Modelos biocinéticos. Aplicación a la dosimetría interna

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- **Notas:**

  La presentación está elaborada con el programa BIOKMOD. En la ayuda del programa están incluido la mayoria de los ejemplos.

  La mayoria de los ejemplos pueden reproducirse directamente en la web (http://www3.enusa.es/webMathematica/Public/biokmod.html)

Septiembre 2015

Dónde queremos llegar

¿Cómo se modeliza un proceso biocinético/farmacocinético? ¿Cómo se pueden obtener los parámetros del modelo experimentalmente? ¿Cual es el diseño óptimo?

¿Que modelos utiliza la ICRP para modelizar la distribución de compuestos e isótopos en el cuerpo humano?¿Cómo se resuelven?

¿Como se obtienen los factor de conversión a dosis (FCD)? Por ejemplo el FCD por inhalación del ^{234}U es 6.8×10^{-6} Sv/Bq ¿Como se llega a este valor?¿Que suposiciones se están haciendo?

¿Como se puede inferir la dosis a partir de bioensayos (Excreción urinaria, CRC, etc.)?

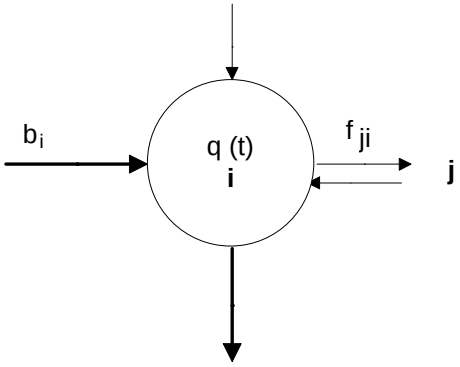
¿Como lo haremos?

Ayudandonos del programa BIOKMOD (requiere *Mathematica* 10) de donde procede el material utilizado y esta disponible el programa para descarga(http://diarium.usal.es/guillermo/biokmod/).

La mayoria de los ejemplos pueden reproducirse directamente en la web con BiokmodWeb (http://www3.enusa.es/webMathematica/Public/biokmod.html) no obstante en la presentación en casi todos los casos está hecho con Biokmod.

Modelización compartimental

Sistema físico o biológico que se descompone en un número finito de componentes llamados compartimentos que intercambian materia (partículas o flujo) entre ellos y/o con el exterior



Algunos usos

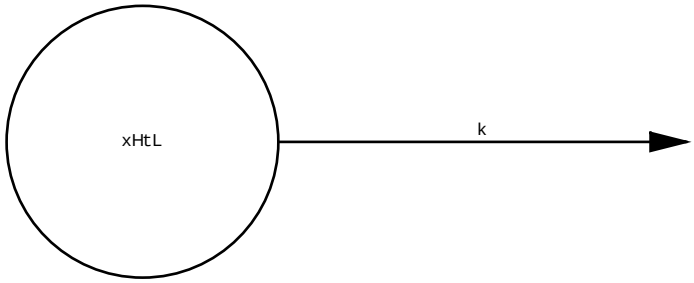
Modelización del metabolismo de la incorporación de partículas inhaladas o ingeridas.

Modelización de la incorporación por ingestión o inyección de compuestos a personas y otros seres vivos en Medicina y en Farmacia.

Transporte de partículas en estudios medioambientales

Ejemplo sencillos

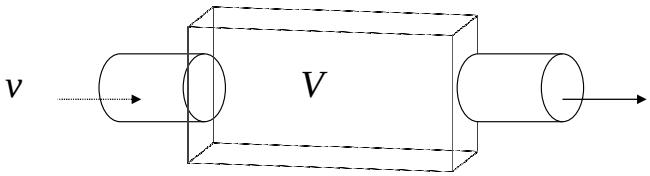
La desintegración radiactiva: A -> B



$$\frac{dx(t)}{dt} = - k\, x(t)$$

Organo aislado

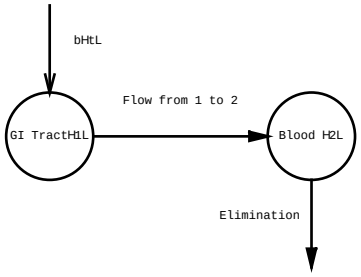
Supongamos un recipiente de volumen V lleno de agua con sal con un concentración q=o en t = o. Hay una entrada agua salada, con caudal v y concentración c, constantes. Se va produciendo instantáneamente una mezcla de concentración q(t) que va saliendo también a un caudal v.



$$q + dq = \frac{\overbrace{V\,q}^{\text{Sal que habia}} + \overbrace{c\,v\,dt}^{\text{Sal que entra}} - \overbrace{q\,v\,dt}^{\text{sal que sale}}}{V} \Rightarrow \frac{dq}{dt} = \frac{v\,(c-q)}{V}$$

Modelo bicompartimental simple

The Figure represents an easy example of a two compartmental system of ingestion and metabolism of a drug. It is supposed that the drug is taken orally flowing to the GI tract (Compartment 1) , then it is absorbed into the blood (Compartment 2) and finally eliminated.



Formulación matematica

Let $x_1(t)$ and $x_2(t)$, where $t \geq 0$, is the mass of the drug in compartment 1 and 2, respectively. Then we can describe the process as follow

$$\frac{dx_1}{dt} = b(t) - \text{drug distribution rate from 1 to 2}$$

$$\frac{dx_2}{dt} = \text{inflow rate (from 1)} - \text{outflow rate (elimination)}$$

The previous equations are commonly called **mass balance equation**. If it is assumed that rate of transference from each compartment *i* is proportional to the mass (or concentration) in this compartment, then

$$\frac{dx_1}{dt} = b(t) - k_{12}\, x_1$$

$$\frac{dx_2}{dt} = k_{12}\, x_1 - k_{20}\, x_2$$

where k_{12} and k_{20} are the constants (>0) of proportionality from 1 to 2 and from 2 to environment (elimination). This process is a simple case of first-order kinetics. Both ordinary differential equations (ODE) with appropriate initial conditions $x_1(0)$ and $x_2(0)$ constitute the compartmental metabolic model. In matrix-vector format the system of ordinary differential equation (SODE) model is

$$\begin{pmatrix} x_1'(t) \\ x_2'(t) \end{pmatrix} = \begin{pmatrix} -k_{12} & 0 \\ k_{12} & k_{20} \end{pmatrix} + \begin{pmatrix} b(t) \\ 0 \end{pmatrix}$$

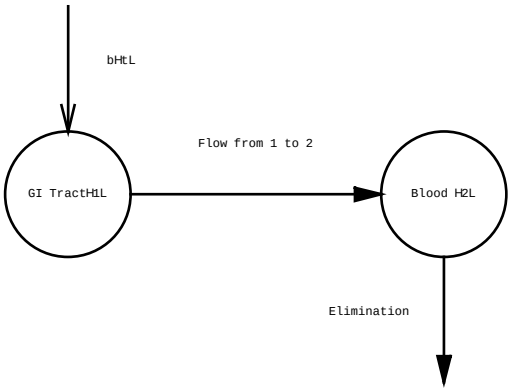
Con Biokmod podemos generar directamente el SEDO y su solución (requiere Mathematica 10). Se requiere cargar el programa

```
Needs["Biokmod`SysModel`"]
```

```
SysModel, version 1.5.1   2013-11-12
```

Tambien pueden resolverse con con BiokmodWeb:
http://www3.enusa.es/webMathematica/Public/biokmod.html

Resuelve con BiokmodWeb el modelo anterior para k12= 0.3, k20 = 0.05 ;b(t) = {0, 0}, con condiciones iniciales {1,0}.



Resolución con BiokmodWeb.

Enter the compartmental matrix.

```
{{1, 2, 0.3}, {2, 0, 0.05}}
```

Number of compartments: 2 Decay constant: 0 Initial conditions at time t = 0: {1,0}

Input function in each compartment : {0, 0}
All values of this field must be {0,.., 0} if it is an impulsive single-input, because the inputs are the initial conditions.

Time t to evaluate the content in each compartment (i.e.: t or {5, 20, 30}) : t

Range of t to be plotted: From t-min 0 to t-max 10

Time t, in days (kij mush be in days), to compute the acumulated disintegrations in each compartment : 50*365

Evaluate

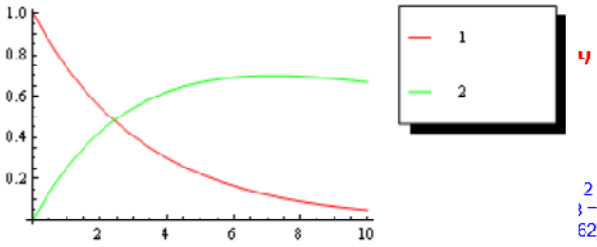
Differential equation

$$(x_1)'(t) = 0.\,x_2(t) - 0.3\,x_1(t)$$
$$(x_2)'(t) = 0.3\,x_1(t) - 0.05\,x_2(t)$$
$$x_1(0) = 1$$
$$x_2(0) = 0$$

Solution

$$x_1(t) \to 1.\,e^{-0.3\,t}$$
$$x_2(t) \to 1.2\,e^{-0.05\,t} - 1.2\,e^{-0.3\,t}$$

Plot



y

2 is the thyroid , compartment
3 − Log[2]/80, k30 − 0.01155 ar
62}, {4, 0, 12}} . Also it assume

Resolución con Biokmod (debe estar cargado Biokmod)

Construimos la matriz compartimental

```
? CompartMatrix
```

CompartMatrix[n,{transcoeff},lambda], gives the
matrix of coefficients,also called constant transfer coefficients matrix.
Where n isthe number of compartments and transcoeff are the transfer coefficients, also
called clearance coeffs. or dissolution rates. They are given as
{{..{i,j,kij},{..},...} where kij is the transfer coeff., in t^{-1},.
from compartment i to compartment j (By default kij = 0); lambda is the
radioactive decay constant, in the same unit as the trans. coef. (by default lambda = 0, which
means thatit is not a radioactive substance.)

CompartMatrix[2, {{1, 2, k12}, {2, 0, k20}}]

```
model1 = CompartMatrix[2, {{1, 2, 0.3}, {2, 0, 0.05}}]
```

```
{{-0.3, 0.}, {0.3, -0.05}}
```

CI = {1,0}; {b1, b2}={0,0}

En muchas ocasiones estamos interesados en el caso que una incorporación única en $t = 0$, esto ecs. $b_1(0) = b_1$ y $b_i(0) = 0$ para $t \neq 0$. Esto es equivalente a tomar como condición inicial = $x_1(0) = b_1$.

```
ShowODE[model1, {1, 0}, {0, 0}, t, x] // TableForm
```

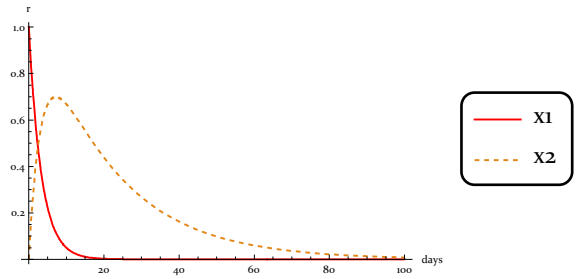
$x_1'[t] == 0. - 0.3\, x_1[t]$
$x_2'[t] == 0.3\, x_1[t] - 0.05\, x_2[t]$
$x_1[0] == 1$
$x_2[0] == 0$

SystemDSolve[modelo, {bo, o}, {o, o}, t, t1, x]

```
{x1[t1_], x2[t1_]} = {x1[t1], x2[t1]} /. SystemDSolve[model1, {1, 0}, {0, 0}, t, t1, x]
```

$\{1.\, e^{-0.3\, t1},\ -1.2\, e^{-0.3\, t1} + 1.2\, e^{-0.05\, t1}\}$

```
Plot[{x1[t], x2[t]}, {t, 0, 100}, PlotRange -> All,
  PlotStyle → {Red, Dashed}, AxesLabel → {"days", "r"},
 PlotLegends → Placed[{"x1", "x2", "x3"}, Right, (Framed[#, RoundingRadius → 5] &)]]
```

