BIOKMOD 5.4

BIOKMOD is a *Mathematica* toolbox for modeling biokinetic systems with special application for solving ICRP Models and bioassay data evaluation .

Author: Guillermo Sanchez; http://diarium.usal.es/guillermo

Last updated: 2015-11-17

In[1]:= **\$Version**

Out[1]= 10.3.0 for Microsoft Windows (64−bit) (October 9, 2015)

This version of BIOKMOD includes (i) a package to solve system of ordinary linear differential equations (SOLDE) with special application to compartmental and physiological models; (ii) A package for fitting data, it can be applied to fit the transfer rates using experimental data; iii) A specific package for optimal design; iv) Some packages for solving the currents ICRP Models, they have special applications to calculate internal dose and bioassay data evaluations.
Some tutorials are included about: i) Compartmental and physiological modeling (linear and non linear), ii) Random intakes in occupational exposures and their implication in the bioassays, iii) Analytical methods to evaluate the uncertainties associated with the biokinetic model parameters, iv) Non linear regression techniques to the bioassay data fitting, v) Optimal design applied to perform bioassay programs

To run BIOKMOD with all capability it is necessary Mathematica 10 or 9 (most of the functions run also in version 6 , 7 or 8). Some of the most usual features of BIOKMOD can be run directly using a web browser at
http://www3.enusa.es/webMathematica/Public/biokmod.html.

Summary

BIOKMOD has the following features to our knowledge are not included in any other.

a) The user himself can build compartmental models in a very easy way generating automatically the system of differential equations and their solutions

b) It gives analytical and numerical solutions (other codes only give the numerical). Even the solutions can be given as function of some parameters. The accumulated disintegrations in a compartment or region can be computed exactly by analytical

integration, what is more precise than the method of the mean resident time often applied for other codes.

c) Apart from acute, chronic and multi-inputs, it can practically be used for any kind of continuous inputs (exponentials, periodic, etc.), even for random inputs.

d) The intakes can be estimated fitting bioassay data where not only the intake quantities but also other parameters (AMAD, f1, etc.) can be also assumed unknown. For non linear fitting are applied the optimization algorithm included in *Mathematica* and a specific package included in BIOKMOD

e) Analytical expressions instead of simulation can be used for sensitivity and uncertainty analysis.

f) Optimal design tools.

g) The full version included practically all Currents ICRP Models.

The help includes many examples.

To install BIOKMOD:

1. Download the package from http://diarium.usal.es/guillermo/biokmod or http://www3.enusa.es/webMathematica/Public/biokmod.html.

2. Extract the file "biokmodXX.zip" with a zip utility (ex:winzip). It will create a folder called Biokmod. Copy this folder in *Mathematica* directory'AddOns\Applications

3 Open Mathematica then in the toolbar chose Help-> Documentation Center , you find in the botton   "Add-ons and Packages" then click, and you will open a new item called Biokmod where is included the help where the usage of BIOKMOD is described.
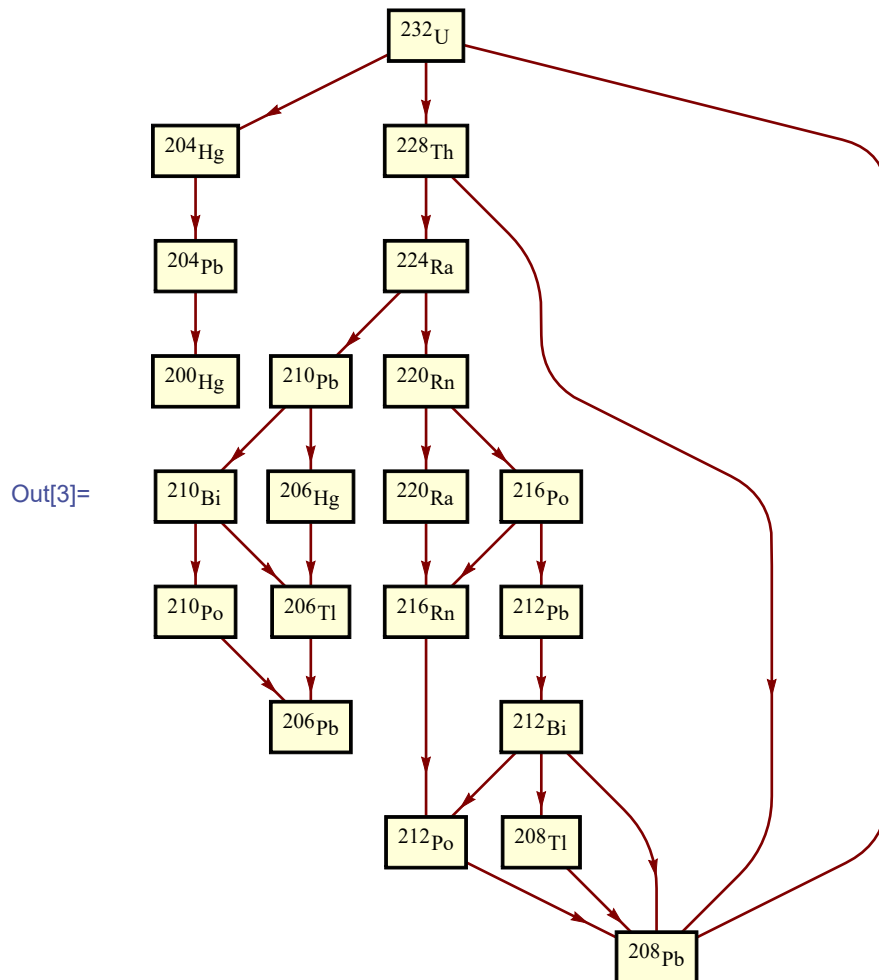

