



# Modelización de la distribución del $^{18}\text{F}$ -FDG en el organismo.

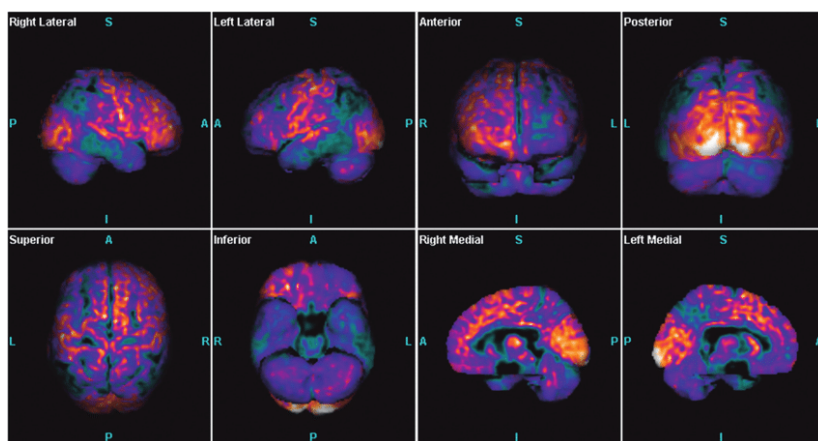
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## Objetivo

En la medicina nuclear diagnóstica ocupa un papel importante la tomografía por emisión de positrones (PET). En este tipo de exploraciones el marcador más utilizado es la  $^{18}\text{F}$ -fludesoxiglucosa (FDG), un radiofármaco que contiene al isótopo radiactivo flúor-18, con el que se generan imágenes que permiten el estudio del metabolismo celular de la glucosa.



Un problema fundamental es calcular las desintegraciones en los distintos órganos como consecuencia de la administración de FDG. Para ello se utiliza modelización compartimental que nos permite conocer la cantidad  $x_i(t)$  retenida en un compartimento  $i$ . A partir de ello se calcula la dosis.

Para evaluar la dosis en los distintos órganos del paciente se emplea las tablas de la ICRP 128, que se basa en el modelo compartimental: Hays y Segall A mathematical model for the distribution of fluorodeoxyglucose in humans. J. Nucl. Med. 40, 1358-1356.(1999). EURADOS ha detectado discrepancias significativas con los valores de la ICRP 128.

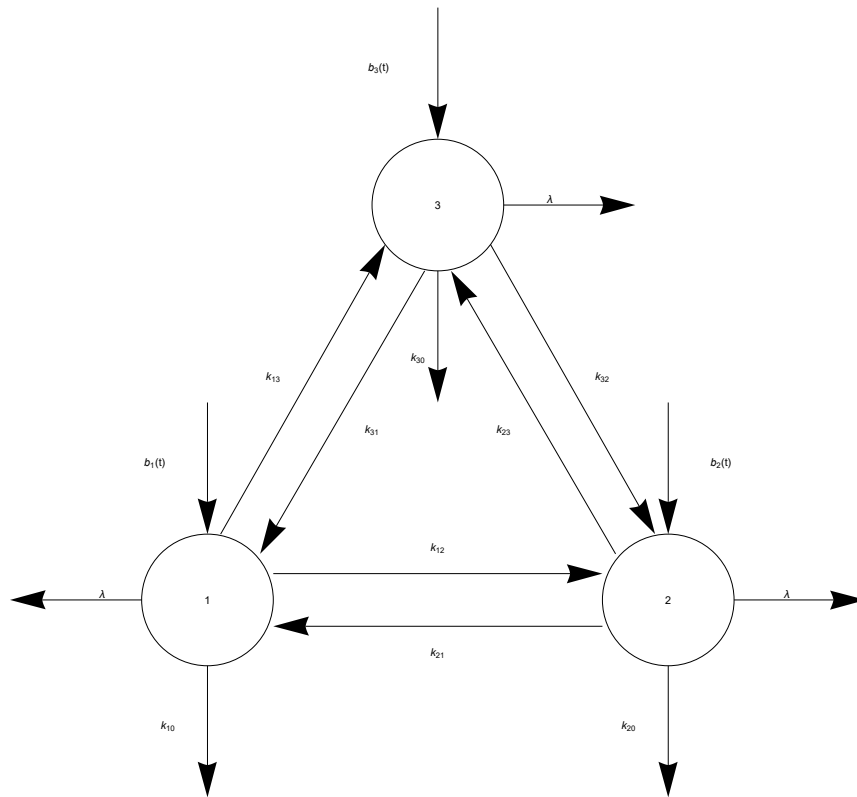
Nosotros hemos modelado independientemente la metabolización del FDG coincidiendo con los resultados de EURADOS. Nuestra aportación más importante es que hemos obtenido las soluciones analíticas del modelo, lo que facilita su aplicación para distintos fines. Además, el modelo desarrollado lo hemos integrado como parte de la aplicación web BIOKMOD, permitiendo que los usuarios modifiquen distintos parámetros.