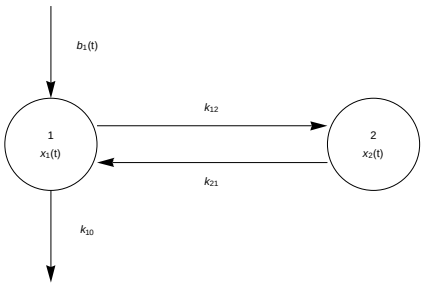


Ejercicio: Interpreta el la gráfica ¿Que sucede si k20 tiene un valor mas alto?

```
Clear[model1, x1, x2]
```

Modelo bicompartimental generalizado

Con entrada y salida al exterior desde el compartimento 1



Formulación matemática

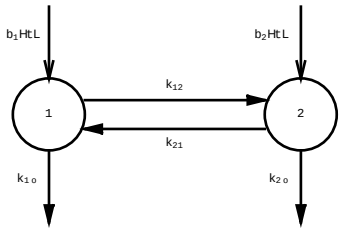
Llamamos $x_1(t)$ y $x_2(t)$ a las variables de estado (concentración, cantidad, etc) y su evolución en el tiempo, entonces el sistemoa podemos describirlo por el sistema de ecuaciones diferenciales siguientes

$\dot{x}_1(t) = -k_{10}\, x_1(t) - k_{12}\, x_1(t) + k_{21}\, x_2(t) + b_1\,(t)$

$\dot{x}_2(t) = \quad k_{12}\, x_1(t) - k_{21}\, x_2(t)$

Con entrada y salida al exterior desde el compartimento 1 y 2

Si en el modelo anterior le añadimos una entrada $b_2\,(t)$ desde el exterior al compartimento 2 y una salida desde 2 (k_{20}) tenemos:



Formulación matemática

$$\frac{dx_1}{dt} = -\overbrace{(k_{12}+k_{10})}^{K_{12}}\, x_1 + k_{21}x_2 + b_1(t)$$

$$\frac{dx_2}{dt} = k_{12}x_1 - \overbrace{(k_{21}+k_{20})}^{K_{21}}\, x_2 + b_2(t)$$

Podemos reformularlo en notación matricial como sigue:

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

$$\mathbf{x}'(t)=\begin{pmatrix} x'_1(t) \\ x'_2(t) \end{pmatrix} \quad \mathbf{A}=\begin{pmatrix} -K_{12} & k_{21} \\ k_{12} & -K_{21} \end{pmatrix} \quad \mathbf{x}(t)=\begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} \quad \mathbf{b}(t)=\begin{pmatrix} b_1(t) \\ b_2(t) \end{pmatrix}$$

Ejemplo: Plantea el modelo general bicompartimental con Biokmod considerando la constante de desintegración λ

Lo primero es construir la matriz compartimental

```
model2 = CompartMatrix[2, {{1, 2, k12}, {2, 1, k21}, {1, 0, k10}, {2, 0, k20}}, λ]
```

```
{{-k10 - k12 - λ, k21}, {k12, -k20 - k21 - λ}}
```

La siguiente función no calcula nada pero permite generar automaticamente el sistema de ecuaciones difrenciales

```
ShowODE[model2, {x1[0], x2[0]}, {b1[t], b2[t]}, t, x] // TableForm
```

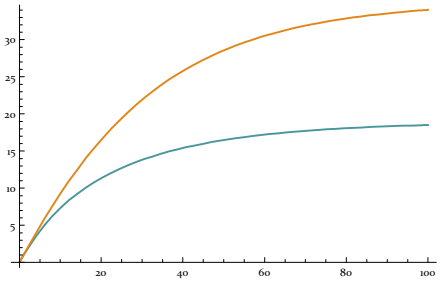
```
x1'[t] == b1[t] + (-k10 - k12 - λ) x1[t] + k21 x2[t]
x2'[t] == b2[t] + k12 x1[t] + (-k20 - k21 - λ) x2[t]
x1[0] == x1[0]
x2[0] == x2[0]
```

Ejemplo: Resuelve el modelo anterior para: k_{10} = 0.05, k_{20} = 0.3, k_{12} = 0.4, k_{21} = 0.3 y λ=0. Supón una incorporación continua constante b1 = 1 y b2 = 1, con condiciones iniciales: $x_1[0]$ = 0, y $x_2[0]$ = 0.

```
modelo = model2 /. {k10 → 0.05, k20 → 0.03, k12 → 0.04, k21 → 0.02 , λ → 0};
entradas = {1, 1};
condicionesiniciales = {0, 0};
{x1[t1_], x2[t1_]} =
 {x1[t1], x2[t1]} /. SystemDSolve[modelo, condicionesiniciales, entradas, t, t1, x]
```

$$\{18.9189 - 4.77824\, e^{-0.104641\, t1} - 14.1407\, e^{-0.035359\, t1},\ 35.1351 + 3.49792\, e^{-0.104641\, t1} - 38.6331\, e^{-0.035359\, t1}\}$$

```
Plot[{x1[t], x2[t]}, {t, 0, 100}]
```



La retención en el compartimento 1 o 2 puede calcularse para cualquier instante t

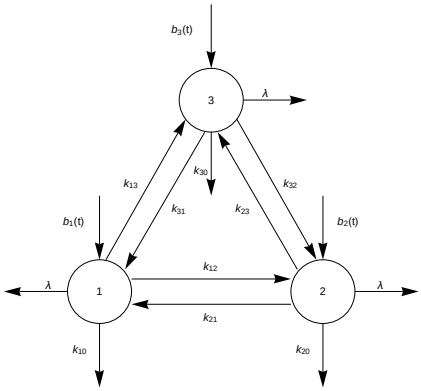
```
{x1[10], x2[10]}
```

```
{7.31176, 9.23689}
```

Las variables definidas si no las vamos a utilizar mas adelante podemos borrarlas:

```
Clear[model2, modelo, entradas, condicionesiniciales, x1, x2];
```

Generalización a n compartimentos



$\dot{\mathbf{x}}(t) = \mathbf{A}\,\mathbf{x} + \mathbf{b}(t),\ t \geq 0$

$\mathbf{x}(0) = \mathbf{x}_0$

donde:

$x(t) = \{x_1(t),\ x_2(t),\ \ldots,\ x_n(t)\}^T$ siendo $x_i(t)$ la cantidad (masa, desintegraciones, concentración, etc) en el compartimento i en función de t.

A es una matriz $n \times n$ conocida como matriz compartimental

(para n = 3) A = $\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix}$;

$a_{11} = -(k_{10} + k_{12} + k_{13} + \lambda)$; $a_{12} = k_{21}$; $a_{13} = k_{31}$;

$a_{21} = k_{12}$; $a_{22} = -(k_{20} + k_{21} + k_{23} + \lambda)$; $a_{23} = k_{32}$;

$a_{31} = k_{13}$; $a_{32} = k_{23}$; $a_{33} = -(k_{30} + k_{31} + k_{32} + \lambda)$;

$\mathbf{b}(t) = \{b_1(t),\ b_2(t),\ \ldots,\ b_n(t)\}^T$ donde $\{b_i(t)\}$ es la entrada hacia el compartimento i desde el exterior del sistema

$\mathbf{x}(0) = \{x_1(0),\ x_2(0),\ \ldots,\ x_n(0)\}^T$ son las condiciones iniciales, esto es $x_i(0)$, representa la cantidad en el compartmento i en $t = 0$.

Solución al modelo n compartimental (coeficientes de trasferencia constantes)

Caso particular : Incoporación puntual

$$\mathbf{x}_u(t) = \mathbf{x}_0\, e^{t\mathbf{A}}$$

Caso general

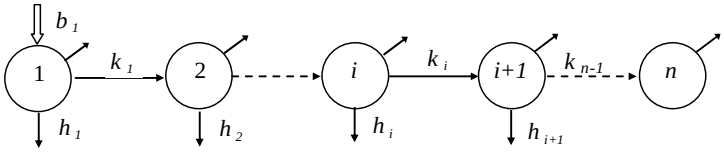
(Teorema de la convolución)

$$\mathbf{x}(t) = \int_0^t \mathbf{x}_u(t-\tau)\,\mathbf{b}(\tau)\,d\tau$$

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

Observese que la solución general parte de la solución puntual

Caso particular: Modelos catenerios

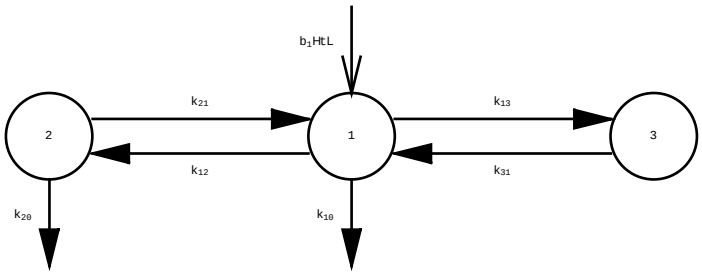


Los sistemas catenarios tienen una solución analítica:

$$q_i(t) = b_1\, e^{-\lambda_k t}\left(\prod_{p=1}^{i-1} k_p\right)\sum_{j=1}^{i}\left(\frac{e^{-K_j t}}{\prod_{\substack{p=1\\ p\neq j}}^{i}(K_p - K_j)}\right) \quad i = 1, 2, \ldots, n$$

Ejemplo a resolver con Biokmod: modelo tricompartimental de inhalación de plomo

El modelo de la figura representa la distribución de plomo en el cuerpo de una persona expuesta a la su inhalación. Consideramos un modelo muy simplificado representado en el diagrama de abajo donde: (1) Sangre, (2) tejidos, (3) huesos.



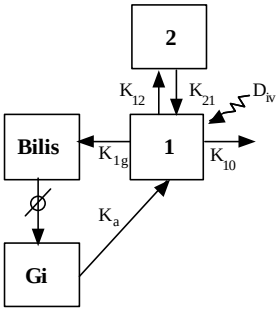
a) Plantea el modelo anterior tomando como condiciones iniciales: $\{x_1(0) = 0,\ x_2(0) = 0,\ x_3(0) = 0\}$. Supón una incorporación constante b1

b) Resuelve el modelo para el caso que una persona inhala una pesona que inhala 49.3 μg/d y que que los valores de k_{ij}, en dias^{-1} son los siguientes:{ k21 = 0.0124;k12 = 0.0111; k13 = 0.0039; k31 = 0.000035; k10= 0.0211; k20 = 0.0162;

c) Interpreta la salida gráfica

```
Clear[b1, k, a, x1, x2, x3, eq1, model3, modelo3];
```

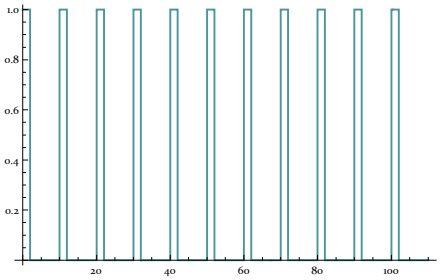
Ejemplo: Coeficientes de transferencia variables



En el modelo de la figura los coef. de trasferencia o microconstante son: $k12 \to 2$, $k21 \to 1$, $k10 \to 0.5$, $k_g \to 0.1$, $k_a \to 2$, $k_{bilis,gi}$ tiene una trasferencia periodica durante 2 horas $k_{bilis,gi} = 1$ seguida de 6 horas sin trasferencia y el ciclo se repite. Resuelve el modelo,

Solución

```
h[t_, a_, d_] := 1 - UnitStep[Mod[t, a + d] - d];
Plot[h[t, 8, 2], {t, 0, 110}, PlotPoints → 1000, PlotRange → All, Exclusions → None]
```