Examples

Example 1: Automatic disintegration chains can be generated (Internet conexion is requiered)

In[2]:= **Needs["Biokmod`SysModel`"]**

   SysModel, version 1.5.1   2013−11−12

Here is represented the disintegration chain for Uranium 232

In[3]:= **IsotopeChainPlot["Uranium232"]**

Out[3]=

Here is shown the disintegration table for Uranium 232

In[4]:= `IsotopeChainData["Uranium232"]`

Out[4]=

|	Half Life (s)	Daughter Nuclides	BranchingRatios
^{232}U	2.17×10^9 s	{thorium−228, lead−208, mercury−204, —}	$\{1.00, 8.9 \times 10^{-12}, 5.0 \times 10^{-14}, 1. \times 10^{-14}\}$
^{228}Th	6.0284×10^7 s	{radium−224, lead−208}	$\{1.00, 1.13 \times 10^{-13}\}$
^{224}Ra	3.1380×10^5 s	{radon−220, lead−210}	$\{1.00, 4.0 \times 10^{-11}\}$
^{220}Rn	55.6 s	{polonium−216, radium−220}	{1.00, —}
^{216}Po	0.145 s	{lead−212, radon−216}	{1.00, —}
^{212}Pb	3.83×10^4 s	{bismuth−212}	{1.00}
^{212}Bi	3633. s	{polonium−212, thallium−208, lead−208}	{0.6405, 0.3594, 0.00014}
^{212}Po	2.99×10^{-7} s	{lead−208}	{1.00}
^{208}Pb	∞	{}	{}

Example 2.- The user can build interactive compartmental models in a very easy way

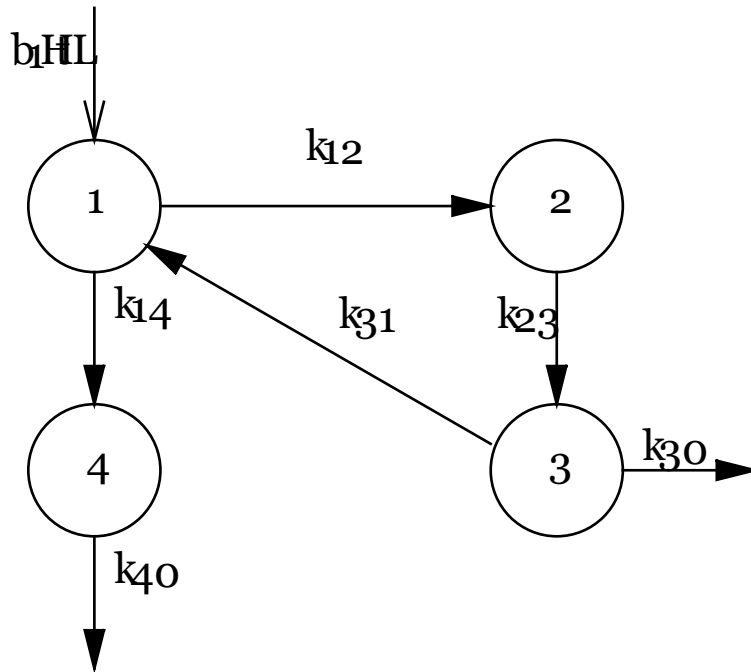In[5]:= `Needs["Biokmod`Humorap3`"]`

Resptract 1.2 2005−05−16

Humorap 3.7 2015−06−15

Here is simulate the evolution in the all body of the Caesium 137 and 134 assuming an acute intake by injection in compatment 1 (Blood) in t=0.