Puede ejecutarse en:

<http://oed.usal.es/webMathematica/Biokmod/biokmod13fluor.jsp> o

<http://oed.usal.es/webMathematica/Biokmod/index.html>.

## El modelo general compartimental



Si el caso anterior lo extendemos a  $n$  compartimentos, la ecuación que da el contenido en cualquier compartimento  $i$  esta dada por

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

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

donde:

$\mathbf{x}(t) = \{x_1(t), x_2(t), \dots, x_n(t)\}^T$   $x_i(t)$  denota la cantidad o contenido de un sustancia en el compartimento  $i$  en el momento  $t$ .

$\mathbf{A}$ :  $n \times n$  es la matriz compartimental o matriz del sistema

$\mathbf{b}(t) = \{b_1(t), b_2(t), \dots, b_n(t)\}^T$   $\{b_i(t)\}$  es la tasa de entrada hacia el compartimento  $i$  desde fuera del sistema.

$\mathbf{x}(0) = \{x_1(0), x_2(0), \dots, x_n(0)\}^T$  son las condiciones iniciales que corresponden al contenido de un sustancia en el compartimento  $i$  en el momento  $t = 0$ .

## Time integrated activity coefficients (TIAC)

The time - integrated activity is calculated as the area under the curve (AUC \*) that describes the activity as a function of time in the source region after the administration of the radiopharmaceutical . The time integrated activity coefficient (TIAC) is defined as the time - integrated activity divided by the administered activity and is given in hours .

(\*) The area under the curve or AUC, in the field of pharmacokinetics, is the definite integral of a curve that describes the variation of a drug concentration in blood plasma as a function of time

Symbol	Quantity	Unit
$\tilde{A}(r_S, T_D)$	Time-integrated activity	Bq · s
$\tilde{a}(r_S, T_D)$	Time-integrated activity coefficient	s
$D(r_T)$	Absorbed dose to the target region $r_T$	Gy
$\dot{D}$	Absorbed dose rate	Gy/s

### 18.1.1. Basic concepts

The time-integration period is commonly chosen from the time of administration of the radiopharmaceutical until infinite time. However, the integration period should be matched to the **biological endpoint** studied in combination with the time period in which the **relevant absorbed dose is delivered** ( $T_D$ ).

$$\tilde{A}(r_S) = \int_0^{T_D} A(r_S, t) dt = \int_0^{\infty} A(r_S, t) dt = \tilde{a}(r_S) \cdot A_0$$

$$\tilde{a}(r_S) = \frac{\tilde{A}(r_S)}{A_0}$$

Is defined as the **time-integrated activity coefficient**, being  $A_0$  the administered activity; it has the unit of time (e.g. s, or h). In the MIRD Primer it was named '**residence time**'

$$D = \tilde{A} \times S$$

gray (Gy)  
(1 J/kg = 1 Gy)

**absorbed dose**

becquerel · s

cumulated activity:  
decays that take place  
in a certain source  
region

Gy · (Bq · s)<sup>-1</sup>  
often mGy · (MBq · s)<sup>-1</sup>

absorbed dose rate per  
unit activity, or absorbed  
dose per cumulated  
activity (or absorbed  
dose per decay)

# Modelo biocinético del F-18

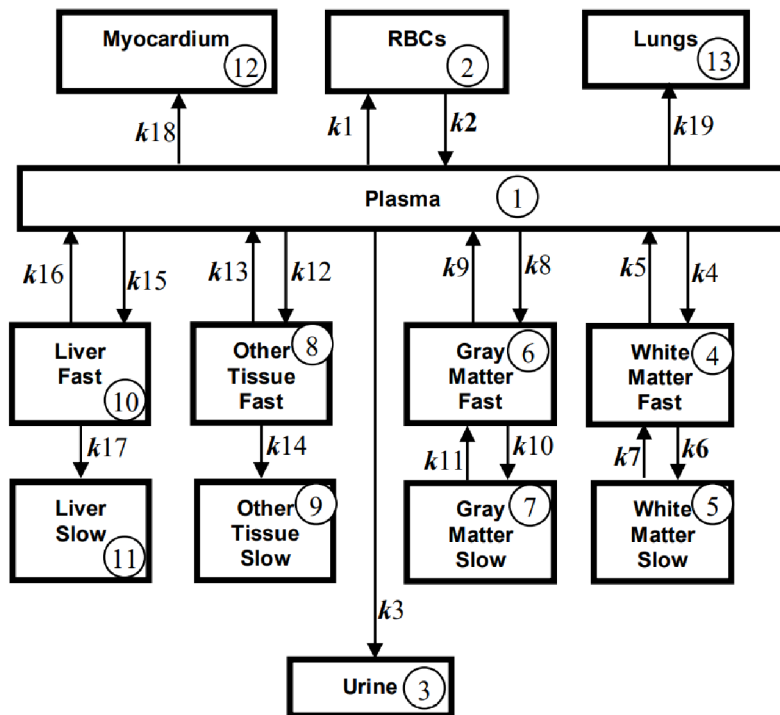


Table 1: Transfer rates\* of the compartmental model for  $^{18}\text{F}$ -FDG by Hays and Segall.