Las constantes de trasferencia son: $\{k12 \to 2,\ k21 \to 1,\ k10 \to 0.5,\ k_g \to 0.1,\ k_a \to 2,\ k_{bilis,gi} \to h[t, 8, 2]\}$

```
matrixhepatic = CompartMatrix[4,
    {{1, 2, k12}, {1, 0, k10}, {2, 1, k21}, {1, 3, kg}, {3, 4, kbilis,gi}, {4, 1, ka}}] /.
  {k12 → 2, k21 → 1, k10 → 0.5, kg → 0.1, ka → 2, kbilis,gi → h[t, 8, 2]};
```

Condiciones iniciales: suponemos un imput x1(0) = 200 en el compartimento 1 en t = 0, y x2=x3=x4=0 en t= 0.

```
ic2 = {200, 0, 0, 0};
ip = {0, 0, 0, 0};
```

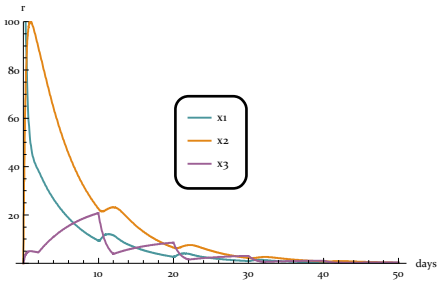
En este caso la solución será numerica por ello tenemos que usar: SystemNDSolve

```
sol2 = SystemNDSolve[matrixhepatic, ic2, ip, {t, 0, 100}, t, x, MaxSteps → 5000];
```

```
{x1[t_], x2[t_], x3[t_], x4[t_]} = {x1[t], x2[t], x3[t], x4[t]} /. sol2
```

```
{InterpolatingFunction[ Domain: {{0., 100.}} Output: scalar ][t],
 InterpolatingFunction[ Domain: {{0., 100.}} Output: scalar ][t],
 InterpolatingFunction[ Domain: {{0., 100.}} Output: scalar ][t],
 InterpolatingFunction[ Domain: {{0., 100.}} Output: scalar ][t]}
```

```
Plot[{x1[t], x2[t], x3[t]}, {t, 0, 50},
 PlotPoints → 1000, PlotRange → {0, 100}, AxesLabel → {"days", "r"},
 PlotLegends → Placed[{"x1", "x2", "x3"}, Center, (Framed[#, RoundingRadius → 5] &)]]
```



Debajo se muestran los valores numericos de { x1[t],x2[t],x3[t],x4[t]}

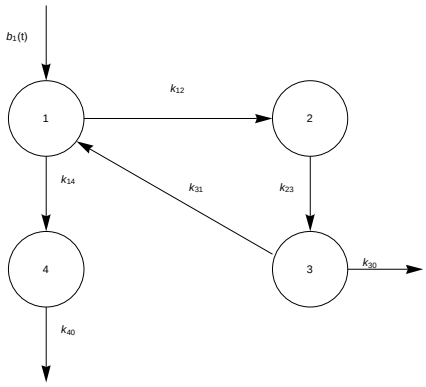
```
Table[{t, x1[t], x2[t], x3[t], x4[t]}, {t, 1, 100, 5}] // TableForm
```

1	48.572	99.9343	4.99672	1.93616
6	18.7684	45.5072	15.3896	0.000765492
11	11.9279	22.0627	8.33475	5.04145
16	5.38796	13.0615	7.00667	0.00095937
21	3.92517	6.71481	3.36405	2.05349
26	1.79818	4.35894	2.55851	0.000382508
31	1.35258	2.27341	1.20531	0.736876
36	0.621503	1.50656	0.900393	0.000136765
41	0.470606	0.788125	0.42263	0.258455
46	0.216373	0.524499	0.314604	0.0000479382
51	0.164059	0.274548	0.147563	0.0902459
56	0.0754393	0.182869	0.109768	0.0000167362
61	0.0572152	0.0957343	0.0514783	0.0314833
66	0.02631	0.0637768	0.0382879	5.83814×10^{-6}
71	0.0199553	0.0333888	0.0179555	0.0109813
76	0.00917634	0.0222439	0.0133544	2.03565×10^{-6}
81	0.00696006	0.0116454	0.00626264	0.00383014
86	0.00320054	0.00775827	0.00465784	7.11903×10^{-7}
91	0.00242756	0.00406169	0.00218433	0.0013359
96	0.0011163	0.00270597	0.00162457	2.48676×10^{-7}

Ejercicio: Modelo del Iodo. ICRP

El modelo

La figura representa el modelo del iodo de la ICRP78 (1: sangre, 2: tiroides, 3: resto del cuerpo). Con k_{ij} en d^{-1}: k_{10}= 1.9404, k_{12}= 0.8316, k_{23} = 0.0086625, k_{30}= 0.01155, k_{31}= 0.0462.



Construye la matriz compartimental suponiendo que es ^{131}I.

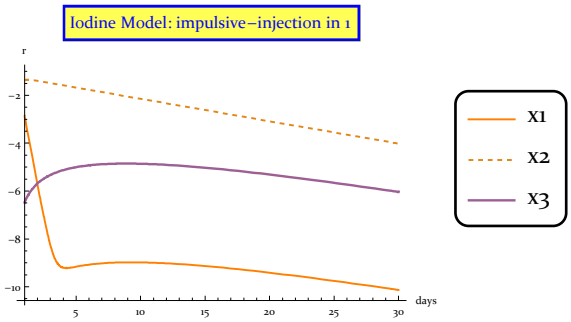
Ejemplo 1.- Resuelve el modelo, considerando los compartimentos 1, 2 y 3, para una inyección puntual de 1 mg en el compartimento 1 en t=0

One specific case is the acute or impulsive-injection input $\mathbf{x}_0$ at t = 0 which is equivalent to making $\mathbf{x}(0) = \mathbf{x}_0$ as initial condition with $\mathbf{b}(t)$ = 0 for $t \geq 0$. In this case is applied the package function `AcuteInput`.

```
{x1[t_], x2[t_], x3[t_]} = Map[Last, AcuteInput[iodine, {1, 0, 0}, t, x]]
```

```
{-1.04434 (0. - 0.957576 ℯ^-2.85833 t) -
   0.0512078 (0. + 0.0164232 ℯ^-0.146508 t) - 0.291417 (0. - 0.00277467 ℯ^-0.092696 t),
 -1.04434 (0. + 0.288178 ℯ^-2.85833 t) - 0.0512078 (0. - 0.26534 ℯ^-0.146508 t) -
   0.291417 (0. - 0.986105 ℯ^-0.092696 t), -1.04434 (0. - 0.000919732 ℯ^-2.85833 t) -
   0.0512078 (0. + 0.964015 ℯ^-0.146508 t) - 0.291417 (0. - 0.166101 ℯ^-0.092696 t)}
```

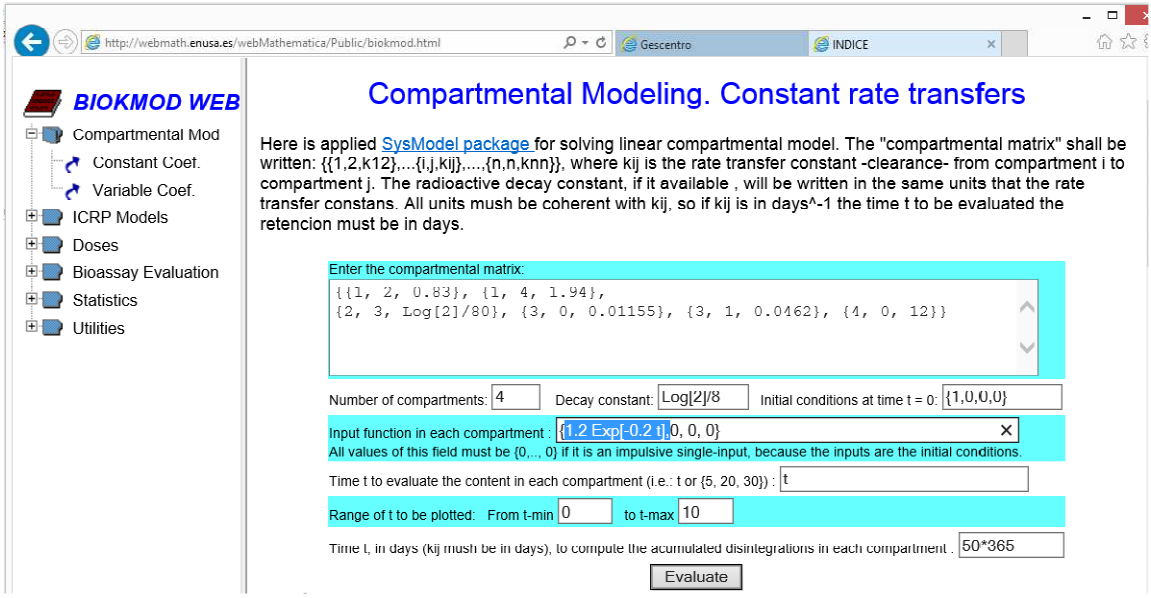
```
LogPlot[{x1[t], x2[t], x3[t]}, {t, 1, 30},
 PlotStyle → {Orange, Dashed, Thick}, AxesLabel → {"days", "r"},
 PlotLegends → Placed[{"x1", "x2", "x3"}, Right, (Framed[#, RoundingRadius → 5] &)],
 PlotLabel → Style[Framed["Iodine Model: impulsive-injection in 1"],
   14, Blue, Background → Lighter[Yellow]]]
```



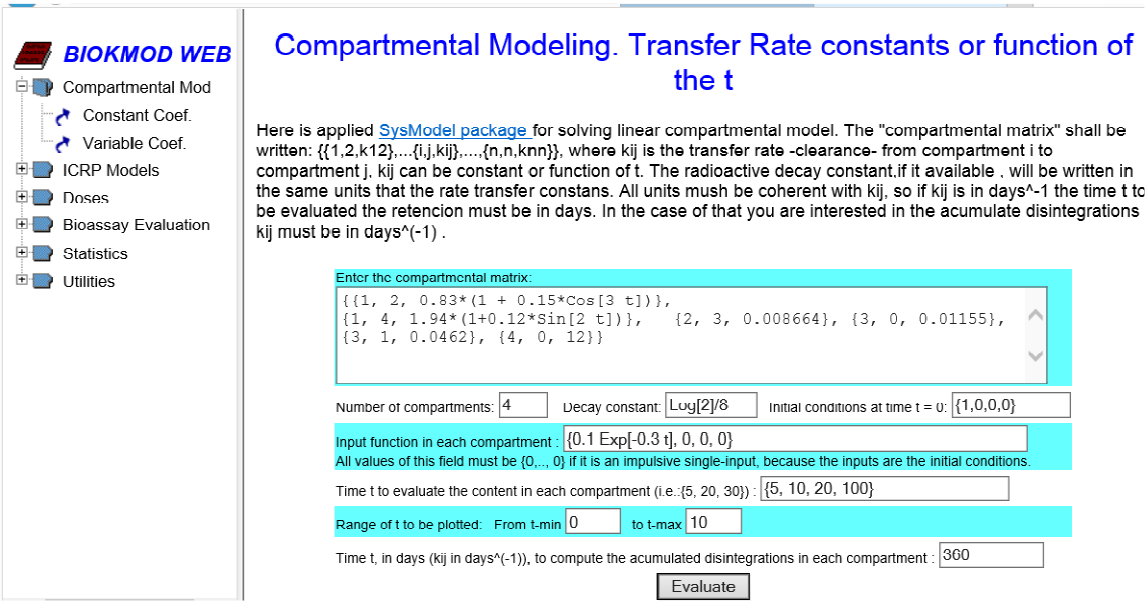

```
Clear[x1, x2, x3]
```

Ejemplo 2.- En el mismo modelo considera $b_1(t) = 1 + \text{Cos}[0.1\ t]$ con condiciones iniciales $x_1(0) = x_2(0) = x_3(0)$

