to the ICRP[1] for modelling the intake of radioactive substances the human body can be divided into three sub-systems (Figure 1):

(1) *The human respiratory tract model or HRTM[2] (Figure 2)*. If a person instantaneously intakes, by inhalation, a quantity I, a fraction is deposited in some compartments labelled 'Particles in Initial State' (PIS) and in anterior nose (ET1). The fraction of I deposited directly from environment to a compartment i of the respiratory tract (RT) is called the Initial Deposition Fraction or $IDF_i(p)$, where p is the activity median aerodynamic diameter (AMAD) value in µm. The AMAD takes into account the following: size, shape, density, anatomical and physiological parameters as well as various conditions of exposure. From each PIS compartment the material is transferred into the body fluids (usually the blood B), at an absorption rate s_p. It is also simultaneously transferred from PIS (at a rate s_{pt}) to a corresponding compartment labelled 'Particles in Transformed State' (PTS). In each compartment in PTS, the isotope is dissolved at a constant rate s_p into the body fluids. From the last compartment of RT, ET2, the flow goes to the gastrointestinal tract (GI). The general model of the RT is common to any element. The absorption rate (s_{pt}, s_p, s_t) values, represented in Figures 1 and 2, are related with the chemical form of the element.

(2) *The gastrointestinal tract or GI (the detailed description is given in ICRP 30[3])*. It includes the stomach (ST), small intestine (SI), upper large intestine (ULI) and lower large intestine (LLI). The flow into the ST can come either from RT (compartment ET2) or from outside of the system by ingestion. Part of ST flow goes to the blood and the rest goes to ULI. The rate constant from SI to B is given by $\lambda_B = f_1 \lambda_{SI}/(1 - f_1)$, where f_1 represents the fraction of the stable element reaching the blood (also called body fluids). The value of f_1 is associated with the element and their chemical form. Part of the flow goes out of the system by faecal excretion.

(3) *Systemic compartments ('Rest of the body' in Figure 1)*. Part of the flow from B goes to the systemic compartments that are specific for each element or groups of elements[4]. The elimination out of the system is done by urine excretion.

Note that the ingestion is a particular case of the model described before where the intake I occurs directly from outside the system to ST. The injection is another particular case where the intake happens directly in the blood.

All the current ICRP[1,5] biokinetic models are represented by a system of ordinary linear differential

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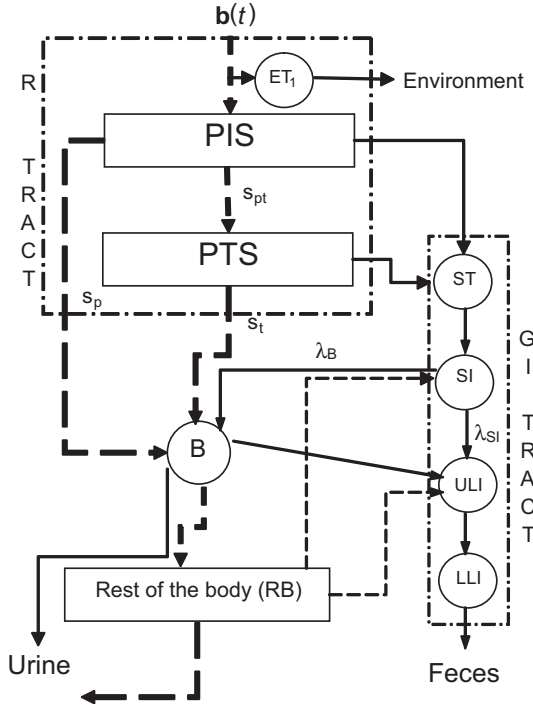*Corresponding author: guillermo@usal.es

Figure 1. Conceptual ICRP Model applied for intake by inhalation. The flow $b(t)$ from the environment is deposited in some compartments of the RT. 'Rest of the body' (RB) represents the systemic compartments. The detailed flow diagram for RB is specific to each kind of element and their chemical form. The rectangular boxes include several compartments (represented in the Figure 2). Circles represent single compartments. The thick dashed arrows mean that the flow comes or goes to more than one compartment. The thin dashed arrows mean that the flow can follow this way or not, depending on the kind of the element.