Out[6]=
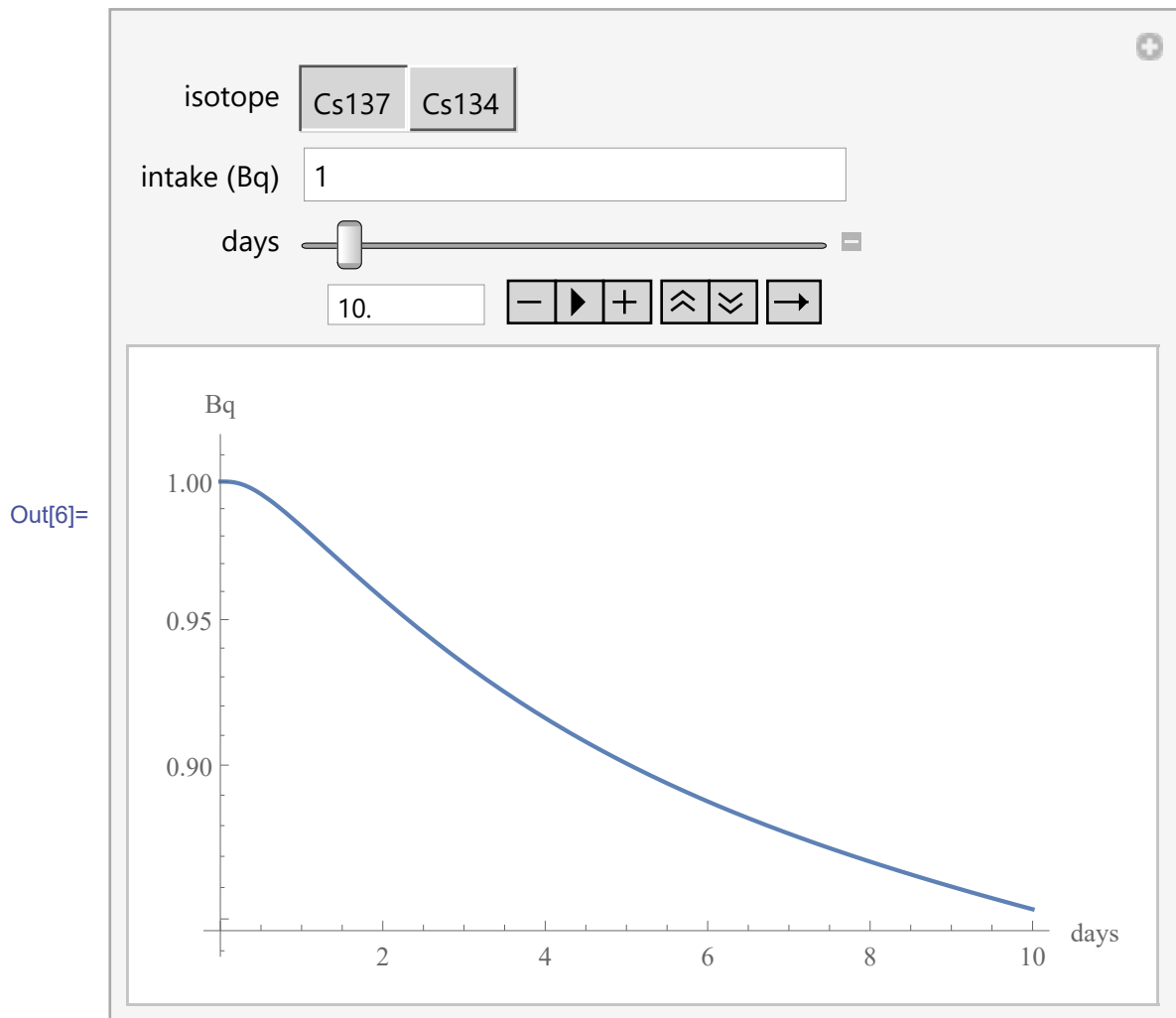
Example 2: Interactive models can be solved as function of some paremeters

The flow diagram represents the iodine model. In this model $k_{24} = k_{10} = 1.9404$ (compartment 4 is not taken into account) $k_{30} = 0.01155$ and $k_{31} = 0.0462$; also is assumed that the input is of Iodine 131 (disintegration constant $= \text{Log}[2]/8.02$ day^{-1}). Then the compartmental matrix of the model is:

```
In[7]:= Needs["Biokmod`SysModel`"]
```

```
In[8]:= 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] ;
```

A input b1=
$27.13\, e^{-24.08\, t} + 27.13\, e^{-2.86\, t} - 0.02\, e^{-0.147\, t} + 0.0194\, e^{-0.093\, t}$ happens in compartment 1, and b=0 in the others

```
In[9]:= 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};
```

In[10]:= `{x1, x2, x3} =`

`{x₁ , x₂, x₃} /. ParametricSystemNDSolve[iodine131matrix,`

`{0, 0, 0}, binput, {t, 0, 100}, x, {k12, k23}]`

Out[10]= { ParametricFunction[➕ [graph] Expression: x_1 / Parameters: {k12, k23}],

