Biokinectic modelling and Optimal design

British-Spanish Workshop on Optimal Design

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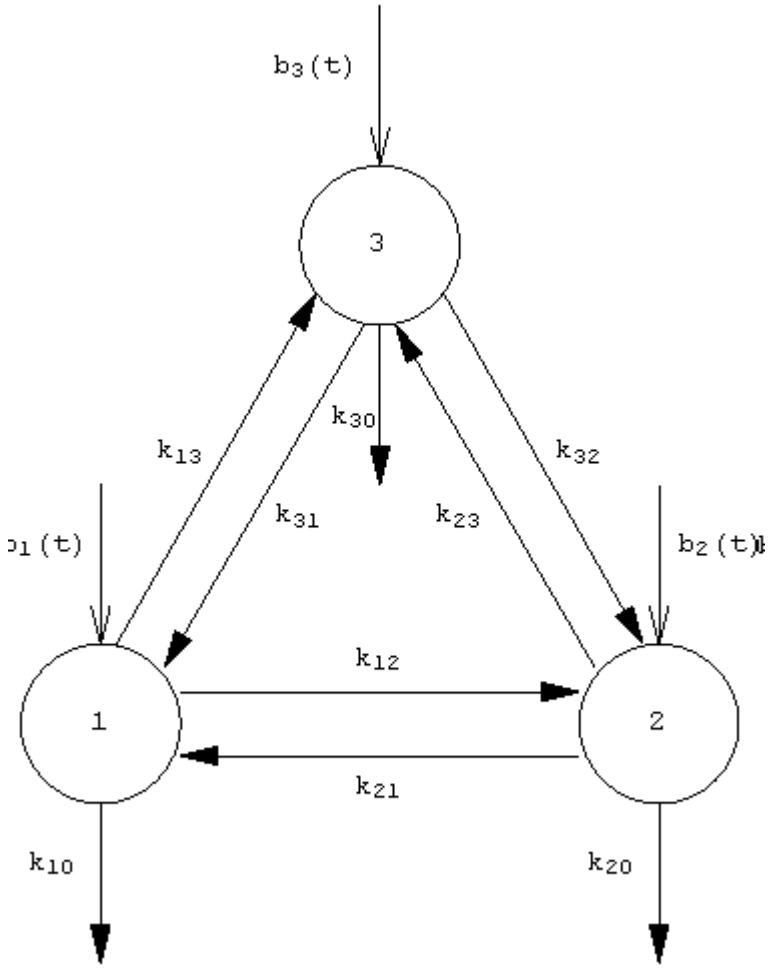


Compartmental analysis has applications in clinical medicine, pharmacokinetics, internal dosimetry, nuclear medicine, ecosystem studies and chemical reaction kinetics. It can be described as the analysis of a system in terms of compartments which separate the system into a finite number of component parts which are called compartments. Compartments interact through the exchange of species. Species may be a chemical substance, hormone, individuals in a population and so on.

$$\begin{pmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{x}_3(t) \end{pmatrix} = \begin{pmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} \\ k_{12} & -(k_{20}+k_{21}+k_{23}) & k_{32} \\ k_{13} & k_{23} & -(k_{30}+k_{31}+k_{32}) \end{pmatrix} \cdot \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} + \begin{pmatrix} b_1(t) \\ b_2(t) \\ b_3(t) \end{pmatrix}$$