Figure 2. HRTM[2,5]. The particles intaken from environment are deposited in compartments with grey background following the ways represented in the flow diagram. The dashed arrow, ⋯⊳, from sub-system PIS to sub-system PTS means that the flow goes from each compartment in PIS to the compartment with the same number in PTS. The hollow arrows, ⇒, means a flow from each compartment in sub-system PIS or PTS to the B. A simple arrow, →, means flow from a single compartment to other.

equations with constant coefficients. The predicted value $R_m(t)$ for a kind of bioassay m can be obtained solving the model for a specific isotope.

We will refer to the case of an acute intake I by inhalation or ingestion at $t = 0$, then the solution can be represented by

$$R_m(t) = I\, r_m(t, k_1, \ldots, k_n) \qquad (1)$$

where $r_m(t, k_1, \ldots, k_n)$ is usually called the retention function. The parameters $k_1, \ldots, k_n$ are associated with specific characteristics of the substance intake, conditions of the exposure and with the parameters of the models, and m is the kind of bioassay [*Lung*: lung retention; *Wb*: whole-body content; *Uri*: daily urine excretion (accumulated in 24 h); *Fec*: faecal excretion (accumulated in 24 h);
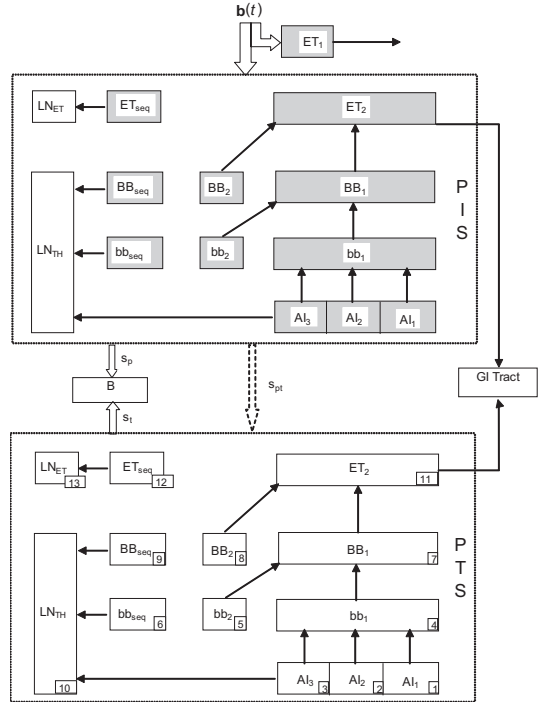
Oth: an specified compartment or organ content (e.g. thyroid)].

Apart from I, we will suppose that one or more parameters, $\beta = (\beta_1, \ldots, \beta_q)$, of the model are unknown (e.g. AMAD, f_1). We will need to know the analytical solution of the model, $R_m(I, \beta, t)$, as function of the parameters unknown. The parameters I and β can be estimated by taking bioassay measurements X_i, with associated uncertainties u_i in different times t_i and then fit these data with $R_m(I, \beta, t)$. It can be done using non-linear regression techniques as the included in the BIOKMOD[6] code.

The question that we want to answer in this paper is when the measurements X_i should be taken. That is, what are the most appropriate values for t_i? With this purpose a method, using optimal design[7], has been developed and implemented in a computer code.

COMPUTING OPTIMAL DESIGNS

To obtain the moments where the bioassay data should be taken we will use optimal design. The most universally accepted is *D*-optimal, which focuses centres on the determinant of the covariance matrix, and thus, minimises the volume of the confidence ellipsoid of the estimation of the parameters. This will be the one used throughout this paper, and *D*-optimal designs with different number of points will be shown for various examples.

Some constraints must be taken into account the following: (1) it cannot be simultaneously applied for different kinds of bioassay (e.g. lung content and also urine excretion); (2) it is necessary to leave some time between consecutive samples; (3) the first bioassay will be taken at $t_0 > 0$. These and other considerations on the problem have been discussed in a previous work[7]. This previous paper was focused on the development of an optimal design method to be applied for the lung counter measured where the AMAD was unknown. Now, we will extend the method to include the following:

(a) Other kinds of bioassay, apart from lung retention, such as urine excretion or whole-body contents;

(b) as well as the AMAD *p*, other parameters whose values are unknown.

Let us suppose that the retention function $R_m(I, \beta, t)$ after an acute input at $t = 0$, for the bioassay *m* chosen, can be expressed as function of the unknown parameters. It has (Appendix A) the following pattern:

$$R_m(I, \beta, t) = I \sum_{r=1}^{q} F_r(\beta) e^{-G_r(\beta)t} \qquad (2)$$

being $F_r(\beta)$ and $G_v(\beta)$ expressions obtained solving the model for the specific case.