ParametricFunction[➕ [graph] Expression: x_2 / Parameters: {k12, k23}],

ParametricFunction[➕ [graph] Expression: x_3 / Parameters: {k12, k23}] }


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

Out[11]=
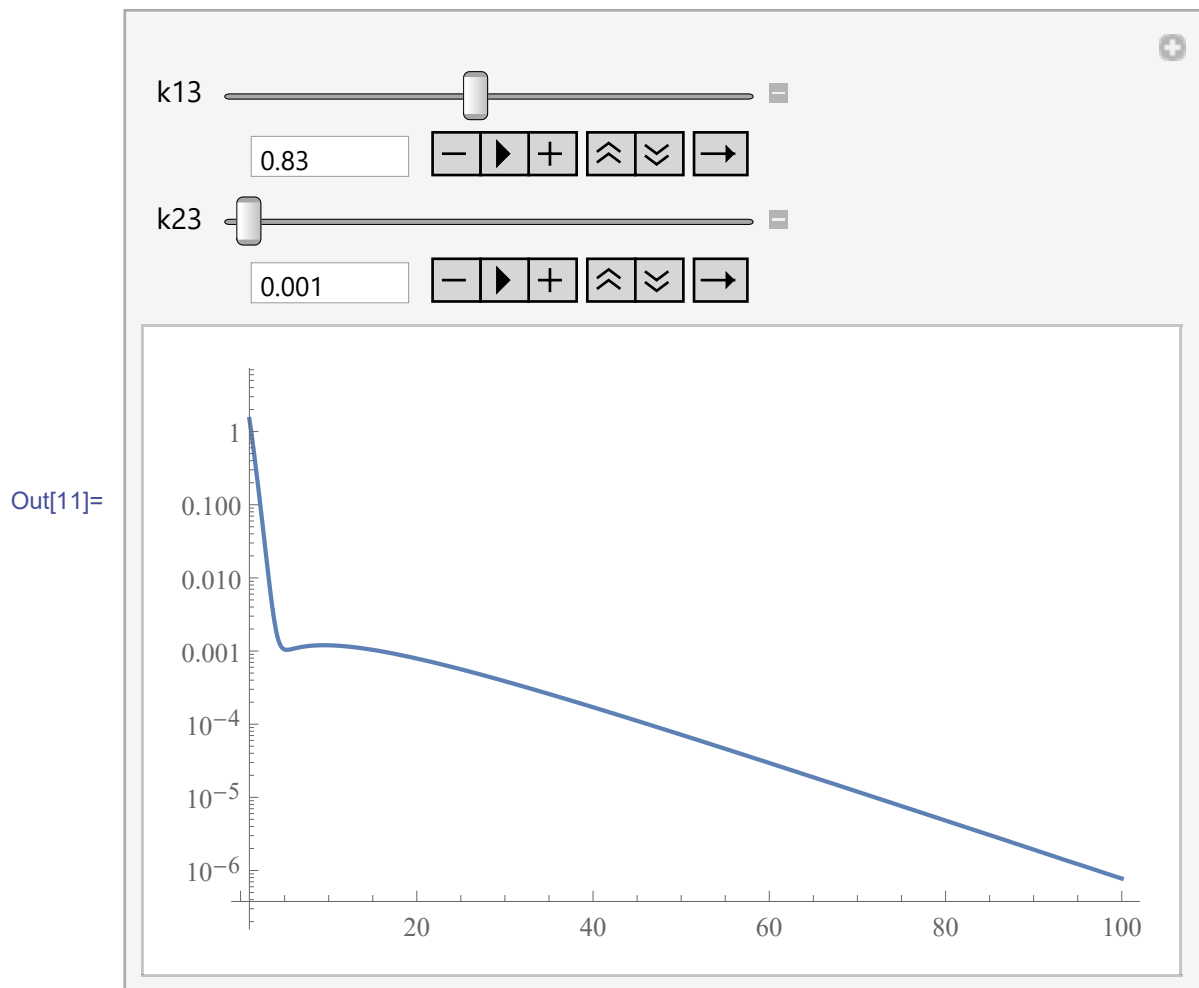
Example 3. The respiratory tract model according to ICRP 66 is included

Here it is plotted the lung retention a time t (in days) after an acute intake as funtion of intake, size of particles intaken (AMAD) and type of metabolization. (Note: Disintegration constan lambda, in days^{-1} by default = 0, but it can be modified by user).

In[12]:= `Needs["Biokmod`Resptract`"]`
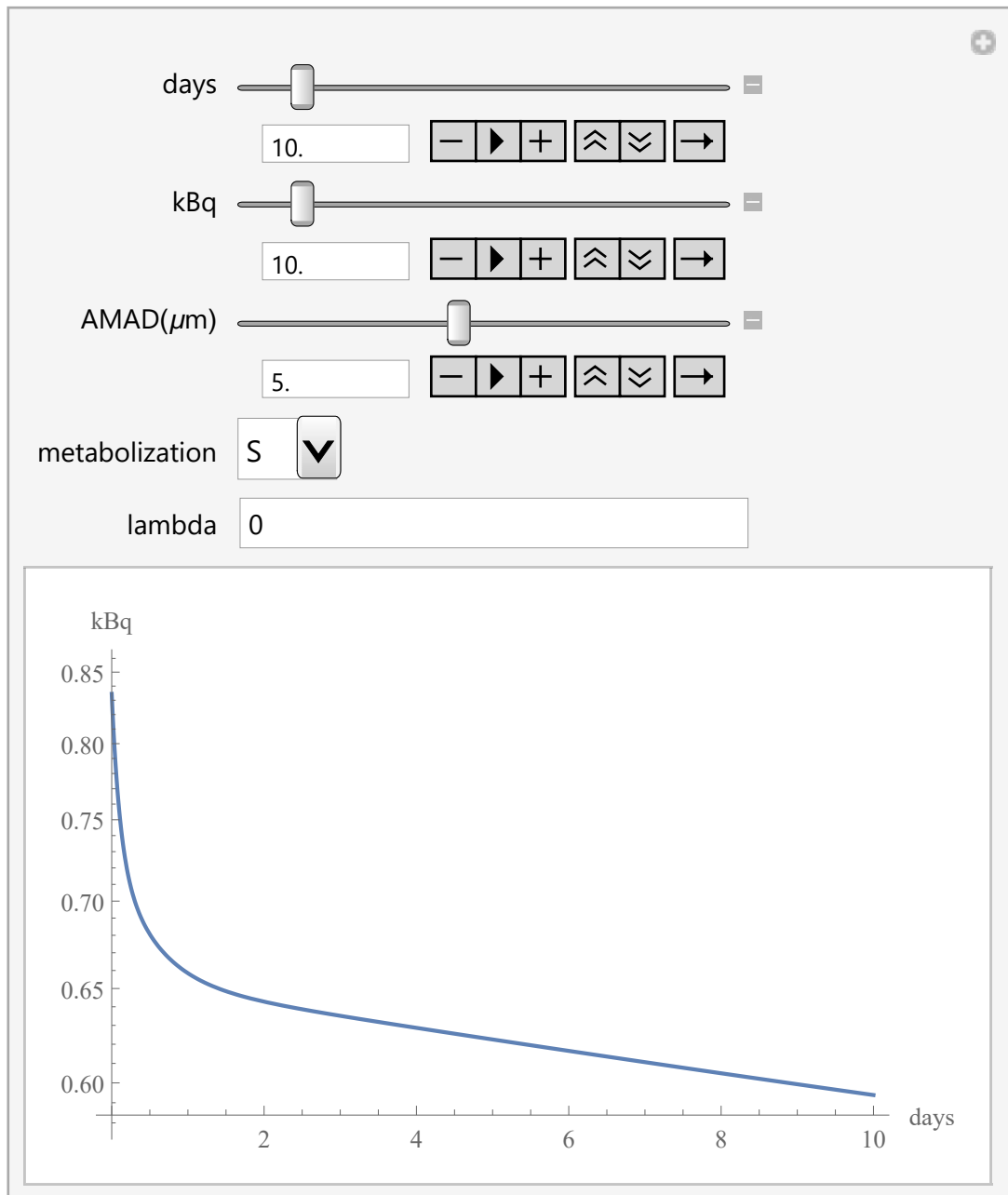
Out[13]=