Ejemplo 3.- Resuelve el modelo del iodo 13 para un input continuo: $b_1(t) = 1.2\ \text{Exp}[-0.2\ t]$, con $x_1(0) = 1$, $x_2(0) = x_3(0) = x_4(0) = 0$



Ejemplo 4.- En el ejemplo 2 considera: {k12=0.83*(1 + 0.15*Cos[3 t]) y k14= 1.94*(1+0.12*Sin[2 t])}


BIOKMOD WEB
Compartmental Mod
Constant Coef.
Variable Coef.
ICRP Models
Doses
Bioassay Evaluation
Statistics
Utilities
Compartmental Modeling. Transfer Rate constants or function of the t
Here is applied SysModel package for solving linear compartmental model. The "compartmental matrix" shall be written: {{1,2,k12},...,{i,j,kij},...,{n,n,knn}}, where kij is the transfer rate -clearance- from compartment i to compartment j. kij can be constant or function of t. The radioactive decay constant,if it available , will be written in the same units that the rate transfer constans. All units mush be coherent with kij, so if kij is in days^-1 the time t tc be evaluated the retencion must be in days. In the case of that you are interested in the acumulate disintegrations kij must be in days^(-1) .
Enter the compartmental matrix:
{{1, 2, 0.83*(1 + 0.15*Cos[3 t])},
{1, 4, 1.94*(1+0.12*Sin[2 t])}, {2, 3, 0.008664}, {3, 0, 0.01155},
{3, 1, 0.0462}, {4, 0, 12}}
Number of compartments: 4
Decay constant: Log[2]/8
Initial conditions at time t = 0: {1,0,0,0}
Input function in each compartment : {0.1 Exp[-0.3 t], 0, 0, 0}
All values of this field must be {0,.., 0} if it is an impulsive single-input, because the inputs are the initial conditions.
Time t to evaluate the content in each compartment (i.e.:{5, 20, 30}) : {5, 10, 20, 100}
Range of t to be plotted: From t-min 0 to t-max 10
Time t, in days (kij in days^(-1)), to compute the acumulated disintegrations in each compartment : 360
Evaluate

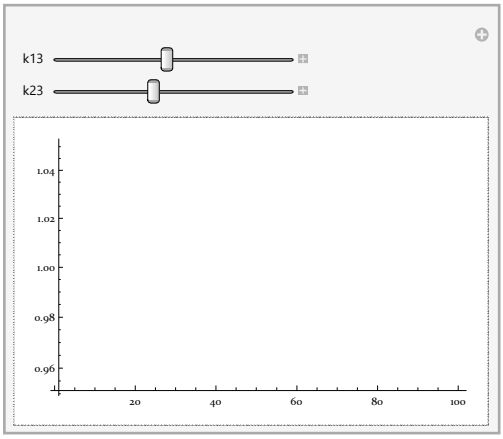
Ejemplo 4.- Modelo interactivo del I131 que muestre la retención en el compartimento 1 en función de los parámetros k12 y k23 con un input: b1(t) =

$$-27.13\, e^{-24.08\, t} + 27.13\, e^{-2.86\, t} - 0.020\, e^{-0.147\, t} + 0.0194\, e^{-0.093\, t}$$

```
Needs["Biokmod`SysModel`"]
iodine131matrix = CompartMatrix[3, {{1, 2, k12}, {1, 0, 1.9404},
    {2, 3, k23}, {3, 0, 0.01155}, {3, 1, 0.0462}}, Log[2] / 8.02];
binput = {-27.13 e^-24.08 t + 27.13 e^-2.86 t - 0.020 e^-0.147 t + 0.0194 e^-0.093 t, 0, 0};
{x1, x2, x3} = {x1, x2, x3} /. ParametricSystemNDSolve[
    iodine131matrix, {0, 0, 0}, binput, {t, 0, 100}, x, {k12, k23}];
```

The retention in blood (compart 1) is plotted as function of parameter k12 and k23.

```
Manipulate[LogPlot[x1[k12, k23][t], {t, 1, 100}],
 {{k12, 0.83, "k13"}, 0.5, 1.2}, {{k23, 0.0086625, "k23"}, 0.001, 0.02}]
```

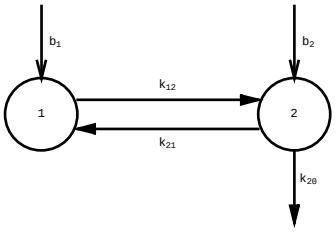


Regresión. Ajuste de modelos

```
Clear["Global`*"]
```

(Solo disponible en Biokmod)

We have the model of the below figure. The rate transfer from compartment 2 to environment is known and its value is k_{20}= 0.05 d^{-1}. The transfer coefficients k_{12} and k_{21} are unknown. The experiment consists of an instantaneous injection b_1= 1 in compartment 1 and b_2= 0.5 in compartment 2 at t = 0 of the model. I



It supposed that in t = 0 the amount of substance in all compartment is "0". The amount in compartment 2 in different times (in days) was measured. Here are the data {t, x} (These data are been obtained by simulation)

```
list1 = {{0, 0.5}, {10, 0.30}, {20, 0.26}, {30, 0.24}, {40, 0.21},
   {50, 0.19}, {60, 0.17}, {70, 0.15}, {80, 0.135}, {90, 0.12}, {100, 0.11}};
```

We intend to estimate the parameters k_{12} and k_{21} by adjusting our model to the experimental data given in list1. We will proceed as follows

Step 1: The compartmental matrix of the model is defined as a function of parameters to be fitted

```
modelTwoCompart = CompartMatrix[2, {{1, 2, k12}, {2, 1, k21}, {2, 0, 0.05}}]
```

```
{{-k12, 0. + k21}, {0. + k12, -0.05 - k21}}
```

Step 2: The model is built by choosing the function of retention in compartment 2. In this case, how is a single-impulsive input, AcuteInput is used.

```
x2[t_, k12_, k21_] = x2[t] /. AcuteInput[modelTwoCompart, {1, 0.5}, t, x];
```

Step 3: Now it is fitted the coefficients k_{12} and k_{21} with the experimental data. Because `x2[t,k12,k21]` is an analytic expression NonlinearRegress can used.

We will need the *Mathematica* package NonlinearFit.

```
nlm = NonlinearModelFit[list1, x2[t, k12, k21], {{k12, 0.01, 0.5}, {k21, 1, 5}}, {t}]
```

```
FittedModel[ -0.230444 (0. + 1. e^(-0.363083 t)) + 0.230444 (0. + 1. e^(-0.0111678 t)) + 0.5 (0.801291 (0. + 1. e^(-0.363083 t)) + 0.198709 (0. + 1. e^(-0.0111678 t))) ]
```

To get the functional form of the `FittedModel` object, use `Normal`:

```
Normal[nlm] // ExpandAll // Chop
```

```
0.170202 e^(-0.363083 t) + 0.329798 e^(-0.0111678 t)
```

The result is returned as a `FittedModel` object, of which properties can be returned:

```
nlm["Properties"]
```

```
{AdjustedRSquared, AIC, AICc, ANOVATable, ANOVATableDegreesOfFreedom,
 ANOVATableEntries, ANOVATableMeanSquares, ANOVATableSumsOfSquares,
 BestFit, BestFitParameters, BIC, CorrelationMatrix, CovarianceMatrix,
 CurvatureConfidenceRegion, Data, EstimatedVariance, FitCurvatureTable,
 FitCurvatureTableEntries, FitResiduals, Function, HatDiagonal,
 MaxIntrinsicCurvature, MaxParameterEffectsCurvature, MeanPredictionBands,
 MeanPredictionConfidenceIntervals, MeanPredictionConfidenceIntervalTable,
 MeanPredictionConfidenceIntervalTableEntries, MeanPredictionErrors,
 ParameterBias, ParameterConfidenceIntervals, ParameterConfidenceIntervalTable,
 ParameterConfidenceIntervalTableEntries, ParameterConfidenceRegion,
 ParameterErrors, ParameterPValues, ParameterTable, ParameterTableEntries,
 ParameterTStatistics, PredictedResponse, Properties, Response,
 RSquared, SingleDeletionVariances, SinglePredictionBands,
 SinglePredictionConfidenceIntervals, SinglePredictionConfidenceIntervalTable,
 SinglePredictionConfidenceIntervalTableEntries,
 SinglePredictionErrors, StandardizedResiduals, StudentizedResiduals}
```

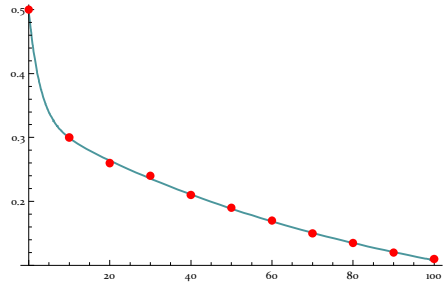
```
nlm[{"ParameterTable", "ANOVATable"}]
```

	Estimate	Standard Error	t- Statistic	P- Value
k12	0.0810965	0.0122266	6.63282	0.0000956024
k21	0.243154	0.0422704	5.75235	0.000275479

	DF	SS	MS
Model	2	0.641483	0.320741
Error	9	0.0000420101	4.66779×10^{-6}
Uncorrected Total	11	0.641525	
Corrected Total	10	0.124414	

Here the fitted function and the experimental data are shown:

```
Plot[x2[t, 0.081, 0.2431], {t, 0, 100},
 Epilog → {Hue[0], PointSize[0.02], Map[Point, list1]}]
```




```
Clear["Global`*"]
```

Se pueden consultar mas ejemplos, incluido modelos multirespuesta en la ayuda de BIOKMOD

Modelos ICRP

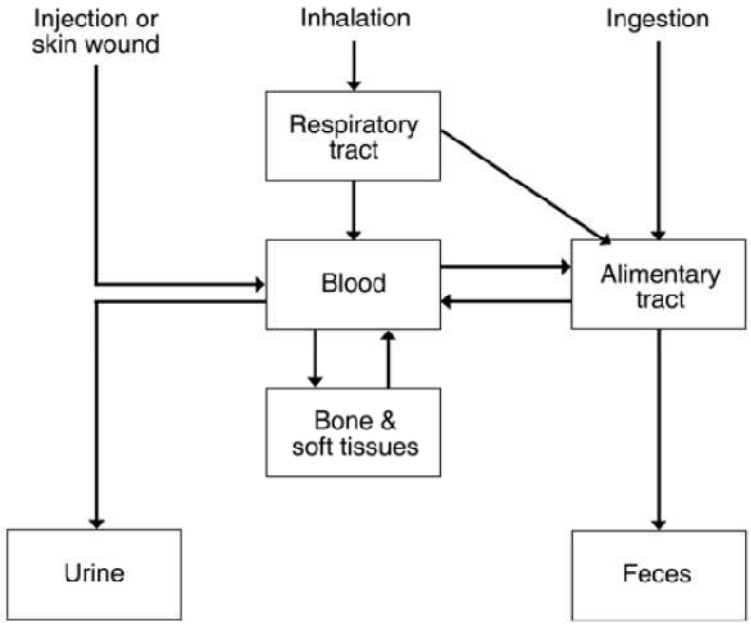
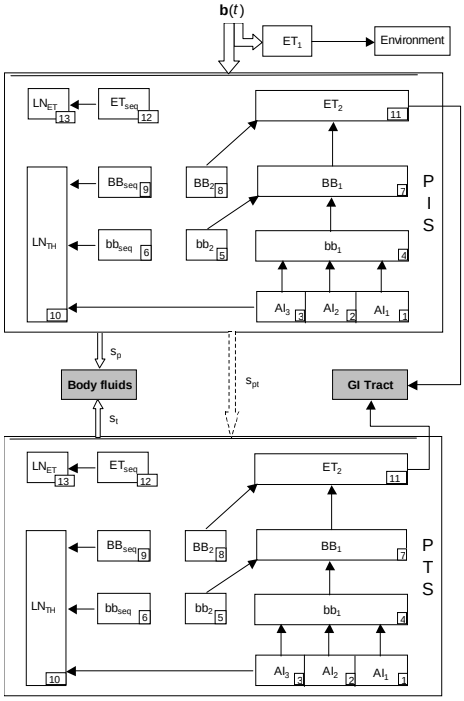


Fig. 3.1. Illustration of the movement of radionuclides in the human body.