Now, we apply the *D*-optimal design method:

Given a model $\eta(t; s)$, where $s = \{I, \beta_1, \ldots, \beta_q\}$, which we rewrite $s = \{s_1, \ldots, s_p\}$, is the vector of unknown parameters, the Fisher information matrix **M** for a specific design $\xi = \{t_1, \ldots, t_n\}$ (t_i is the time when the *i*th sample should be taken) will be

$$M = E\left[\frac{\partial \log l}{\partial s_i} \frac{\partial \log l}{\partial s_j}\right], \qquad (3)$$

where *l* denotes the likelihood function for the regression residuals.

When the model is not linear with respect to the parameters, the information matrix (and then the optimal designs) will depend on the unknown parameters. In this case, initial values are needed for the 'non-linear' parameters[8], and the designs computed will be locally optimal.

A *D*-optimal design will be one that leads the determinant of the information matrix to a maximum.

The information matrix is the main tool for computing optimal designs, since it is asymptotically proportional to the inverse of the covariance matrix of the estimators of the model parameters.

If the model $\eta(t; s)$ is differentiable with respect to the parameters with a continuous derivative, the information matrix for design ξ and normally distributed random errors can be written as

$$\mathbf{M} = \mathbf{X}^T \Sigma^{-1} \mathbf{X}, \qquad (4)$$

where **X** is the $n \times p$ matrix whose *i*th row is

$$\nabla \eta(t_i, s) = \left(\frac{\partial \eta(t_i, s)}{\partial s_1}, \ldots, \frac{\partial \eta(t_i, s)}{\partial s_p}\right) \qquad (5)$$

and Σ denotes the covariance matrix of the residuals.

Since all the bioassays are performed on an individual worker it is convenient to consider a non-trivial covariance matrix. One of the common choices used in literature [Cresie[9]] is $\Sigma = \sigma^2 \Gamma$, where σ^2 is the standard deviation associated with the system of measurement, and $\Gamma = (l_{ij})$ with $l_{ij} = \exp(-\rho |t_i - t_j|)$, meaning that the relationship between samples decays exponentially with increasing time–distance between them. The parameter ρ is characteristic of the worker, being a typical value $\rho = 1$ that will be used in the examples of the next section. For computational purposes we have found more appropriate to use the distance $d_i = t_i - t_{i-1}$ instead of t_i. The *D*-optimal design will be the set of values of t_i that leads det|**M**| to a maximum.

We will show the method, step by step, with an easy example:

(1) Let us suppose $R(I,p,t) = I \exp(-0.02t + 0.2p)$ being the unknown parameters $s = \{I, p\}$.

(2) Then substituting at Equation 5 we obtain that
$$\nabla R(I,p,t) = \{\partial R/\partial I, \partial R/\partial p\}$$
$$= \{\exp(-0.02t + 0.2p),$$
$$0.2I \exp(-0.02t + 0.2p)\}.$$

(3) The user defines the *n* value (number of points where the measurements should be taken). We chose $n = 2$, that is $\{t_0, t_1\}$.

(4) **X** is obtained by evaluating $\nabla R(I, p, t)$ at points $\{t_0, t_1\}$. For the same points $\Gamma = (l_{ij}) = [\{1, \exp(-|t_0 - t_1|)\}, \{\exp(-|t_0 - t_1|), 1\}]$.

(5) Now $\Sigma = \sigma^2 \Gamma$ is computed (for this example $\sigma = 2$ is taken) and then $\mathbf{M} = \mathbf{X}^T \Sigma^{-1} \mathbf{X}$ is calculated.

(6) Finally, the user chooses a value for t_0 and then the *D*-optimal design will be $\{t_0, t_1\}$, with t_1 the value that leads det|**M**| to a maximum. For instance, if we choose $t_0 = 0.5$ d the best value for t_1 is $t_1 = 2.4$ d. This means that the more appropriate time to take the second measurement is $t_1 = 2.4$ d after the acute intake happened.

The previous method has been used for developing a software called *Optdesign*. It has been implemented as a *Mathematica* (Woffram Research, Inc., Champaign, IL, USA) package. It can be applied along with BIOKMOD[6] to establish a bioassay programs using the ICRP models. These recourses are available at http://web.usal.es/guillermo.