Compartmental general equation

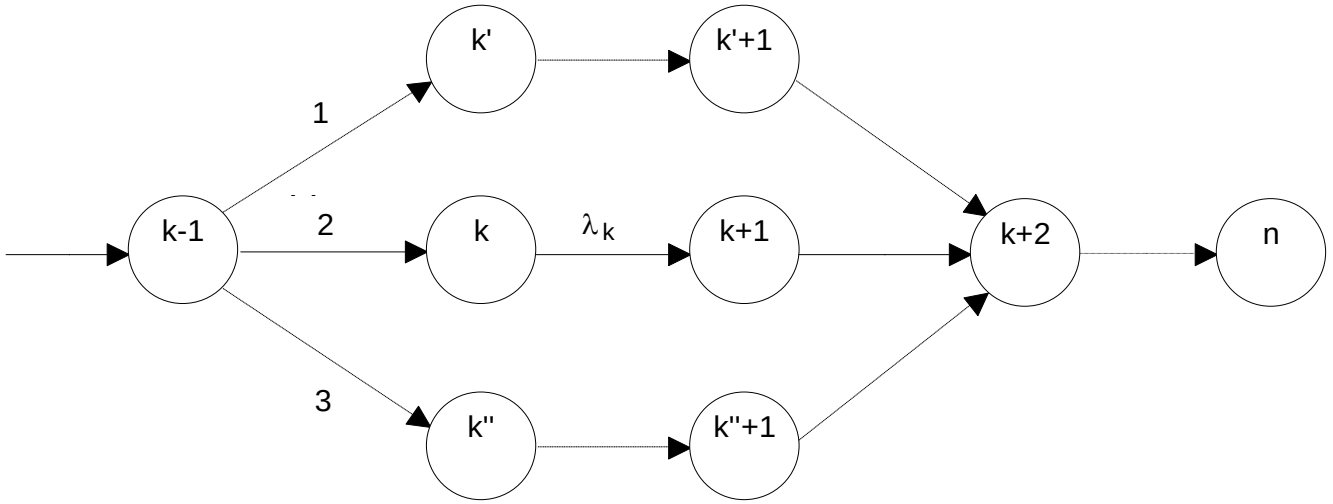
$$\mathbf{x}'(t) = \mathbf{A}\,\mathbf{x}(t) + \mathbf{b}(t)$$

$$\mathbf{x}(t) = \mathbf{x}_0\, e^{t\mathbf{A}} + \int_0^t \mathbf{b}(\tau) e^{(t-\tau)\mathbf{A}}\, d\tau$$