Modelo ICRP 66 del tracto respiratorio



Condiciones físicas: Isótopo y AMAD, modelo de incorporación (puntual, constante, etc)

Condiciones químicas: Solubilidad/tipo de metabolización

Default absorption parameters	s	**F**	**M**	**S**
Initial disolution rate $\left(d^{-1}\right)$	s_p	100	10	0.1
Transformation rate $\left(d^{-1}\right)$	s_{pt}	0	90	100
Transformation rate $\left(d^{-1}\right)$	s_t	0	0.005	0.0001

Modelo ICRP 66 interactivo

```
Clear["Global`*"]
```

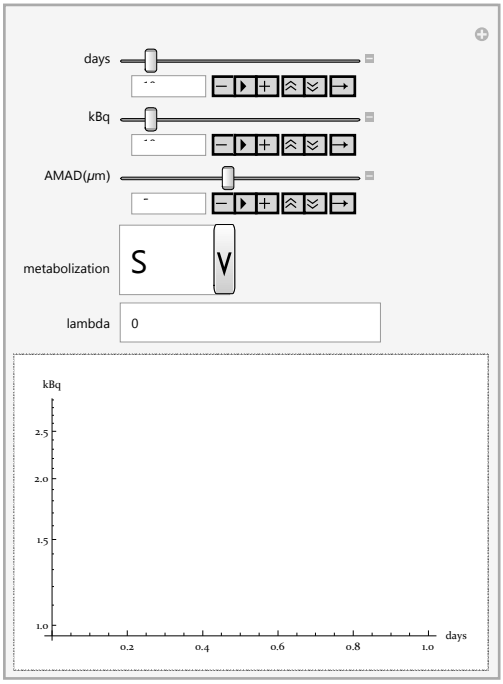
Pueden resolverse con BiokmodWeb:

http://www3.enusa.es/webMathematica/Public/biokmod.html ->ICRP Models ->Lung

o pueden resolverse que Biokmod (esta en la ayuda eligiendo ICRP 66)

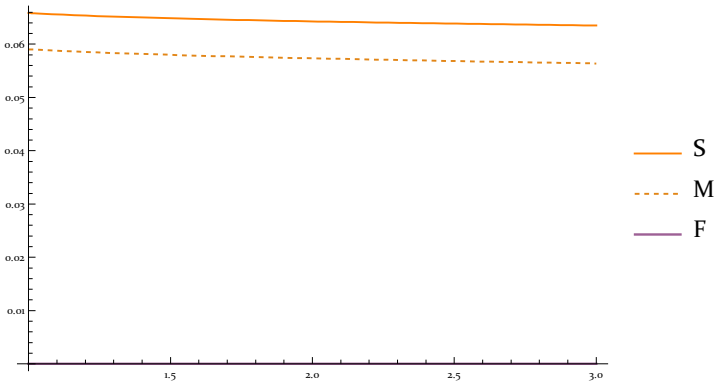
```
Needs["Biokmod`Resptract`"] // Quiet
```

```
Resptract 1.2  2005-05-16
```



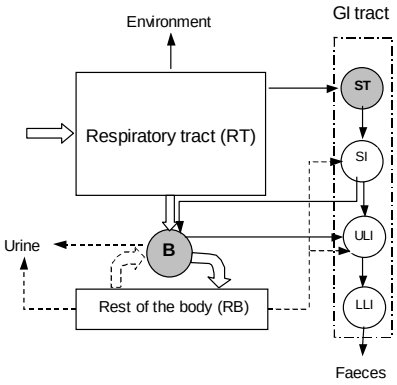
(La constante de desintegración para cada isótopo puede obtenerse como se ha visto antes, si es muy pequeña puede tomarse "o" como ocurre con los isótopos U238, U235, U234)

Debajo se comparan la retención pulmonar para las diferentes solubilidades (la retención pulmonar para tipo F es casi nula):



Modelo ICRP 78.- Bioensayos

Uno de las aplicaciones de la modelización compartimental es la modelización de bioensayos (por ej: excreción urinaria, fecal o retención pulmonar o en todo el cuerpo). Se trata de estimar la cantidad incorporada a partir del bioensayo U(En la grafica se representa el modelo GI de la ICRP 30, sustituido por la ICRP Publication 100, en la practica se sigue utilizando la ICRP30).



B y RB representa conceptualmente el modelo especifico de cada elemento.

Los modelos de la ICRP 78 están incluidos en:

http://www3.enusa.es/webMathematica/Public/biokmod.html ->ICRP Models ->General

o pueden resolverver que Biokmod

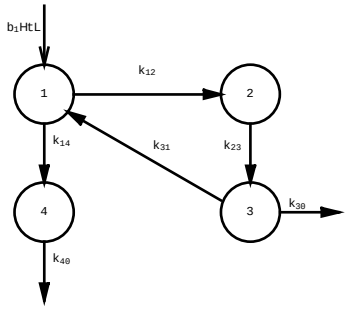
```
Needs["Biokmod`Biokdata`"]
```

```
Humorap 3.7 2015-06-15
```

iodine::shdw : Symbol iodine appears in multiple contexts {Biokmod`Biokdata`, Global`}; definitions in context Biokmod`Biokdata` may shadow or be shadowed by other definitions. ≫

```
Biokdata 1.2.2 2004-09-3
```

Ejemplo: Modelo del iodo incluyendo el TGI (B es el compartimento 1)



The halt-life of the blood is 0.25 days, the uptake to thyroid is 30% and to the bladder is 70%, the halt-life of Thyroid is 80 days, and the halt-life of "Rest of Body" is 12 days to 20 % faecal excretion and 80% to blood, therefore the rate transfer are, in d^{-1}: Blood (Log[2]/0.25), compartment 1, Thyroid (Log[2]/80), compartment 2 and Rest of body (Log[2]/12, compartment 4. As usual, the rate transfers from bladder is 12 d^{-1}, also it mush be added URI (compartment 5), ULI(compartment 6), LLI (Compartment 7) and FEC (compartment 8) .

Con la inforamación anterior se construye la matriz de trasferencia:

```
TableForm[TransferRates[iodine],
 TableHeadings → {None, {"From", "to", "Tranfer Rates(days^-1)"}}]
```

From	to	Tranfer Rates$(days^{-1})$
1	2	0.831777
1	4	1.94081
2	3	$\frac{\text{Log}[2]}{80}$
3	6	0.0115525
3	1	0.0462098
4	5	12
6	7	k_{ULI}
7	8	k_{LLI}

```
iodineMatrix = CompartMatrix[8, {{1, 2, 0.83}, {1, 4, 1.94}, {2, 3, Log[2]/80},
    {3, 6, 0.01155}, {3, 1, 0.0462}, {4, 5, 12}, {6, 7, kULI}, {7, 8, kLLI}}];
```

En el caso de una incorporación puntual de iodio 131 la función de retención es (para el iodo f1 = 1, y para I131 T1/2 = 8.02 d),

```
BioassayReport[iodineMatrix, 1, t1, Log[2] / 8.02,
  IntakeWay → "Injection", IntakeType → "Acute"] // TableForm
```

$$qDailyUrine[t1] \to -34\,208.3\, e^{-12.0864\, t1} + 13.6205\, e^{-2.85638\, t1} - 0.00168984\, e^{-0.146559\, t1} + 0.00157422$$
$$qDailyFaecal[t1] \to 0.0000627959\, e^{-2.85638\, t1} - 0.000173203\, e^{-1.88643\, t1} + 0.000194267\, e^{-1.08643\, t1} - 0$$
$$qWholebody[t1] \to -0.210184\, e^{-12.0864\, t1} + 0.910589\, e^{-2.85638\, t1} - 0.0000343\, e^{-1.88643\, t1} + 0.000113059$$

Todos los pasos anteriores podemos obvierlos y usar directamente (las pequeñas diferencias son debidas a que se emplean mas decimales en los coef. de trasferencia):

```
BiokdataReport[iodine, "Injection", "Acute", "Automatic", 1, 1, t1,
  Log[2] / 8.02, CompartNumbers → "True", TransferRates → "True"] // Chop
```

$$\{qDailyUrine[t1] \to -34\,232.2\, e^{-12.0864\, t1} + 13.6549\, e^{-2.85897\, t1} - 0.00169077\, e^{-0.146574\, t1} + 0.00157512\, e^{-0.0927512\, t1},$$
$$qDailyFaecal[t1] \to 0.0000626808\, e^{-2.85897\, t1} - 0.00017315\, e^{-1.88643\, t1} + 0.000194443\, e^{-1.08643\, t1} - 0.000647024\, e^{-0.146574\, t1} + 0.000566524\, e^{-0.0927512\, t1},$$
$$qWholebody[t1] \to -0.210331\, e^{-12.0864\, t1} + 0.910375\, e^{-2.85897\, t1} - 0.0000342894\, e^{-1.88643\, t1} + 0.000113161\, e^{-1.08643\, t1} - 0.0377108\, e^{-0.146574\, t1} + 0.337588\, e^{-0.0927512\, t1}\},$$

$\{$Compart numbers $\to$

1	Blood
2	Thyroid
3	Rest
4	Bladder
5	Urine
6	ULI
7	LLI
8	FEC

$\}$,

$\{$Transfer Rates $\to$

From	to	Tranfer Rates$(days^{-1})$
1	2	0.831777
1	4	1.94081
2	3	$\frac{\text{Log}[2]}{80}$
3	6	0.0115525
3	1	0.0462098
4	5	12
6	7	k_{ULI}
7	8	k_{LLI}

$\}\}$

Incorporaciones irregulares y aleatorias

```
SeedRandom[]
```

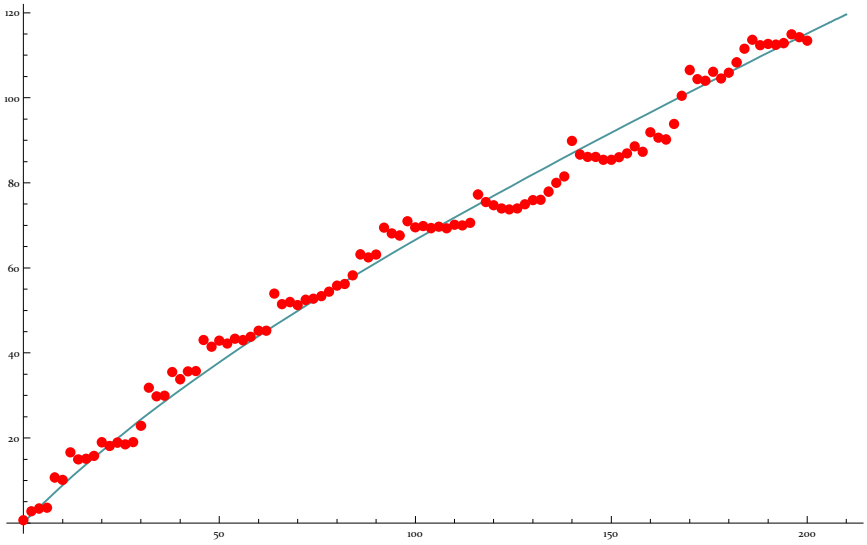
En la práctica los trabajadores están expuestos a una incorporación continuada de caracter aleatorio.

http://www3.enusa.es/webMathematica/Public/biokmod.html ->ICRP Models ->Random intake

Aun en estos casos en periodos largos bajo determinadas condiciones la retención se aproxima a una incorporación crónica (constante). En el ejemplo se supone una incorporación aletoria durante 100 dias: $\{d, \text{intake}_d\}$. Suponemos que la incorporación es lognormal (mean 3 Bq, sigma = 1 Bq). La función Log Normal presenta una gran variabilidad. Esta elección no es por capricho, varios estudios realizados por el autor y publicados en HP así lo demuestran.