APPLICATIONS

In this section, some applications of *Optdesign* are described. These examples, including the information about the method of the measurements (minimum detectable activity, precision, etc.) are based on IAEA 1996[10].

The models described here can be expressed by $R(I, \beta, t) = Ir(t, \beta)$, where $\beta = p$ (being p the AMAD value) in Example 1 and $\beta = f_1$ (being f_1 the fraction absorption) in Example 2.

We have found that the *D*-optimal designs will depend neither on I nor on σ^2, but they do depend on non-linear parameter p or f_1.

The first measure should be made as soon as possible. In both examples, the first measurement is taken at $t_0 = 0.5$ d.

Example 1: Lung counter applied to the estimation of uranium intake by inhalation

A worker has accidentally intaken by inhalation an unknown I quantity of UO_2 being the AMAD p also unknown. We wish to estimate I measuring the uranium lung content using a lung body counter with $\sigma = 1.8$ Bq. It will be assumed that the worker has not previously been exposed to significant uranium intakes.

Note: The disintegration constants can be assumed '0' for all uranium isotopes because their half-lives are too long. The AMAD p value is expected in the range between 1 and 10 μm.

In this case the unknown variables are I and AMAD p. To define the optimal design, the first step to obtain the lung retention function R_{Lung} (I, p, t) for these kinds of radioactive aerosols (Equation A3). It can be made with BIOKMOD choosing metabolism type S.

We have used $p = p_0 = 5$ μm as the initial value for this parameter when computing optimal designs. The designs obtained taking an initial value $p_0 = 5$ μm have proved to be very robust with respect to this choice, giving very high efficiencies in every case.

The designs computed for different number of sample points are shown in Table 1. Mimicking the real situation, the function forces the distance between samples to be at least one day.

For big values of ρ, which in practice mean independent observations, *D*-optimal designs tend to be a two-point design. When forcing the several points

to be different what we obtained is a 'two-nucleoid' design, each nucleoid composed by a set of points with the minimum possible distance between them. For instance, for $\rho = 100$, the six-point design (0.5, 5, 69, 77, 84, 92), i.e. the first two observations as soon as possible and the rest around 70 d later, being one day the distance between them, i.e. the (fixed) minimum distance between samples defined in function *Doptize* from the package *Optdesign*.

Non-linear estimations of the parameters were made for all the designs in Table 1. To test the behaviour of the standard error of these estimations a 10,000 runs simulation was performed for every case, allowing for normally distributed random errors with corresponding covariance matrix and taking $I = 10,000$, $p = 6$ (different from the initial value $p_0 = 5$ used for the computations of the optimal designs) and $\sigma^2 = 3$. The standard error for the estimation of I and for p was computed for the different designs. Table 2 shows the evolution of these errors that decrease increasing the number of measurements.

This information should be used to decide the number of measurements that should be taken. It can be seen that the decay in the standard error is more noticeable in the first designs, while is not so important in the last ones. That means that, always depending on the aim of the experiment and the practitioner's opinion, in many cases it will be enough to choose one of the intermediate designs,

Table 1. Results of the *D*-optimal designs for uranium retention (solubility *S* and $\rho = 1$) in the lungs as function of *n* (number of points used for the estimation).

n	Days after the intake happened									
2	0.5	69								
3	0.5	65	73							
4	0.5	61	69	77						
5	0.5	58	66	73	81					
6	0.5	5	69	77	84	92				
7	0.5	5	66	74	81	88	95			
8	0.5	4	9	72	80	87	94	102		
9	0.5	4	8	12	77	84	91	98	106	
10	0.5	4	8	12	74	81	88	95	102	109
11	0.5	4	8	65	72	78	85	91	97	104	111

Table 2. Relative standard error (%) for estimation of the parameter vs. *n* (number of points in the *D*-optimal design used for the estimation) for parameters *I* and AMAD *p* from model for the uranium lung retention.

n	3	4	5	6	7	8	9	10	11
I	9.0	8.2	7.8	7.5	7.2	6.9	6.7	6.6	6.5
p	10.8	9.9	9.4	9.1	8.6	8.5	8.4	8.3	7.8

since the gain in accuracy when taking more samples is not so prominent.