$\mathbf{x'}(t) = [x'_1(t), x'_2(t), \ldots, x'_n(t)]^T$
$\mathbf{x}(t) = [x_1(t), x_2(t), \ldots, x_n(t)]^T$
$\mathbf{b}(t) = [b_1(t), b_2(t), \ldots, b_n(t)]^T$
$\mathbf{x0} = [x_1(0), x_2(0), \ldots, x_n($

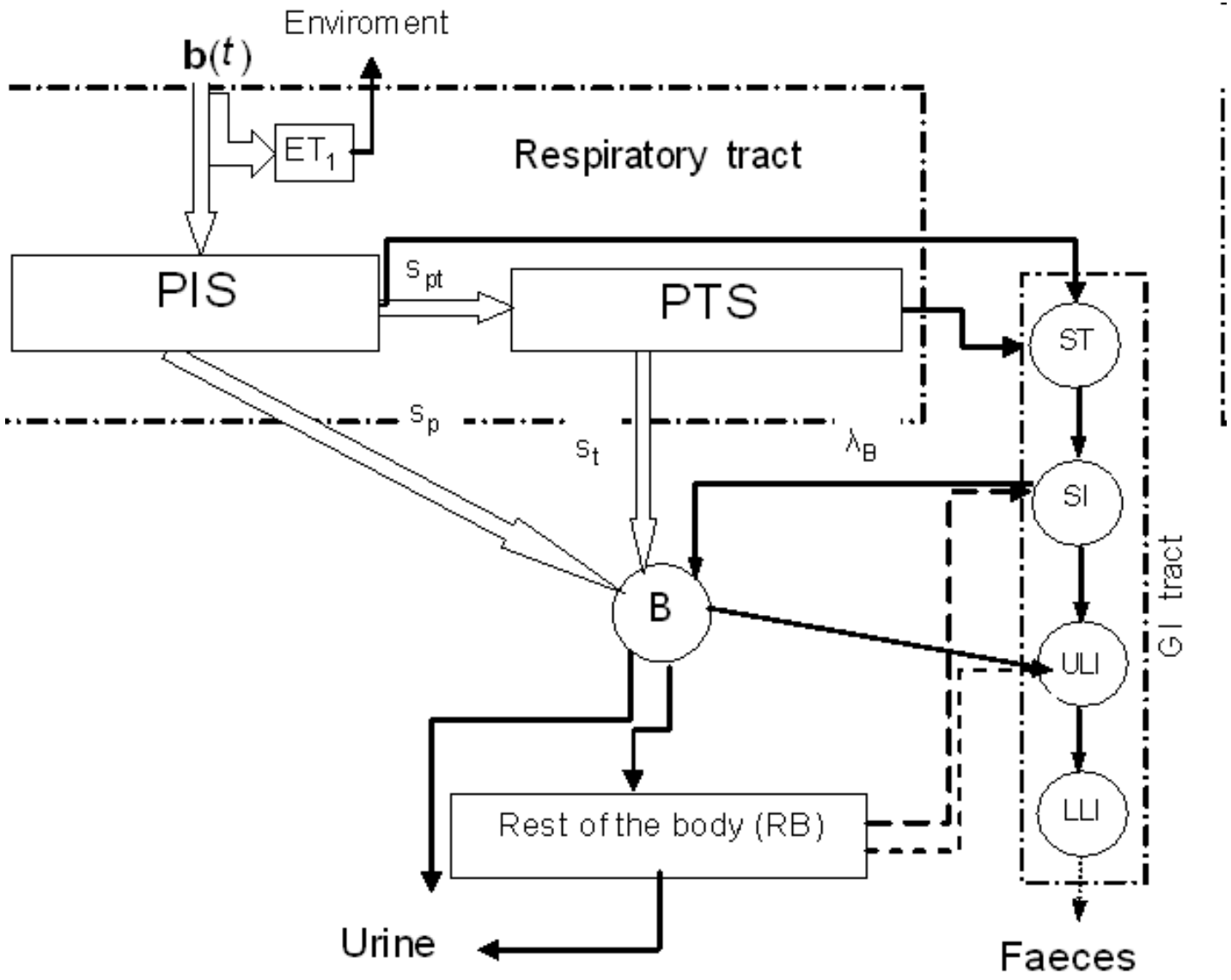
$$x_i(t) = \sum_{r=1} a_r\, e^{-k_r t}$$