Codigo

Se compara la retención pulmonar asumiendo una incorporación constante de aerosoles de UO2 (utilizando la media de las incorporaciones reales) vs incorporaciones reales (aleatorias con gran variabilidad). Se observa que la retención pulmonar apenas se desvia de la incorporación constant



Bioensayos. Estimación de la cantidad incorporada a partir de un bioensayo

Idealmente a partir de un bioensayo podemos estimar la cantidad incorporada: Supuesto el modelo estándar y el resultado de una muestra, m tomada ti tras una incorporación puntual (sin incertidumbre estadística) podemos determinar la cantidad incorporada

$$\mathbf{q(t) = I\ r(t),\ con\ q(ti) = m \text{-> } I = m/r(ti)}$$

Ejemplo: A un paciente se le ha penetrado a través de una herida (modelo inyección) una cantidad desconocida de iodo 131. 5 dias despues se mide 5.4 kBq en una muestra urinaria de 24 horas ¿Que cantidad incorporó?

```
BiokdataReport[iodine, "Injection",
  "Acute", "Automatic", 1, 1, t1, Log[2] / 8.02] // Chop
```

```
{qDailyUrine[t1] →
  -34232.2 ℯ^(-12.0864 t1) + 13.6549 ℯ^(-2.85897 t1) - 0.00169077 ℯ^(-0.146574 t1) + 0.00157512 ℯ^(-0.0927512 t1),
 qDailyFaecal[t1] → 0.0000626808 ℯ^(-2.85897 t1) - 0.00017315 ℯ^(-1.88643 t1) +
   0.000194443 ℯ^(-1.08643 t1) - 0.000647024 ℯ^(-0.146574 t1) + 0.000566524 ℯ^(-0.0927512 t1),
 qWholebody[t1] → -0.210331 ℯ^(-12.0864 t1) + 0.910375 ℯ^(-2.85897 t1) - 0.0000342894 ℯ^(-1.88643 t1) +
   0.000113161 ℯ^(-1.08643 t1) - 0.0377108 ℯ^(-0.146574 t1) + 0.337588 ℯ^(-0.0927512 t1)}
```

De la salida anterior copiamos lo correspondiente a la excrección urinaria y calculamos I

```
r[t_] = 34208 ℯ^(-12.0866 t) + 13.620 ℯ^(-2.85656 t) - 0.00168983 ℯ^(-0.14677 t) + 0.001574 ℯ^(-0.09297 t);
5.4 / r[5] "kBq"
```

```
29008.3 kBq
```

Evaluación de bioensayos 1.- Se tienen los resultados de un tipo de bioensayo. Se quiere determinar la incorporación, se asumen valores estandares de la ICRP

Evaluación ensayos con BIOKMODWEB

http://www3.enusa.es/webMathematica/Public/biokmod.html ->Bioassay Evaluation

Biokmod: requiere el el paquete

```
Needs["Biokmod`Biokdata`"]
Needs["Biokmod`Fitmodel`"]
FitModel 1.3b3 2015-07-02
```

The bioassay measurements can be used to estimate the intake and, then, infer the internal dose. The features included in BIOKMOD can be used to evaluate and minimize the uncertainties.

If all parameters (AMAD, absorption parameters, etc.) of the model, except the quantities intakes, are assumed to be known, the only uncertainties will be the ones of the measurements, and then we have a linear statistical model. Eqns are applied to estimate I and its associated uncertainty.

$$I = \frac{\sum_{i=1}^{N} r_{C,j}(t_i)\,\frac{m_i}{u_i^2}}{\sum_{i=1}^{N} \frac{r_{C,j}^2(t_i)}{u_i^2}}$$

$$u_I = \frac{1}{\sum_{i=1}^{N} \frac{r_{C,j}^2(t_i)}{u_i^2}}$$

where

t_i is the time from the start of the intake to the measurement i.
m_i and u_i are the measurement and their associated uncertainties (calculated with the same confidence level that u_I).
$r_{C,j}(t)$, with C = {A (acute) or Cr (Chronic)} is the retention function, with $I_o = 1$ or $I_d = 1$, associated with measurement m_i.and j is the type of bioassay (note: different kinds of bioassays can be applied simultaneously)

Other authors recommend the maximum likelihood method which uses the following eqn

$$\text{Log}\,(\hat{I}) = \frac{\sum_{i=1}^{N}\left(\text{Log}\left(\frac{m_{i,j}}{r_{C,j}(t_{i,j})}\right)\Big/(\text{Log}(\text{SF}_{i,j})^2)\right)}{\sum_{i=1}^{N}(1/\text{Log}(\text{SF}_{i,j})^2}$$

being SF_i the scattering factor for m_i. If the bioassay data are log normally distributed then SF is the geometric standard deviation (SG) of the log-normal distribution.

This equiation is applied by **`MLFitLog`**

```
? MLFitLog
```

MLFitML[data1, model1, , data2, model2, ...,t]

Ejemplo: Trabajador ha recibido una incorporación puntual de UO2 (no se tienen en cuenta exposiciones previas) y es sometido a medidas con el CRC que da los siguientes valores.{ti, mi, si}

```
sampleLungUnc = {{1, 39, 5}, {10, 36, 5}, {30, 29, 5}, {60, 26, 5},
   {90, 23, 5}, {120, 22, 5}, {180, 20, 5}, {270, 18, 5}, {350, 14, 5}};
MLFitLog[sampleLungUnc, LungsRetention[1, AMADAdultW[5], S, t, 0], t]
```

Mean → 603.899

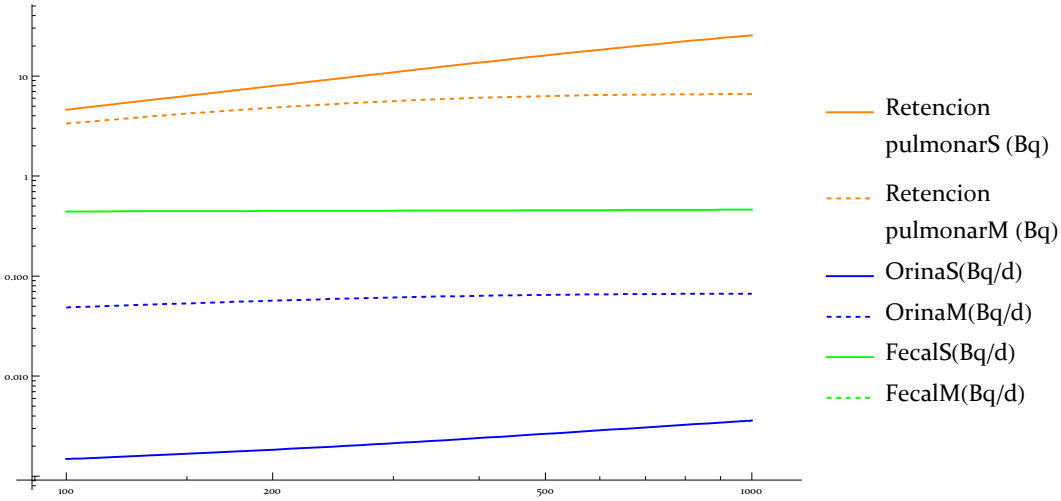
Evaluación de bioensayos 2.- Se tienen los resultados de un tipo de bioensayo. Se quiere determinar la incorporación, se asumen que el tipo de metabolismo de lo inhalado puede ser una mezcla S/M. El programa calcula I y las fracciones S y M.

Bioensayos. Aplicacion al uranio. Tipo S y M

Debajo se comparan tres tipos de bioensayos para el caso de una incorporación constante de aeroles de UO2 AMAD5 metabolismo S y M

```
Needs["Biokmod`Biokdata`"]
```

```
Resptract 1.2  2005-05-16
SysModel, version 1.5.1   2013-11-12
Humorap 3.7 2015-06-15
Biokdata 1.2.2 2004-09-3
```



¿Como interpretas las gráficas?

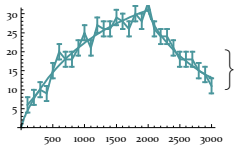
Example (Medida CRC)).- A worker has been exposed to an (unknown) chronic intake of uranium aerosols during 2000 days then ceased the intake, during this time has been exposed to a average daily intake 5 Bq/natural day . With a lung counter have been taken measured m_i with uncertainty u_i: {{t1, m1, u1},....}. We wish to know the accidental quantity intaken assuming that the metebolism beheviour is a mix of type S and M. The function finds

the fraction of S and M that best fit at the bioassay measurements

```
sample1 = {{100, 6, 2}, {200, 8, 2}, {300, 10, 2}, {400, 9, 2}, {500, 15, 2},
   {600, 20, 2}, {700, 18, 2}, {800, 18, 2}, {900, 21, 2}, {1000, 25, 2},
   {1100, 21, 2}, {1200, 27, 2}, {1300, 26, 2}, {1400, 26, 2}, {1500, 29, 2},
   {1600, 28, 2}, {1700, 26, 2}, {1800, 30, 2}, {1900, 28, 2}, {2000, 33, 2},
   {2100, 26, 2}, {2200, 24, 2}, {2300, 24, 2}, {2400, 21, 2}, {2500, 18, 2},
   {2600, 18, 2}, {2700, 18, 2}, {2800, 15, 2}, {2900, 14, 2}, {3000, 11, 2}};
lung = LungBioassayEvaluation[sample1, 0, 2000, 5]
```

{Ji2 → 20.9928, Total intake → 2116.22,

Fraction S → 0.768057, Fraction M → 0.231943,



}

Ejemplo (Medida excreción urinaria).- Un trabajador ha estado profesionalmente expuesto a la inhalación de aerosoles de UO2 de forma ininterrumpida desde 01/06/1982 hasta 14/05/1990. Las medidas de la excreción urinaria diaria han sido {dia desde el inicio, Bq/dia, std}

Calculamos, para uso posterior, el tiempo que ha estado expuesto a una exposición constante

```
timecronic = QuantityMagnitude[DateDifference[{1982, 06, 01}, {1990, 05, 14}]]
```

2904

Las medidas de la excreción urinaria diaria han sido {dia desde el inicio, Bq/dia, std}

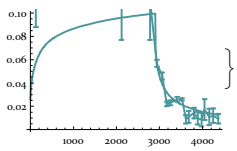
```
sample = {{27, 0.55, 0.16}, {125, 0.125, 0.037},  {2116, 0.11, 0.033},
   {2418, 0.17, 0.053}, {2575, 0.16, 0.048}, {2780, 0.11, 0.033},
   {2939, 0.057, 0.003}, {3061, 0.046, 0.003}, {3170, 0.022, 0.002},
   {3249, 0.023, 0.002}, {3408, 0.026, 0.002}, {3523, 0.026, 0.001} ,
   {3614, 0.00893, 0.0035575}, {3680, 0.011, 0.005}, {3802, 0.01428, 0.00446},
   {3886, 0.00984, 0.0053}, {3977, 0.00856, 0.0058}, {4048, 0.01724, 0.00889},
   {4156, 0.01093, 0.007064}, {4250, 0.01198, 0.0061209}, {4369, 0.0094, 0.00421}};
```

La contidad total incorporada estimada es la siguiente (se asume que la solubildad es mezcla S y M, el programa calcula el mejor ajuste

```
UrineBioassayEvaluation[sample, uranium, 0, 2904, AMAD5, 0.002, 0.02]
```

{Ji2 → 94.1651, Total intake → 24 762.7,

Fraction S → 0.896341, Fraction M → 0.103659,



}

Evaluación de bioensayos 3.- Se tienen los resultados de un tipo de bioensayo. Se quiere determinar la incorporación, algún parámetro (ej:. AMAD) se supone desonocido, se estimará a partir de los resultados del bioensayo