Example 4.- Practically all current ICRP models are available

In[14]:= **Needs["Biokmod`Biokdata`"]**

      Biokdata 1.2.2 2004−09−3

The user will chose: a) the activity intaken (in Bq or other unit), the range of the time where wish compute the retention or excretion; the element and the isotope, the class of metabolization (S, M, or F), the "IntakeWay" (inhalation, ingestion or inyection), the "IntakeType" (acute or constant), and the type of the "Report".

The input is the intaken at time t=0 (if acute) or the daily intake (if constant). The time means the happened time since the acute intake or since start the intake (if constant).
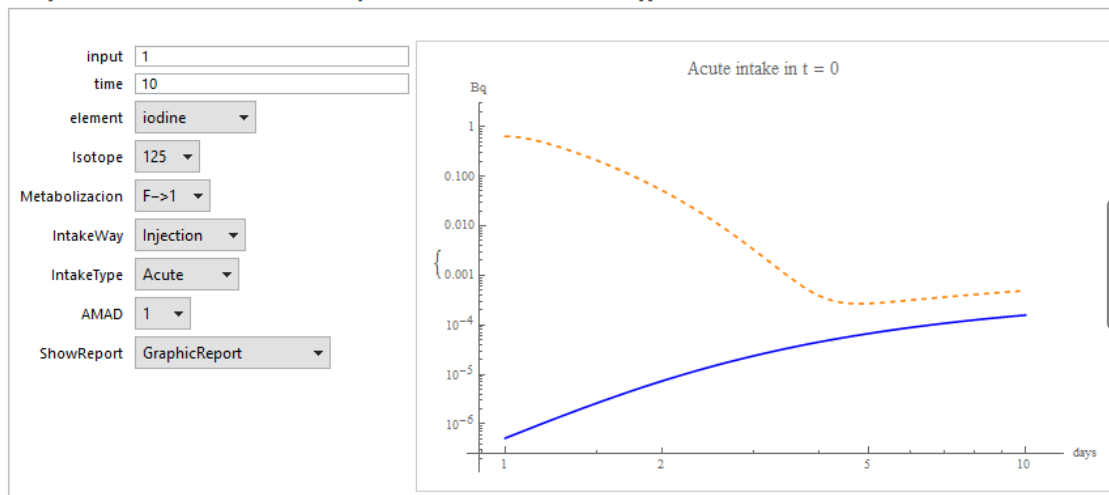
Example 5 .- The intakes can be estimated fitting bioassay data

It is assumed that are taken samples of iodine in compartment 1

In[16]:= **dataIodine = {{0, 0.002}, {50, 0.106}, {100, 0.077},**
        {150, 0.056}, {200, 0.041}, {250, 0.032}, {300, 0.023},
        {350, 0.018}, {400, 0.011}, {450, 0.011}, {500, 0.007}};

An input to the compartment 1 is given by

In[17]:= **iodo129h = 34.4 e$^{-200.\,t}$ + 1.09 e$^{-110.\,t}$ +**
        0.808 e$^{-102.\,t}$ + 6.414 e$^{-100.\,t}$ + 5.458 e$^{-24.\,t}$;