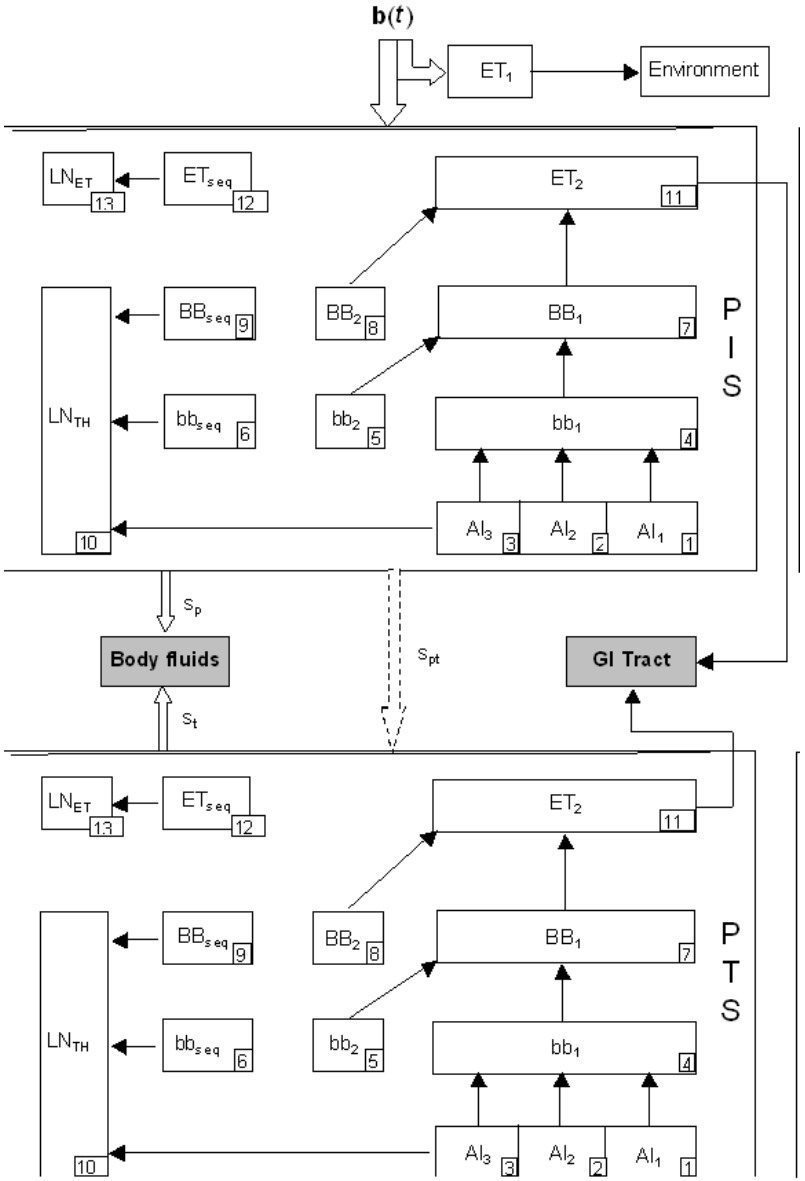
Catenary branches



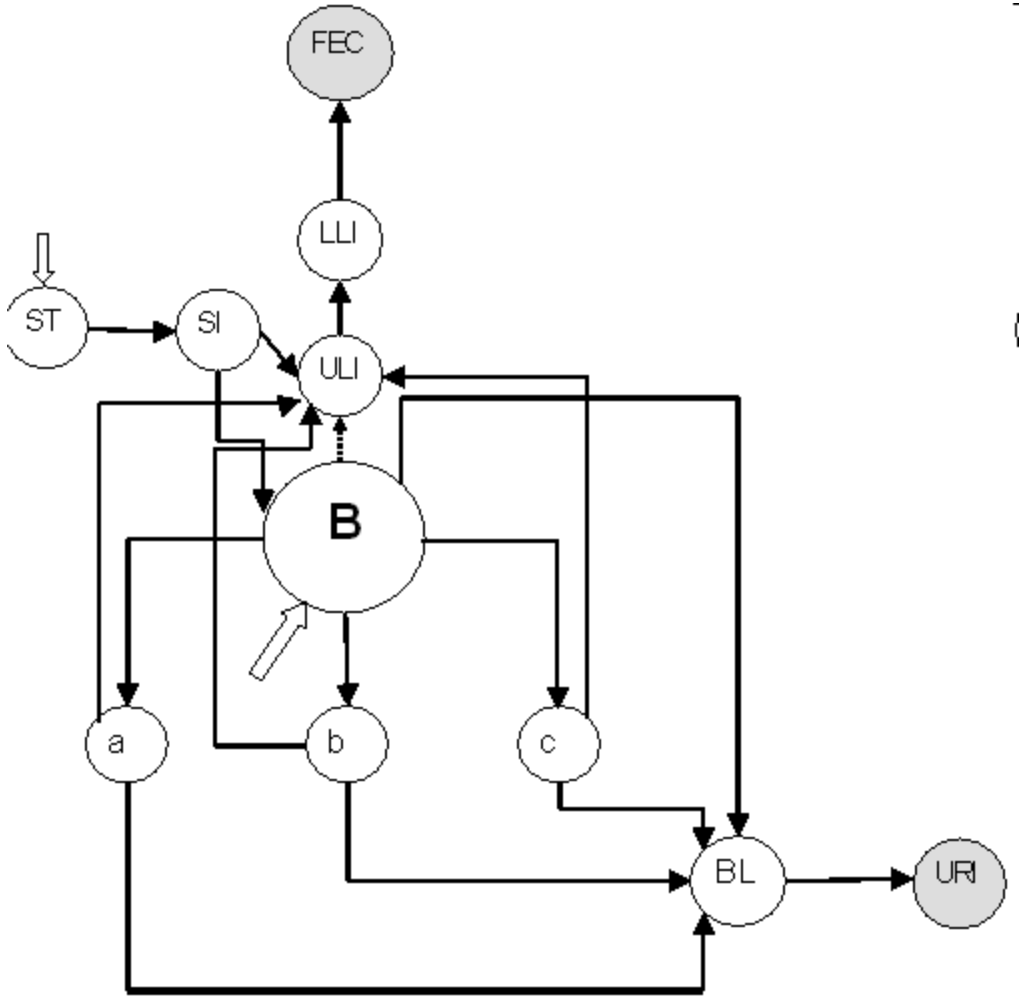
$$r_i(t) = e^{-\lambda_R t} \sum_C F_C \left(\prod_{p=1}^{i-1} k_p \right) \sum_{j=1}^{i} \left(\frac{e^{-K_j t}}{\prod_{\substack{p=1 \\ p \neq j}}^{i} \left(K_p - K_j \right)} \right) \qquad i = 1, 2, \ldots, n$$