When it is assumed, that not only the intake but also other parameters $\{k_1,\ldots, k_r\}$ are unknown (AMAD, f_1, etc.) then we have a problem of nonlinear fitting. BIOKMOD applies eqn (15) for fitting the bioassay data (It is minimized $\chi 2$):

$$(\hat{I}, k_1, \ldots, k_r) : \text{Arg} \underset{[I,k_1,\ldots,k_r]}{\text{Min}} \left[\sum_{i=1}^{N} \left(\frac{I\, r_{C,i}(t_i, k_1, \ldots, k_r) - m_i}{u_i}\right)^2\right]$$

Restrictions: $I > 0,\ k_{1\,(\min)} \le k_1 \le k_{1\,(\max)},\ \ldots,\ k_{r(\min)} \le k_r \le k_{r(\max)}$

If the bioassay data are log normally distributed then the below eqn is used

$$(\hat{I}, k_1, \ldots, k_r) : \text{Arg} \underset{[I,k_1,\ldots,k_r]}{\text{Min}} \left[\sum_{i=1}^{N} \left(\frac{\text{Log}[I\, r_{C,i}(t_i, k_1, \ldots, k_r)] - \text{Log}[m_i]}{\text{SG}_i}\right)^2\right]$$

Restrictions: $I > 0,\ k_{1\,(\min)} \le k_1 \le k_{1\,(\max)},\ \ldots,\ k_{r(\min)} \le k_r \le k_{r(\max)}$

Example

A worker has been exposed to an (unknown) acute intake of uranium aerosols (class S) by inhalation in $t = 0$. With a lung counter have been taken measured {day after intake, Bq U235, 2 sig}:

{{1,39,5},{10,36,5},{30,29,5},{60,26,5},{90,23,5},{120,22,5},{180,20,5},{270,18,5},{350,14,5}}

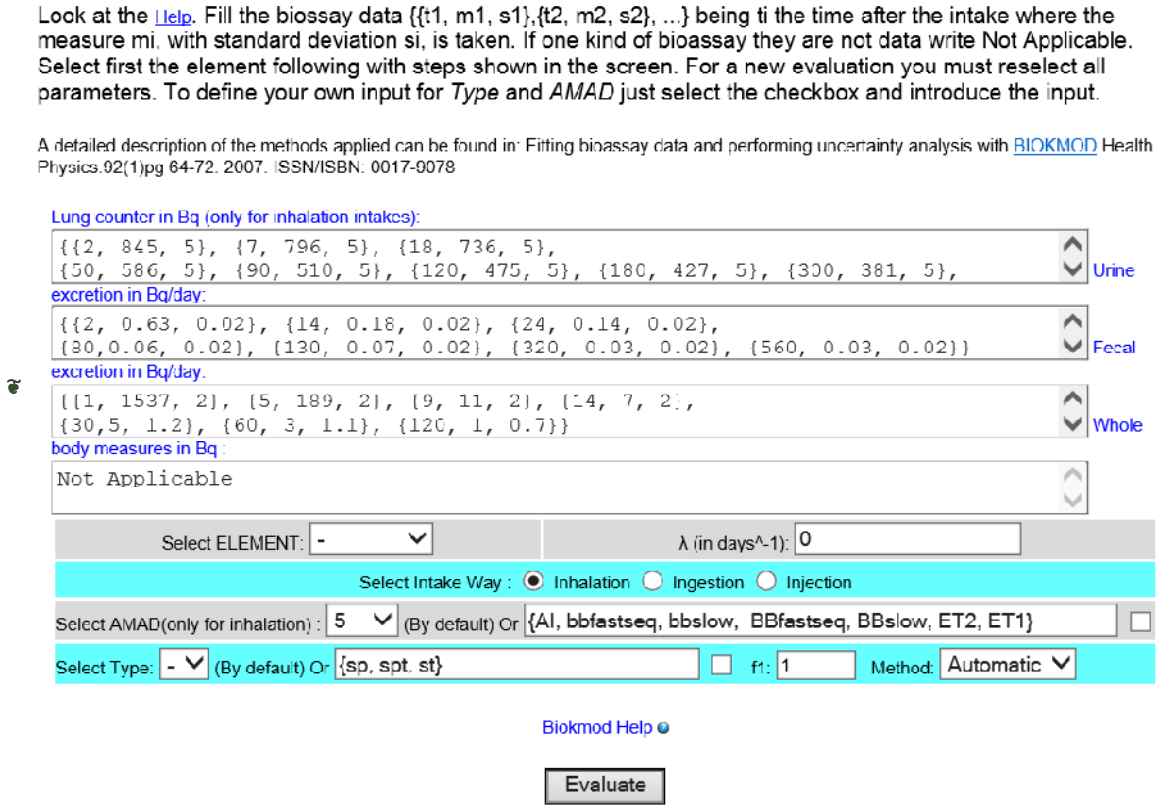
Intake and AMAD?

```
sampleLungUnc = {{1, 39, 5}, {10, 36, 5}, {30, 29, 5}, {60, 26, 5},
   {90, 23, 5}, {120, 22, 5}, {180, 20, 5}, {270, 18, 5}, {350, 14, 5}};
model1[t_, int_, p_] = LungsRetention[int, AMADfit[p], S, t, 0];
FindMinimum[X2FitE[{int, p}, sampleLungUnc, model1[t, int, p], t],
  {int, 500, 1000}, {p, 3, 10}] // Timing
{2.375, {0.334318, {int → 725.608, p → 6.21949}}}
```

Evaluación de bioensayos 4.- Casos en los que se estima un parametro a partir de diversos tipos de bioensayos o determinaciones en varios compartimentos. En *Mathematica* ver ejemplos en la ayuda de Biokmod

Ejemplos:

http://www3.enusa.es/webMathematica/Public/biokmod.html ->ICRP Models ->Random intake



Evaluación de bioensayos 5. Modelos & asunciones indistinguibles

En la evaluación de bioensayos de incorporaciones por inhalación de isotopos con metabolización F lleva a resultados similares con distintos AMAD como se muestra en el ejemplo siguiente (Sánchez G; "Fitting bioassay data and performing uncertainty analysis with BIOKMOD" Health Physics.. 92(1). 2007.)

A researcher has been exposed to a single acute intake of ^{125}I. After the exposure it has been measured the ^{125}I in the thyroid obtaining: {Days after accidental intake, Thyroid activity measured (Bq)} = {{7, 5143},{14, 4773},{15, 4403},{21, 4070}, {28,3471}, {42, 2546}}. (Bioassay data taken from French C. S. et Al, 2003. The data in French C. S are in nCi, they has been converted to Bq). What was the intake?

Sol (asume distintos AMAD y compara la estimación)

Evaluación de bioensayos. Incertidumbres

The estimation of isotope content in a compartment or region involves many uncertainties even assuming that the ICRP metabolic models are a good representation of the real behaviour of the particles intake in the human body. This is so because most of the true values of the parameters at a real situation are unknown. The parameters usually applied are based on the reference values given in ICRPs.
Let's be $r(t)$ expressed as function of certain parameters $\{k_1, \ldots, k_r\}$ with their associated uncertainties: $\{u(k_1), \ldots u(k_r)\}$, then

$r(t) = F(k_1, \ldots, k_n, t) \pm u_C(t)$
being $u_C(t)$ the combined standard uncertainty.
Assuming that $\{k_1, \ldots, k_r\}$ are uncorrelated and taking the first-order Taylor series terms of $F(k_1, \ldots, k_n, \lambda, t)$, then $u_C(t)$ can be evaluated using

$$u_c^2(r(t)) = \sum_{i=1}^{r} \left(\frac{\partial F}{\partial k_i}\right)^2 u^2(k_i)$$

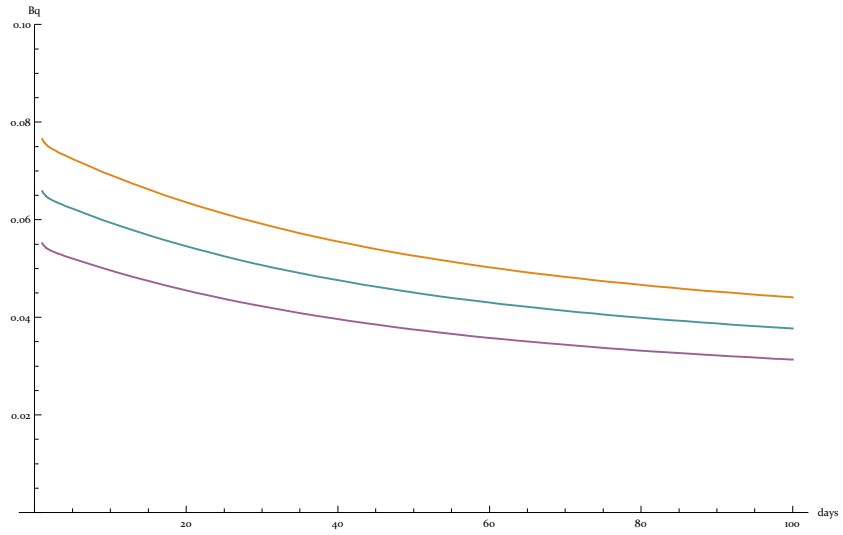
This is the expression used by BIOKMOD.

Lung retention predicted for a single intake of 1 Bq at t = 0, type S, decay constant negligible ($\lambda_R \to 0$) and AMAD p = 5 μm and $u_p = s_p$ = 0.5 μm . The dashed lines represent the confidence interval (95%) associated with the AMAD uncertainties.

```
rLung[p_, t_] = LungsRetention[1, AMADfit[p], S, t, 0] // Chop;
```

The evolution of the content with their associated uncertainties for a coverage factor k = 2 is computed and represented as follow

```
yu[t1_] =
  {"mean", "uL", "lL"} /. Uin[rLung[p, t1], {p}, {σp}, 2] /. {p → 5, σp → 0.5};
```

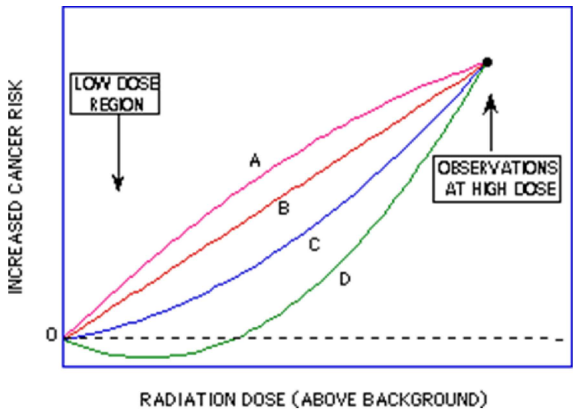


It can be observed that a small difference in the AMAD value has an important consequence in the lung retention predicted. For this reason, when the value for AMAD is

used to evaluate bioassay data and it it is not known then the intake estimated could have important uncertainties.

¿Qué es la dosis? ¿Qué implica la hipotésis lineal?

Las incorporaciones se convierten en dosis ¿pero que es la dosis? ¿Por qué las dosis son aditivas linealmente?.

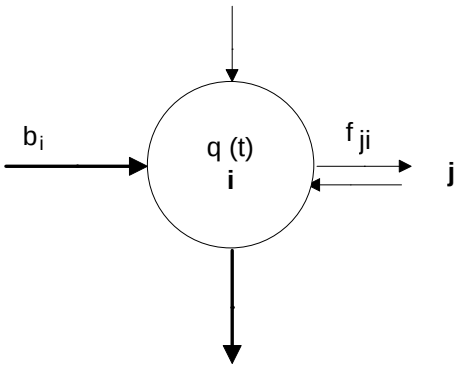


Consecuencia de la hipotesis lineal (para un mismo isotopo y tipo de incorporación): Un incorporación única de 365 Bq produce la misma dosis que si se incopora 1 Bq/dia durante 365 dias.

Dosis interna. Definición de dosis comprometida efectiva

Concepto

The committed equivalent dose $H_T(\tau)$ is defined as the time integral of equivalent dose rate in a particular tissue or organ that will be receive by an individual following intake of radioactive material into the body, where τ is the integration time in years following the intake. Usually is taken τ = 50 y for adult .