Organ		Parameter	Transfer rate ( $\text{min}^{-1}$ )	
From	To		Arithmetic mean	Geometric mean
Plasma	RBCs	$k_1$	4.8	4.07
RBCs	plasma	$k_2$	8.07	7.35
Plasma	Urine bladder	$k_3$	0.0088	0.0085
Plasma	WM Fast	$k_4$	0.054	0.052
WM Fast	Plasma	$k_5$	0.109	0.10
WM Fast	WM Slow	$k_6$	0.045	0.042
WM Slow	WM Fast	$k_7$	0.0058	0.0055
Plasma	GM Fast	$k_8$	0.102	0.099
GM Fast	Plasma	$k_9$	0.13	0.115
GM Fast	GM Slow	$k_{10}$	0.062	0.059
GM Slow	GM Fast	$k_{11}$	0.0068	0.0066
Plasma	Other Fast	$k_{12}$	0.371	0.348
Other Fast	Plasma	$k_{13}$	0.102	0.097
Other Fast	Other Slow	$k_{14}$	0.0167	0.015
Plasma	Liver Fast	$k_{15}$	0.068	0.038
Liver Fast	Plasma	$k_{16}$	0.219	0.186
Liver Fast	Liver Slow	$k_{17}$	0.018	0.006
Plasma	Myocardium	$k_{18}$	0.0053	0.003
Plasma	Lungs	$k_{19}$	0.0017	0.0016

The half-life of  $^{18}\text{F}$  was taken from ICRP 107 (ICRP, 2008):  $T_{1/2} = 109.77$  min, i.e. the physical decay constant is  $\lambda_p = 0.0063 \text{ min}^{-1}$ .

La resolución del modelo compartimental nos dará la función respuesta (contenido de F presente en un compartimento  $i$ , tras la inyección en  $t=0$ , en el compartimento 1 de una cantidad  $q(0) = 1$ ;  $r_i(t)$ ). Lo hemos calculado utilizando ambos tipos de tasas de transferencia

# El paquete

El modelo lo hemos incorporado en un paquete de Mathematica

```

In[ ]:= Needs["Biokmod`OIRModels`"]

SysModel, version 2.0.b7    2020-11-30

OIRModels 1.1b2    2022-03-24

In[ ]:= CompartmentalnumbersF

Out[ ]:= {{Plasma,1}, {RBCs,2}, {Urine,3}, {WhiteMatterFast,4}, {WhiteMatterSlow,5},
          {GrayMatterFast,6}, {GrayMatterSlow,7}, {OtherTissueFast,8},
          {OtherTissueSlow,9}, {LiverFast,10}, {LiverSlow,11}, {Myocardium,12}, {Lungs,13}}

```

## Características isotópicas

```

In[ ]:= IsotopeDecayModes["Fluorine18"]

"BetaPlusDecay"
"β+"
In[ ]:= 1. 3.
633.023`6. keV

BetaPlusDecay
β+
Out[ ]:= 1.00
633.023 keV

In[ ]:= fluorine-18 ISOTOPE ["Properties"]

Out[ ]:= {atomic mass, atomic number, atomic symbol, binding energy per nucleon, biological half-life,
          biological lifetime, branching ratios, critical diameter, critical mass, critical organs,
          daughter nuclides, decay constant, Q-value, decay modes, decay modes, decay products,
          diagnostic applications, diagnostic applications to diseases, effective half-life, effective lifetime,
          entity classes, entity type list, Elevel, half-life τ1/2, excited state lifetimes, excited state parities,
          excited state spins, width Δ, external exposure advisory, final decay products, full symbol,
          half-life, half-value layer, isotope abundance, mean lifetime, magnetic moment, mass defect,
          mass excess, mass number, diagnostic applications, memberships, molar mass, molar radioactivity,
          name, neutron number, parity, electric quadrupole moment, type of particle, radioactivity,
          specific activity, spin, spin parity Jπ, stable, brief symbol, tenth-value layer, width}

In[ ]:= fluorine-18 ISOTOPE ["HalfLife"]

Out[ ]:= 109.73 min