Optimal Design applied to optimization of bioassays for people exposed to intake of radioactive sustances


Enviroment
b(t)
ET1
Respiratory tract
PIS
spt
PTS
ST
SI
ULI
LLI
GI tract
sp
st
λB
B
Rest of the body (RB)
Urine
Faeces



If a person intakes by inhalation instantaneously a quantity I, it is deposited directly in some compartments of PIS (AI, bb1, bb2, bbseq, BB1 , BB2, BBseq, ET2 and ETseq) and ET1. The fraction deposited in each compartment is called Initial Deposition Factor or IDF. It is a function of Activity Median Aerodynamic Diameter (AMAD), which includes size, shape, density, anatomical and physiological parameters as well as various conditions of exposure. The .
The general model of the RT is common to any element except the absorption rates {spt, sp, st} that are related with the chemical form of the element. ICRP gives default values of absorption rates according to types F, M or S.


FEC
LLI
ST
SI
ULI
B
a
b
c
BL
URI

Bioassay: Lung, urine and fecal excretion

$$\gamma_i(t) = F_i(l_1, \ldots, l_m, s_p, s_{pt}, s_t, f_1, \lambda_1, \ldots, \lambda_n, h_1 \ldots, h_r, \lambda_R, t)$$

$$r_m(t) = \sum_{j,v} \mathrm{IDF}_j(p)\, c_{j,v}\, e^{-a_{j,v}\, t}$$

$$\begin{aligned}
&-0.000186053\, e^{-4.35327\, p-2.0001\, t} - 0.000533918\, e^{-0.170111\, p-2.0001\, t} - \\
&0.0000805063\, e^{-0.147244\, p-2.0001\, t} + 0.0124915\, e^{-0.0878945\, p-2.0001\, t} + \\
&0.0213271\, e^{-4.35327\, p-0.0301\, t} - 0.0110729\, e^{-1.11147\, p-0.0301\, t} + 0.0092284\, e^{-0.147244\, p-0.0301\, t} + \\
&0.0110729\, e^{-0.123578\, p-0.0301\, t} + 0.0388835\, e^{-0.170111\, p-0.0201\, t} + \\
&0.0768815\, e^{-0.170111\, p-0.0011\, t} + 0.0106723\, e^{-0.170111\, p-0.00022\, t} + \\
&0.000148842\, e^{-4.35327\, p-0.0001\, t} - 0.00007751\, e^{-1.11147\, p-0.0001\, t} - \\
&0.000120097\, e^{-0.566783\, p-0.0001\, t} + 0.00213432\, e^{-0.170111\, p-0.0001\, t} + \\
&0.000064405\, e^{-0.147244\, p-0.0001\, t} + 0.00007751\, e^{-0.123578\, p-0.0001\, t} + \\
&0.0000704456\, e^{-0.0878945\, p-0.0001\, t} + 0.000120097\, e^{-0.0577835\, p-0.0001\, t}
\end{aligned}$$