$H_T(\tau)$ to organ or target tissue, T, as consequence of disintegration of a radionuclide in a source region, S, is given by (S and T can be the same compartment)

$$H_T(\tau) = \sum_R U_s(\tau)\, \mathrm{SEE}(T \leftarrow S)$$

where:

$U_s(\tau)$ = Número de transformaciones nucleares (Bq s) en τ años (por defecto τ = 50 para adultos) en el órgano o region S seguida a una incorporacion puntual.

$$U_s(\tau) = \int_0^\tau x(t)\, dt$$

x_j (t) es la actividad, en Bq, del nucleido R presente en el compartimento j en el instante t.

SEE(T←S) en Sv/(Bq s), es la energía específica efectiva que se deposita en T como consecuencia por cada desintegración (o trasformación nuclear), siguientes a una incorporación puntual en producida en los j órganos fuente S, donde representa los órganos o tejidos cuyas radiaciones llegan a T, incluida las que se producen en T. Se expresa en Sv/(Bq s).

$$\mathrm{SEE}(T \leftarrow S) = \frac{1.6 \times 10^{-13}}{m_T} \sum_R Y_R\, E_R\, w_R\, \mathrm{AF}(T \leftarrow S)_R$$

Y_R = yield of radiation R per nuclear transformation $(\mathrm{Bq}\ s)^{-1}$
E_R = energy of radiation R (MeV/Transformation)
$1.6 \times 10^{-13}\ \left(\frac{J}{\mathrm{MeV}}\right)$ is used for transform MeV in J
w_R = radiation weighing factor for radiation R (see table 8 of ICRP 68, typical values are: 20 for alpha particles and 1 for photons and electrons)
$\mathrm{AF}(T \leftarrow S)_R$= absorbed fraction in T per transformation in S for radiation R
m_T = mass of target tissue, T (kg).

When a nuclei decay in other nuclei which itself is radioactive, the contribution of the decay product to the dose is evaluated using a similar set of equations for the decay products. It usually is assumed that these decay products adopted the biokinectic of their parents.

Definición (The committed effective dose) (from ICRP 68 and ICRP 2001) :

The committed effective dose over a period τ (50 year for adult) is obtained as the sum of the weighted committed equivalent doses to organs or tissues.

$$e(\tau) = \sum_R H_T(\tau)\, W_T$$

Dosis interna. Calcula las desintegraciones acumuladas (Us) para I-131 en los distintos organos 1, 10 y 100 después de una inyección puntual y los factores de dosis equivalente efectiva.

```
Quit[]
```

Este ejemplo como en otras ocasiones pueden calcularse con BiokmodWeb o con Biokmod

http://www3.enusa.es/webMathematica/Public/biokmod.html ->Doses

```
Needs["Biokmod`Doses`"] // Quiet
```

```
 Doses 1.2   2015-08-27
```

Estudiemos la cadena de desintegracion del iodo 131 (se requiere conexión a internet).

```
IsotopeDecayModes["Iodine131"]
```

```
 BetaDecay
    β⁻
   1.00
970.848 keV
```

```
IsotopeChainPlot["Iodine131"]
```


```
IsotopeChainData["Iodine131"]
```

	Half Life (s)	Daughter Nuclides	BranchingRatios
^{131}I	6.9338×10^{5} s	{ xenon-131 }	{1.00}
^{131}Xe	∞	{}	{}

It can be obtained the accumulated disintegration for different times: 1, 10 and 100 (in days after the acute intake by inhalation happened)

```
Disintegrations["I", "Injection", 1, 1, {1, 10, 100},
  Decayconst["I 131"], DisintegrationReport → "True"] // Chop
```

Compartment	day	10 day	100 day
ST	0		
SI	0		
B	28 486.5	30 293.3	30 475.7
ULI	0.122826	27.8161	97.6904
LLI	0.0423318	39.8548	161.818
Thyroid	16 228.1	158 721.	265 946.
UB_Content	4488.03	4864.2	4893.64
Other	54.1284	4898.09	15 954.1

```
CommittedDose["I 131", "Injection", 1, 1, 50 * 365.25]
```

Accumulted disintegration, in Bq, as function of the time

Compartment	18 262.5 day
ST	0.
SI	0.
B	30 475.8
ULI	97.7169
LLI	161.866
Thyroid	265 971.
UB_Content	4893.65
Other	15 958.2

Dose accumulated, in Sv, as function of the time

Sv/Bq	18 262.5 day
Testes	4.03538×10^{-11}
Ovarius	4.80886×10^{-11}
Red Marrow	1.00785×10^{-10}
Colon	5.69096×10^{-11}
Lungs	1.03046×10^{-10}
St Wall	4.28633×10^{-11}
Bladder Wall	7.65253×10^{-10}
Mama	5.86911×10^{-11}
Liver	4.75816×10^{-11}
Oesophagus	1.53732×10^{-10}
Thyroid	4.35955×10^{-7}
Skin	6.88474×10^{-11}
Bone Surface	1.32242×10^{-10}
Muscle	1.26693×10^{-10}
Brain	1.45286×10^{-10}
Small intestine	4.34103×10^{-11}
Kidneys	4.33654×10^{-11}
Pancreas	4.92598×10^{-11}
Spleen	4.63269×10^{-11}
Thymus	1.53732×10^{-10}
Uterus	5.74355×10^{-11}
Adrenals	4.80134×10^{-11}
Extrathoracic airways	1.48732×10^{-10}
Effective, e(50)	2.19033×10^{-8}

Dosis interna. Compute Us and $e(\tau)$ for U-234

```
Needs["Biokmod`Doses`"] // Quiet
```

```
Doses 1.2   2015-08-27
```

Example. Compute the Us for U-234 by inhalation class S, AMAD 5. para 1.0, 10, 100 days and 50 year after de intake.

```
Disintegrations["U", "Inhalation", 1, AMADAdultW[5], S, 0.002,
 {1.0, 10, 100, 365.25 * 50}, Decayconst["U 234"], DisintegrationReport → "True"]
```

Compartment	1. day	10 day	100 day	18 262.5 day
AI	4575.67	44 457.6	365 595.	4.62183×10^6
bb1	253.681	415.796	1007.99	2323.13
bb2	372.765	3267.59	11 951.7	12 571.4
bbseq	6.63094	63.3892	419.516	659.842
BB1	150.653	193.702	338.463	603.415
BB2	503.454	4413.19	16 142.	16 978.9
BBseq	10.6738	102.037	675.293	1062.15
ET2	359.496	364.994	382.993	409.74
ET1	18 498.2	29 262.3	29 263.6	29 263.6
ETseq	17.206	171.21	1630.22	15 650.1
LNth	0.0912561	8.86631	681.157	444 580.
LNet	0.0086042	0.857331	82.7266	128 776.
ST	1497.44	1520.73	1595.79	1707.25
SI	5946.68	6069.49	6370.18	6815.34
B	4.56307	7.62247	11.8638	51.4604
ULI	14 668.2	20 217.7	21 232.	22 719.6
LLI	9839.19	36 340.	38 209.9	40 895.3
Soft Tissues	9.79703	66.9513	345.6	35 240.5
UB_Content	5.06875	6.55302	10.6588	46.7088
Kydneys	8.31607	80.3483	209.534	1898.84
Liver	1.03657	10.345	38.3212	4289.51
TrabSurface	5.65715	48.3707	136.774	771.04
CorticalSurf	4.52017	38.6488	109.267	613.893
Trab. Vol.	0.159548	17.9245	390.022	29 727.8
Cort. Vol	0.127503	14.3244	312.708	96 706.8

Observa como la desintegraciones acumuladas van aumentando con el tiempo.

Example. Compute the committed effective dose $e(\tau)$ for U234.-

```
CommittedDose["U 234", "Inhalation", 1, AMAD5, S, 0.002, 50 * 365.25]
```

Accumulted disintegration, in Bq, as function of the time

Compartment	18 262.5 day
AI	4.62183×10^{6}
bb1	2323.13
bb2	12 571.4
bbseq	659.842
BB1	603.415
BB2	16 978.9
BBseq	1062.15
ET2	409.74
ET1	29 263.6
ETseq	15 650.1
LNth	444 580.
LNet	128 776.
ST	1707.25
SI	6815.34
B	51.4604
ULI	22 719.6
LLI	40 895.3
Soft Tissues	35 240.5
UB_Content	46.7088
Kydneys	1898.84
Liver	4289.51
TrabSurface	771.04
CorticalSurf	613.893
Trab. Vol.	29 727.8
Cort. Vol	96 706.8

Dose accumulated, in Sv, as function of the time

Sv/Bq	18 262.5 day
Testes	8.92743×10^{-9}
Ovarius	8.92838×10^{-9}
Red Marrow	2.79777×10^{-8}
Colon	2.35625×10^{-8}
Lungs	0.0000411132
St Wall	9.45685×10^{-9}
Bladder Wall	8.9576×10^{-9}
Mama	8.93058×10^{-9}
Liver	3.6994×10^{-8}
Oesophagus	8.92958×10^{-9}
Thyroid	8.9279×10^{-9}
Skin	8.92788×10^{-9}
Bone Surface	2.70324×10^{-7}
Muscle	8.93545×10^{-9}
Brain	8.92756×10^{-9}
Small intestine	1.02435×10^{-8}
Kidneys	9.49537×10^{-8}
Pancreas	8.92871×10^{-9}
Spleen	8.93053×10^{-9}
Thymus	8.92958×10^{-9}
Uterus	8.9275×10^{-9}
Adrenals	8.93057×10^{-9}
Extrathoracic airways	0.0000752694
Effective, e(50)	6.8311×10^{-6}

Dosis interna. Evaluación de dosis con valores no estándares

En el ejercicio anterior: "An worker was exposed from 1982.06-01 to 1990-05-14 to a chronic inhalation of enriched UO2 radioactive aerosols of AMAD 5. Urine samples were taken before and after the exposured ceased. .."Encontramos que la mejor solución correspondia a:

{"Ji2" -> 94.1651, "Total intake" -> 24762.7, "Fraction S" -> 0.896341, "Fraction M" -> 0.103659}

```
DoseEnrichedUranium[24762.7, 4, AMAD5, 0.8963]
```

```
131.943
```

Si suponemos que todo es S

```
DoseEnrichedUranium[24762.7, 4, AMAD5, 1]
```

```
142.502
```

Si suponemos que todo es M

```
DoseEnrichedUranium[24762.7, 4, AMAD5, 0]
```

```
40.6841
```

Mas lejos: Modelos no lineales (Ver ejemplos en la ayuda del programa).

Diseño óptimo de experimentos: (Ver ejemplos en la ayuda del programa y referencias al final)

Material adicional:
http://diarium.usal.es/guillermo

http://diarium.usal.es/guillermo/biokmod/

Mathematica más allá de las matemáticas. 2ª Edición (marzo 2015, actualizado a Mathematica 10). Disponible en GoogleBooks y Playstore

Tutoriales y presentaciones en youtube: http://diarium.usal.es/guillermo/mathematica/

Bibliografia: http://diarium.usal.es/guillermo/publicaciones/especializadas/

Sobre Biokmod, bioensayos y modelización compartimental

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Lopez-Fidalgo J; Sánchez G; Statistical Criteria to Establish Bioassay Programs. Health Physics.. 89 (4). 2005. ISSN/ISBN: 0017-9078

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Sobre diseño óptimo:

Juan M. Rodríguez-Díaz;Guillermo Sánchez-León:"Design optimality for models defined by a system of ordinary differential equations" Biometrical Journal 56 (5), pag 886–900, September 2014

G. Sánchez; 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

Lopez-Fidalgo J Rodri1guez-Díaz J.M.,Sánchez G; G., Santos-Martín M.T. Optimal designs for compartmental models with correlated observations" Journal of Applied Statistic. 32, 2006 ISSN/ISBN: 0266-4763