Example 2: Whole-body counter applied to estimation of ^{60}Co intake by ingestion

An adult male has been exposed to a simple accidental intake by ingestion of ^{60}Co being both I and the fractional absorption f_1 unknown. The aim is to estimate I using a whole-body counter with $\sigma = 10$ Bq. It will be assumed that the individual has not been previously exposed to a negligible ^{60}Co intake.

In this case the unknown variables are I and f_1 where $0 \leq f_1 \leq 1$ being 0.1 its most probable value. To define the optimal design we need to obtain the whole-body (Wb) retention function $R_{\mathrm{Wb}}(I, k, t)$. The biokinetic ^{60}Co model[4] does not involve recycling and $R_{\mathrm{Wb}}(I, k, t)$ has the pattern given by Equation (A4) being $k = \lambda_{\mathrm{B}} = f_1 \lambda_{\mathrm{SI}}/(1 - f_1)$. We want to define the optimal design to establish the best times t_i to make the following measures. The program *Optdesign* can be used for obtaining the t_i values.

The three-point D-optimal designs for different values of f_1 are shown in Table 3 proving that the optimal designs are very robust with respect to the election of the initial value for parameter f_1.

DISCUSSION

In the case of an acute internal exposure for an individual, bioassays are usually applied to estimate the intake I (unknown). We need to know other parameters such as AMAD p or f_1 to evaluate the effective dose, parameters that are usually unknown. We have described a method, and developed software that applies D-optimal designs for such estimation. A set of times where to perform the bioassays is given as a solution. However, on each particular case, the practitioner should decide the number of measurements to be taken. Some factors may influence this decision: undoubtedly the bigger the design is the more accurate the estimations will be, but on the other hand there are some reasons that can lead to smaller designs, depending on how long one can wait to get the results, the health and availability of the person, the economic cost of each bioassay, etc. A proper utility function taking into account all

these reasons (and possibly different ones) may be the right tool to choose the 'best' design for a particular case. Another factor to be considered is that according to the first measurements, the retention predicted for later measurements could be below the lower detection limit of the measured system.

The study of the different possibilities to choose the right one for a specific problem could be the subject of a future work.

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APPENDIX A—SOLVING THE ICRP MODELS AS A FUNCTION OF SOME PARAMETERS

The retention function $R_m(t)$ for a kind of bioassay m (e.g. lung or whole-body retention) as function

Table 3. Results of D-optimal designs for ^{60}Co whole-body retention varying the initial value of f_1.

f_1	Days after the intake happened		
0.05	0.5	4.00	7.04
0.10	0.5	3.97	7.01
0.15	0.5	3.94	6.99
0.20	0.5	3.91	6.96

of I and the AMAD p after a single intake I, by inhalation, at $t = 0$. It can be shown[5] that

$$R_m(t) = I \sum_{j,v} IDF_j(p) c_{j,v} e^{-d_{j,v}t} \qquad (A1)$$

being $IDF_j(p)$ the initial deposition fractions as a function of the AMAD p, c_v and d_v are the coefficients obtained solving the model for the specific case.

The $IDF_j(p)$ values, with $j = \{1, \ldots, 12\}$ (Table 4), may be either calculated following the procedure described in ICRP 66[2] or obtained from Annex F of ICRP 66[2]. ICRP 66[2] already gives the procedure to obtain what we called the initial deposition derivated fraction $IDDF_k(p)$, being $k = \{AI, bb_{(fast+seq)}, bb_{(slow)}, BB_{(fast+seq)}, BB_{(slow)}, ET2, ET1\}$, which involves large algebraic expressions. Table A1 shows the relationships between $IDF_j(p)$ and $IDDF_k(p)$. They have been established using Table 17.B of ICRP 66[2].

We have found that the IDDF parameters in the range of interest of the AMAD p [0.5 μm, 20 μm], for the reference worker (similar expressions can be obtained for other kinds of population) may be fitted using least squared estimators as follows:

$$IDDF_{AI}(p) \approx 0.12819 e^{-0.17011p},$$

$$IDDF_{bb(fast+seq)}(p) \approx 0.010074 e^{-0.087894p},$$

$$IDDF_{bb(slow)}(p) \approx 0.021284 e^{-4.3533p}$$
$$+ 0.00921 e^{-0.14724p},$$

$$IDDF_{BB(fast+seq)}(p) \approx 0.017174 e^{-0.057783p}$$
$$- 0.017174 e^{-0.56678p},$$

$$IDDF_{BB(slow)}(p) \approx 0.011084 e^{-0.12358p}$$
$$- 0.011084 e^{-1.11147p},$$

$$IDDF_{ET2}(p) \approx 0.45501 e^{-0.016182p}$$
$$- 0.45501 e^{-0.63700p}$$

$$IDDF_{ET1}(p) \approx 0.37714 e^{-0.0083037p}$$
$$- 0.37714 e^{-0.57901p} \qquad (A2)$$