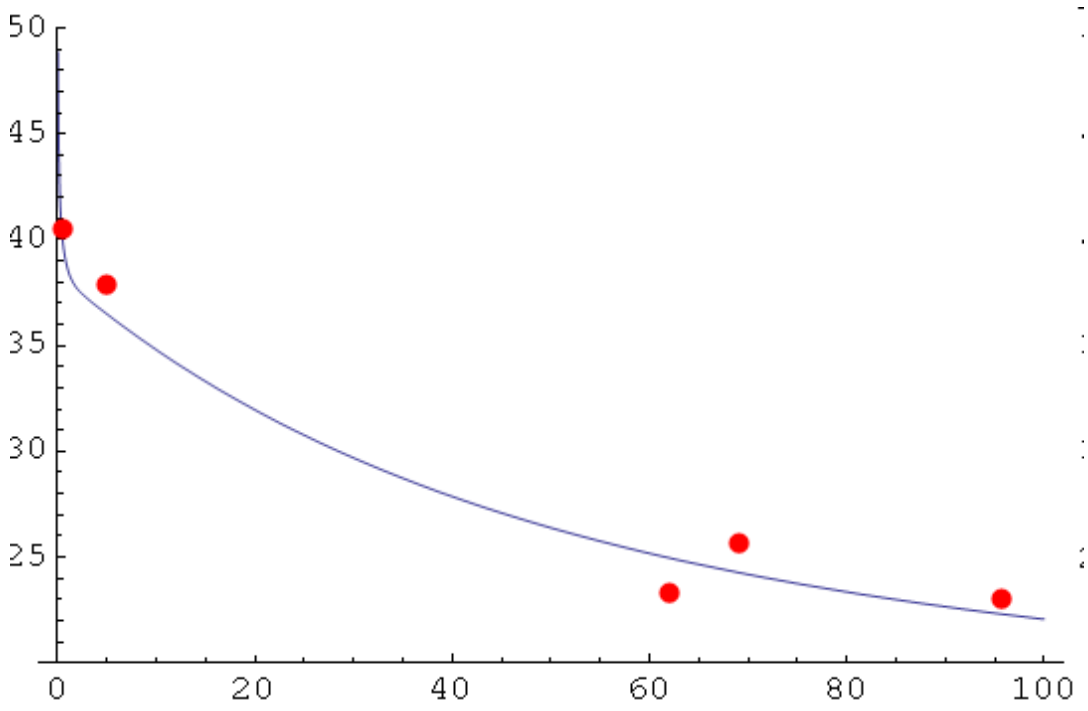
The below method is described in Sánchez G; Rodríguez-Díaz J. M. 2006

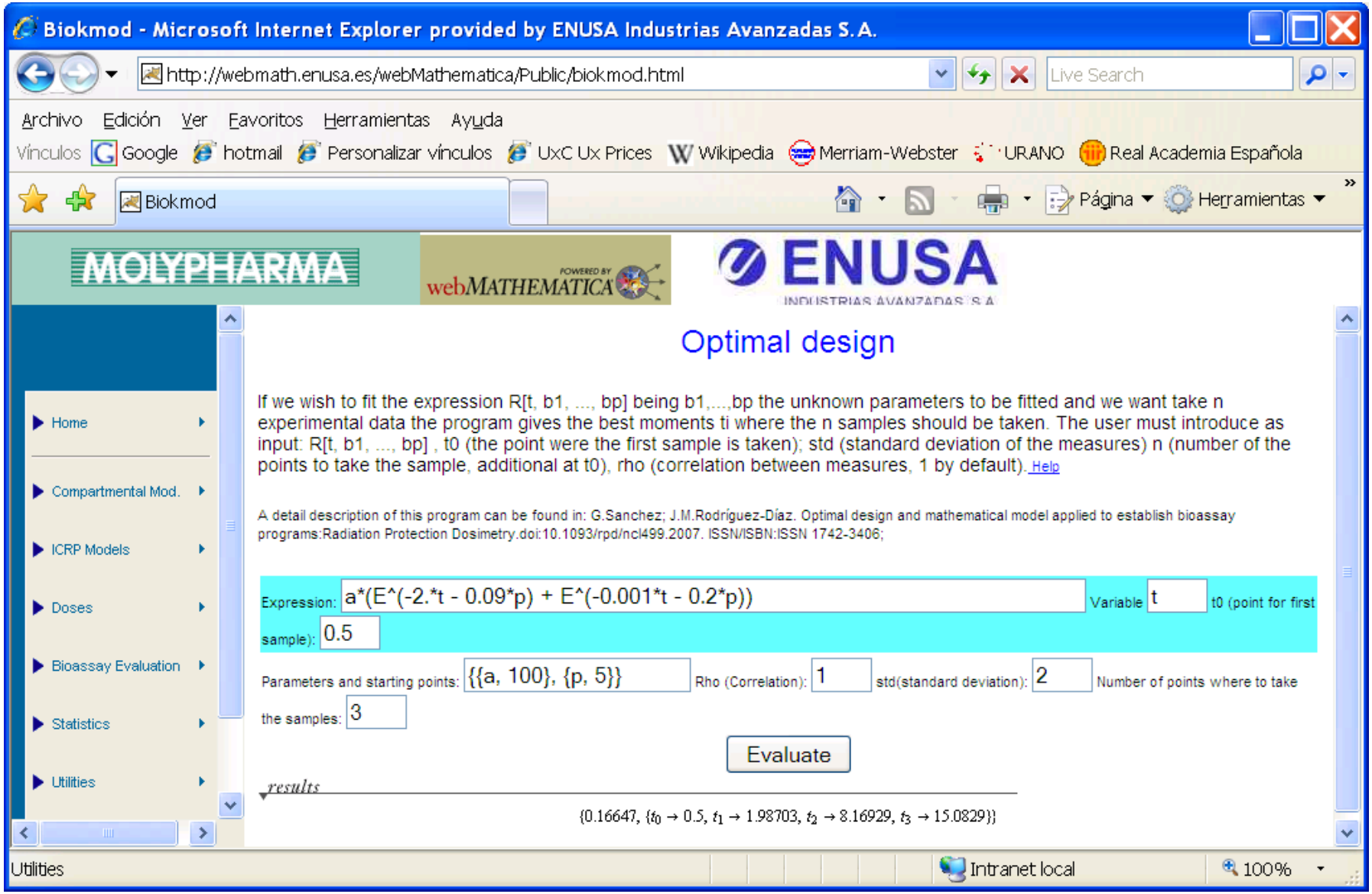
Be the function $r(t, \beta)$ where , where $\beta = \{\beta_1, \ldots, \beta_p\}$ are parameters unknowns to be fitted using experimental data . We wish chose the best moments $\{t_0, .., t_i, \ldots t_n\}$ to take the experimental data. It will be assumed that all measured have more or less the same uncertainties, that is $\sigma^2 \simeq \sigma_i^2$. The Fisher information matrix for a specific design $\{t_1, .., t_i, \ldots t_n\}$= ($t_i$ is the time when the i-th sample should be taken) will be used to compute the optimal design. A D-optimal design will be a design that leads the determinant of the information matrix to a maximum.