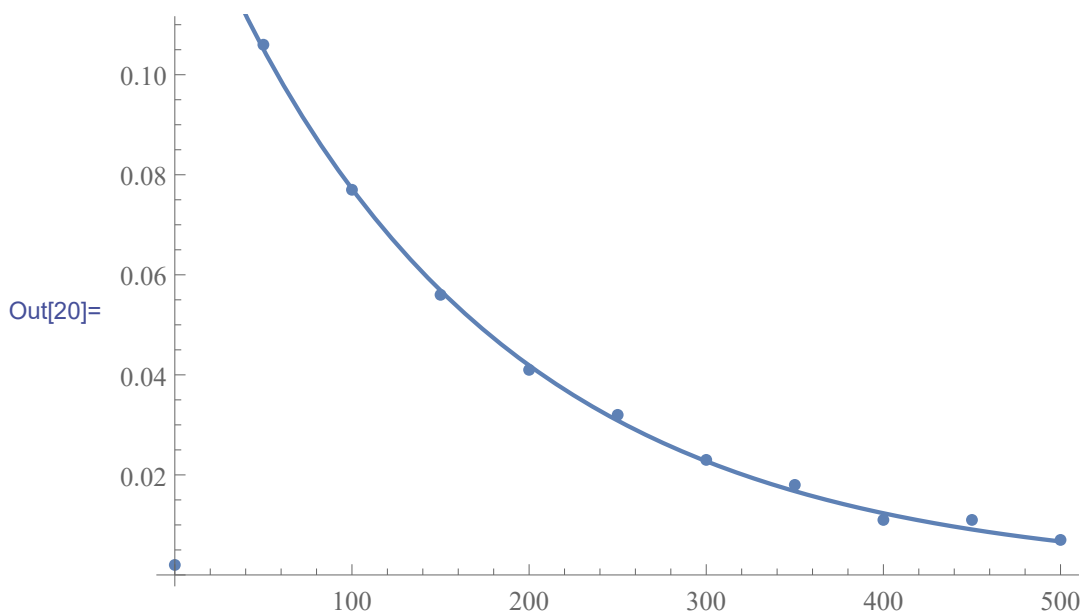We wish fit the coeff. k12 and k23 of the models

```
In[18]:= model[t1_?NumberQ, k12_?NumberQ, k23_?NumberQ] :=
    x₂[t1] /. SystemNDSolve[
        CompartMatrix[3, {{1, 2, k12}, {1, 0, 1.9404},
            {2, 3, k23}, {3, 0, 0.01155}, {3, 1, 0.0462}}],
        {0, 0, 0}, {iodo129h, 0, 0}, {t, 0, 500}, t1, x];
```

```
In[19]:= nlm = NonlinearModelFit[dataIodine, model[t, a12, a23],
    {{a12, 0.8}, {a23, 0.007}}, {t}, Method → Gradient]
```

Out[19]= FittedModel[model(*t*, 0.8647, 0.00844593)]

Out[20]=

Example 6.- Bioassay data fitting

```
In[22]:= Needs["Biokmod`Fitmodel`"]
```

FitModel 1.3 2015−11−17

A worker has been exposed from $t = 0$ to $t = 2000$ day to a chronic intake by inhalation of 3 BqU/day of UO_2 aerosols type S and AMAD 5 μm. On the day $t = 2000$ he accidentally intakes by inhalation an unknown *I* quantity of UO_2. The uranium lung content has been measured using a lung body counter obtaining: {Days after accidental intake, Lung content (BqU), uncertainties with a confidence level of 95%} {{1,196,30},{5,190,30},{30,166,30},{70,146,30},{120,131,30},{250,112,30}}. It is supposed that the measured . 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

In[20]:= **sampleLung = {{1, 196, 30}, {5, 190, 30}, {30, 166, 30},**
        {70, 146, 30}, {120, 131, 30}, {250, 112, 30}};

In[22]:= **LungAccidentalIntake[sampleLung, 3, 0, 2000, 5]**

Out[22]= {Ji2 → 0.00125218, fS → 0.810662, Mean → 1668.89,

s → 265.352,

}
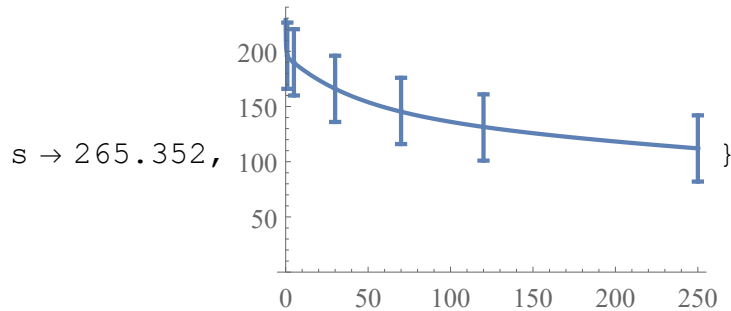
Example 7 .- Multibioassay data fitting

An operator has been exposed to an simple accidental intake by inhalation of ^{60}Co. The cobalt form was metal and oxide. A program of in-vivo monitoring was carried out ten days after the event and continued up to 3 years (Table 1). Urine samples were also taken (Table 2). Additional information: It is recommended to assume that the whole body and urine measurements be approximated by a log-normal distribution with a geometric standard deviation of 1.07 Bq and 1.8 Bq

In[79]:= **Clear["Global`*"]**

In[90]:= **sampleWBCo60 =**
      {{10, 23 900}, {14, 29 200}, {17, 20 100}, {20, 18 200},
       {27, 21 600}, {40, 19 800}, {60, 21 600}, {80, 17 500},
       {190, 11 600}, {370, 8100}, {747, 4800}, {1010, 2700}};

In[91]:= **sampleUriCo60 = {{14, 709}, {27, 64}, {40, 71},**
        {60, 37}, {80, 29}, {190, 11}, {370, 1.7}};

Table 1.-Whole body activity measurement

```
In[82]:= TableForm[sampleWBCo60, TableHeadings →
            {None, {"Time of measurement\n after intake in days",
              "Whole body\n activity of 60Co (Bq)"}}]
```
Out[82]//TableForm=