The retention function $R_m(I, p, t)$ can be obtained as a function of I and p using Equation (A1), and the approximation given by Equation (A2) with the relationship established in Table A1. Then

$$R_m(I, p, t) = I \sum_{r=1}^{q} A_r e^{a_r p + d_r t} \qquad (A3)$$

being A_r, a_r and d_r the coefficients for the specific case. It can be obtained for most isotopes and kinds of bioassays with BIOKMOD[6].

In other occasions we can be interested in obtaining the $R_m(I, k, t)$ as a function of I and k, where

Table A1. Compartments where the radioactive aerosols intake by inhalation are deposited and relationship between IDF and IDDF.

|	Compartment	IDF vs. IDDF
1	AI_1	$IDF_1(p) = 0.3\ IDDF_{AI}(p)$
2	AI_2	$IDF_2(p) = 0.6\ IDDF_{AI}(p)$
3	AI_3	$IDF_3(p) = 0.1\ IDDF_{AI}(p)$
4	bb_1	$IDF_4(p) = 0.993\ IDDF_{bb(fast+sec)}(p) - 0.007\ IDDF_{bb(slow)}(p)$
5	bb_2	$IDF_5(p) = IDDF_{bb(slow)}(p)$
6	bb_{seq}	$IDF_6(p) = 0.007\ IDDF_{bb(fast+sec)}(p) + IDDF_{bb(slow)}(p)$
7	BB_1	$IDF_7(p) = 0.993\ IDDF_{BB(fast+sec)}(p) - 0.007\ IDDF_{BB(slow)}(p)$
8	BB_2	$IDF_8(p) = IDDF_{BB(slow)}(p)$
9	BB_{seq}	$IDF_9(p) = 0.007\ IDDF_{BB(fast+sec)}(p) + IDDF_{BB(slow)}(p)$
10	ET_2	$IDF_{10}(p) = 0.9995\ IDDF_{ET2}(p)$
11	ET_{seq}	$IDF_{11}(p) = 0.0005\ IDDF_{ET2}(p)$
12	ET_1	$IDF_{12}(p) = IDDF_{ET1}(p)$
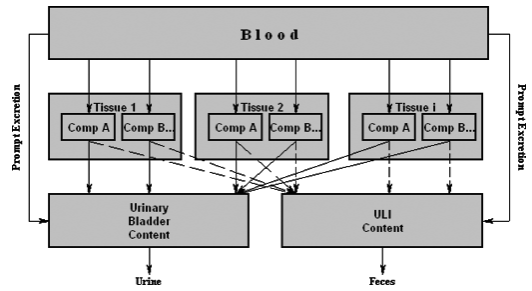
Figure A1. Systemic compartment for elements with ICRP 30 metabolic model structure (compiled in ICRP 2001[1]).

k represents any parameter of the model (e.g. the fraction absorption f_1). The analytical expression of $R_m(I, k, t)$ can be obtained only in particular cases. However, there are many practical situations in which this is feasible. For instance, an analytical solution as function of rate transfer parameters k_{ij} can be obtained for models that do not involve recycling. In these cases the system can be decomposed in catenary branches[5]. This condition is verified by many elements: all of them where the ICRP 30 metabolic model structure (Figure A1) is still applicable.

In these cases the analytical solution can be obtained using the method described by Sánchez and López-Fidalgo[5] or using the equation for solving catenary systems described in Skrable *et al.*[11] It has the pattern given by

$$R_m(I, k, t) = I \sum_{r=1}^{q} A_r(k) e^{a_r(k)t} \qquad (A4)$$

being

$$A_r(k) = \frac{b_r k}{c_{1r} + c_{2r}k + c_{3r}k^2 + \ldots};$$

$$a_r(k) = d_{1r} + d_{2r}k$$

where k is the unknown transfer rate of the model that we want to obtain by fitting.

The method can be extended to model where I, p and k are unknown combining Equations (A3) and (A4).