`Optdes[R[t, β1, ..., βp], t, {{β1, β10}, ..., {βp, βp0}}, t0, ρ, σ, n, opts]` being $\beta_1, \ldots, \beta_p$ the unknown parameters and $\beta_{10}, \ldots, \beta_{p0}$ their the initial values, t_0 is the point were is takes the first measured, ρ *(relationship between samples that decays exponential),* usually will be used ρ=1 (it is assumed that there not correlation between samples will be written "NoCorrelation"); σ is the standard deviation of the measures, n is the number of the point (additional at t_0) where we want to take measured; *opts* is a option to close the maximization method (The are the same that used by NMaximize).The function will give the values for $\{t_0, .., t_i, \ldots t_n\}$.

```
Table[{n, Optdes[inp rlung[t, p], t, {{inp, 1000}, {p, 5}}, 0.5, 1, 2, n]}, {n, 1, 3}] //
 TableForm
```

```
1  0.000033437
   t0 → 0.5      t1 → 70.2305
2  0.0000668091
   t0 → 0.5      t1 → 66.2152 t2 → 74.7861
3  0.000100107
   t0 → 0.5      t1 → 62.5845 t2 → 70.6721 t3 → 78.8042
```

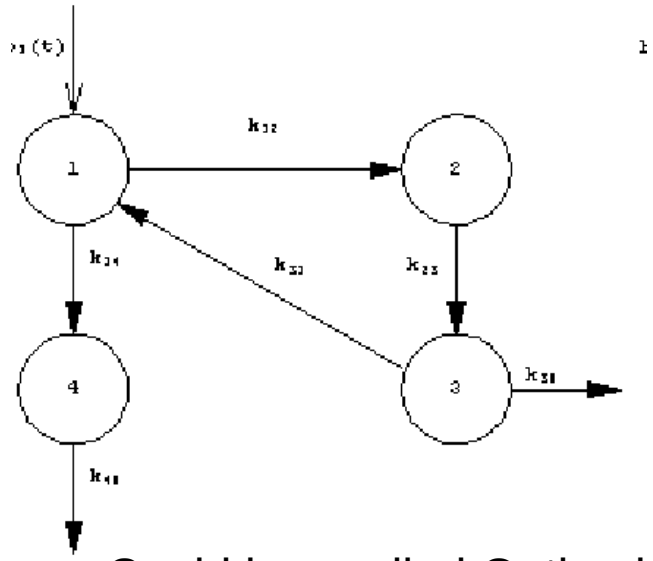



Biokmod - Microsoft Internet Explorer provided by ENUSA Industrias Avanzadas S.A.
http://webmath.enusa.es/webMathematica/Public/biokmod.html
Live Search
Archivo Edición Ver Favoritos Herramientas Ayuda
Vínculos Google hotmail Personalizar vínculos UxC Ux Prices Wikipedia Merriam-Webster URANO Real Academia Española
Biokmod
Página Herramientas
MOLYPHARMA
webMATHEMATICA
ENUSA
INDUSTRIAS AVANZADAS S.A.
Optimal design
Home
Compartmental Mod.
ICRP Models
Doses
Bioassay Evaluation
Statistics
Utilities
If we wish to fit the expression R[t, b1, ..., bp] being b1,...,bp the unknown parameters to be fitted and we want take n experimental data the program gives the best moments ti where the n samples should be taken. The user must introduce as input: R[t, b1, ..., bp] , t0 (the point were the first sample is taken); std (standard deviation of the measures) n (number of the points to take the sample, additional at t0), rho (correlation between measures, 1 by default). Help
A detail description of this program can be found in: G.Sanchez; J.M.Rodríguez-Díaz. Optimal design and mathematical model applied to establish bioassay programs:Radiation Protection Dosimetry.doi:10.1093/rpd/ncl499.2007. ISSN/ISBN:ISSN 1742-3406;
Expression: a*(E^(-2.*t - 0.09*p) + E^(-0.001*t - 0.2*p))
Variable t
t0 (point for first sample): 0.5
Parameters and starting points: {{a, 100}, {p, 5}}
Rho (Correlation): 1
std(standard deviation): 2
Number of points where to take the samples: 3
Evaluate
results
{0.16647, {t0 → 0.5, t1 → 1.98703, t2 → 8.16929, t3 → 15.0829}}
Utilities
Intranet local
100%

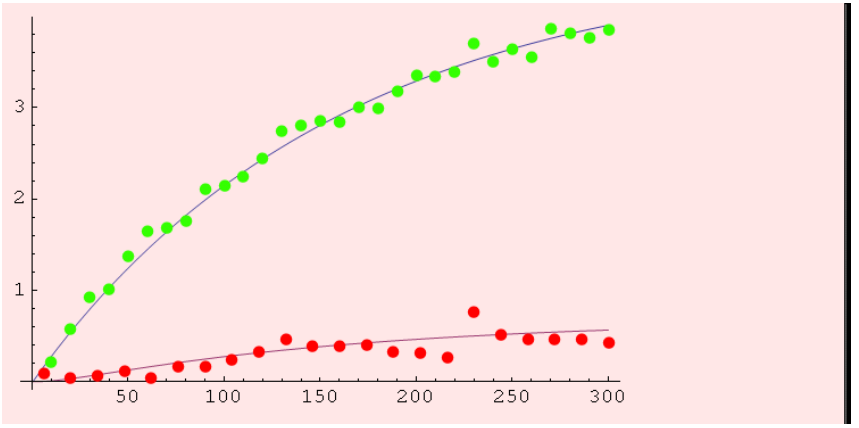
Futures Development: multiresponse models

Suppose that k_{12} and k_{23} are unknown. We want estimated k_{12} and k_{23} using experimental data of $x_2(t)$ and $x_3(t)$.
The usual way is fitting $x_1 = f_1(t, k_{12}, k_{23})$ and $x_2 = f_2(t, k_{12}, k_{23})$ but the analytical expression can not be obtained.

$$\begin{pmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{x}_3(t) \end{pmatrix} = \begin{pmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} \\ k_{12} & -(k_{20}+k_{21}+k_{23}) & k_{32} \\ k_{13} & k_{23} & -(k_{30}+k_{31}+k_{32}) \end{pmatrix} \cdot \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix}$$



0.508007, k12 → 0.830821, k23 → 0.00855833



Could be applied Optimal Design for this situation (Multiresponse problem where the analytical expression of the functions to be fitted can not be obtained however the underline SODE is known)?