Time of measurement after intake in days	Whole body activity of 60Co (Bq)
10	23 900
14	29 200
17	20 100
20	18 200
27	21 600
40	19 800
60	21 600
80	17 500
190	11 600
370	8100
747	4800
1010	2700

Table 2.- Urine activity measurement

```
In[18]:= TableForm[sampleUriCo60, TableHeadings →
            {None, {"Time of measurement\n after intake in days",
              "Daily urinary excretion\n rate of 60Co (Bq)"}}]
```
Out[18]//TableForm=

Time of measurement after intake in days	Daily urinary excretion rate of 60Co (Bq)
14	709
27	64
40	71
60	37
80	29
190	11
370	1.7

Assuming standard values the values for Cobalt 60 AMAD 5 Type M adding the uncertainties of the measurement the best fit is:

```
In[92]:= sampleUriCo60U = {{14, 709, 1.8},
        {27, 64, 1.8}, {40, 71, 1.8}, {60, 37, 1.8},
        {80, 29, 1.8}, {190, 11, 1.8}, {370, 1.7, 1.8}};
```

```
In[93]:= sampleWBCo60U =
        {{10, 23 900, 1.2}, {14, 29 200, 1.2}, {17, 20 100, 1.2},
        {20, 18 200, 1.2}, {27, 21 600, 1.2}, {40, 19 800, 1.2},
        {60, 21 600, 1.2}, {80, 17 500, 1.2}, {190, 11 600, 1.2},
        {370, 8100, 1.2}, {747, 4800, 1.2}, {1010, 2700, 1.2}};
```

```
In[94]:= BioassayFit[cobalt, "Inhalation", "Acute", "MLM",
        AMADAdultW[5], M, 0.1, Log[2] / (5.27 * 365.24),
        {NA}, sampleUriCo60U , {NA}, sampleWBCo60U]
```

```
Out[94]= {Mean → 481 332., Ji2 → 71.7327}
```

If we assumed that Intake, AMAD p, s_{pt}, s_p, s_t are unknown, then the best fit is:

```
In[99]:= fitType1[p_ , s1_ , s2_ , s3_] :=
        BioassayFit[cobalt, "Inhalation", "Acute", "MLM",
        AMADAdultW[p], {s1, s2, s3}, 0.1, Log[2] / (5.27 * 365.24),
        {NA}, sampleUriCo60U, {NA}, sampleWBCo60U]
```

```
In[100]:= BioassayBestfit[fitType1,
        {p, 4.5, 5.5, 0.5}, {s1, 9, 10, 1},
        {s2, 90, 100, 10}, {s3, 0.0002, 0.0007, 0.0005}]
```

```
Out[100]= {Mean → 398 553., Ji2 → 15.5141, 5.5, 10, 90, 0.0007}
```

The best fit obtained corresponds to 398.5 kBqU with AMAD 5.5 μm, $\{s_{pt}, s_p, s_t\}$ ={10, 90, 0.0007} with f1 = 0.1. The committed effective dose, E(50) calculated using these values is: 4.5 mSv.

Example 8 .- .- Lung retention uncertainties (AMAD *p* ± *u*ₚ)

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 ± 0.5 μm . The dashed lines represent the confidence interval (95%) associated with the AMAD uncertainties.

```
In[9]:= 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

```
In[10]:= yu[t1_] = {"mean", "uL", "lL"} /.
           Uin[rLung[p, t1], {p}, {σp}, 2] /. {p → 5, σp → 0.5};
```

```
In[11]:= Plot[Evaluate[yu[t]], {t, 1, 100},
          PlotRange → {0, 0.1}, AxesLabel → {"days", "Bq"}]
```

Out[11]=
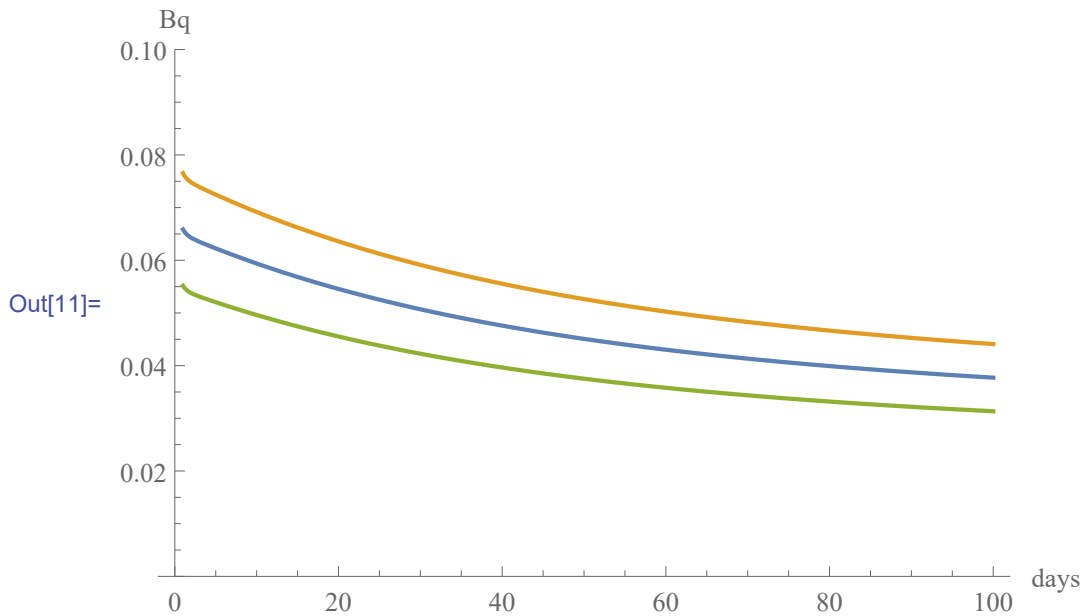
It can be observed that a small difference in the AMAD value has an important consequence in the lung retention predicted. For this reason, when the value for AMAD is used to evaluate bioassay data and it it is not known then the intake estimated could have important uncertainties.

Example 9 .- Irregular and random intakes estimation

A worker has been exposed during the last 300 days of an intake by inhalation of radioactive aerosols (type S, AMAD 5) 5 days per week. It know that the daily average intake was 3.3 Bq/day with and standard deviation of 5.5 Bq/day. According to the dosimetry historial of this worker, before of this period he intaken 3500 Bq during 1200 days. We wish estimate the daily urine excretion.

The first step is obteined the IRF for a simple input 1

```
In[26]:= {urineExc, faecalExc, wholebodyRet} =
    {qDailyUrine[t], qDailyFaecal[t], qWholebody[t]} /.
     BiokdataReport[uranium, "Inhalation", "Acute",
      "Automatic", 1, AMADAdultW[5], S, 0.002, t, 0];
```

Now it is applied the function qRandom (See in Help: Advance function)

```
In[27]:= sol =
    qRandom[3500, 1200, urineExc, 3.3, 5.1, 1.96, 300, 5, t];
```

```
In[28]:= {days, me, int, ul, ll} = Transpose[sol];
```

The blue color represents the confidence interval for the daily urine excretion, it can be observed the effect of the weekeng where there are not intakes.

```
In[29]:= ListPlot[{Transpose[{days, ll}], Transpose[{days, ul}]},
    AxesLabel → {"days", "Bq/day"}, Filling -> {1 → {2}},
    FillingStyle → Lighter[Blue, 0.7]]
```
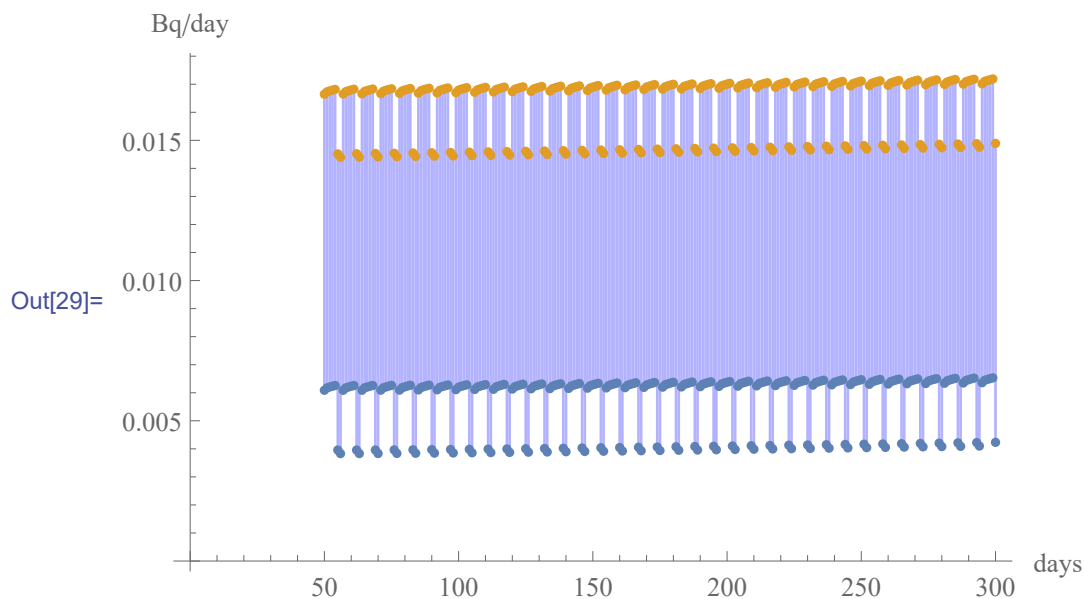

References

Some studies has been published where BIOKMOD has been used (some available at the author website: http://diarium.usal.es/guillermo).

Sánchez G; Lopez-Fidalgo J "Mathematical Techniques for Solving Analytically Large Compartmental Systems" Health Physics..: 85 (2): 2003. ISSN/ISBN: 0017-9078

Sánchez G; Biokmod: A Mathematica toolbox for modeling Biokinetic Systems. Mathematica in Education and

Research: 10 (2) 2005. ISSN/ISBN: 1096-3324

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

Lopez-Fidalgo J Rodriıguez-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

Sánchez G; Fitting bioassay data and performing uncertainty analysis with BIOKMOD Health Physics.. 92(1) :64-72. 2007. ISSN/ISBN: 0017-9078

Sánchez G; 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

Sánchez.G. Biokmod applied to evaluate bioassay data. IRPA 11, 11 International Congress of Radio Protection Association, Madrid. May 2004. ISBN-84-87078-05-02.

Sánchez G and Lopez-Fidalgo J. Uncertainties Predicting Radionuclides Distribution In ICRP Models With Random Inputs. IRPA 11 International Congress of Radio Protection Association. Madrid. May 2004. ISBN-84-87078-05-02

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