```

## ☞ Funciones respuesta:

*In[ ]:=* **qF18Injection[t] // Chop // Short**

*Out[ ]//Short=*

$$\left\{ \begin{aligned} x_1[t] &\rightarrow 0.395683 e^{-13.1132 t} + 0.430092 e^{-0.51053 t} + \\ &\quad \ll 4 \gg + 0.000262063 e^{-0.0105465 t} + 0.0161431 e^{-0.00868373 t}, \\ x_2[t] &\rightarrow \ll 1 \gg, \ll 9 \gg, \ll 1 \gg, x_{13}[t] \rightarrow \ll 15 \gg + \ll 21 \gg e^{\ll 1 \gg} \end{aligned} \right\}$$

*In[ ]:=* **qF18InjectionG[t] // Chop // Short**

*Out[ ]//Short=*

$$\left\{ \begin{aligned} x_1[t] &\rightarrow 0.379079 e^{-11.6304 t} + 0.454068 e^{-0.465429 t} + \\ &\quad \ll 4 \gg + 0.000254002 e^{-0.010303 t} + 0.0183932 e^{-0.00835775 t}, \\ x_2[t] &\rightarrow \ll 1 \gg, \ll 10 \gg, x_{13}[t] \rightarrow \ll 15 \gg + \ll 21 \gg e^{\ll 1 \gg} \end{aligned} \right\}$$



## Incorporaciones de distinto tipo

A partir de la función respuesta pueden realizarse multitud calculos. Por ejemplo; El total, como suma en todos los compartimentos, o realizarse representaciones gráficas

```

In[ ]:= Total[Table[xi[t], {i, 1, 13}]/. qF18Injection[ t]] // Chop

Out[ ]:=  $5.55112 \times 10^{-17} e^{-13.1132 t} + 3.21965 \times 10^{-15} e^{-0.51053 t} + 2.08167 \times 10^{-16} e^{-0.230225 t} +$   

 $1.38778 \times 10^{-16} e^{-0.186303 t} + 5.55112 \times 10^{-17} e^{-0.156732 t} + 1.43219 \times 10^{-14} e^{-0.0294228 t} +$   

 $2.62984 \times 10^{-15} e^{-0.0105465 t} + 6.24223 \times 10^{-14} e^{-0.00868373 t} + 1. e^{-0.00631449 t}$ 

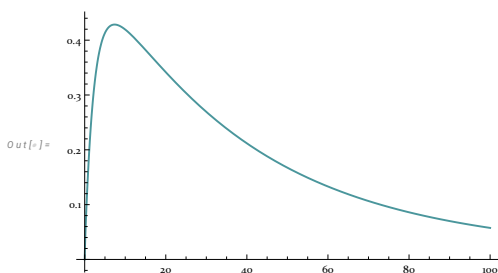
In[ ]:= u[t_] = x8[t] /. qF18InjectionG[t] // ExpandAll // Chop

Out[ ]:=  $-0.0114592 e^{-11.6304 t} - 0.455226 e^{-0.465429 t} - 0.00851962 e^{-0.194332 t} - 0.0589342 e^{-0.170587 t} -$   

 $0.0411823 e^{-0.14548 t} + 0.516291 e^{-0.0278065 t} + 0.000818364 e^{-0.010303 t} + 0.0582123 e^{-0.00835775 t}$ 

In[ ]:= Plot[u[t], {t, 0, 100}]

```



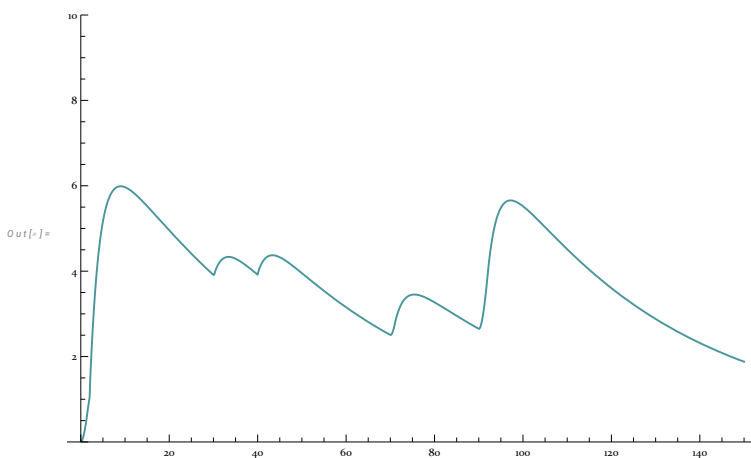
## Inputs multiples

```

In[ ]:= inputs = {{5, 0, 1.5}, {9, 2}, {2, 30, 0.3}, {2, 40}, {3, 70, 1}, {8, 90, 2}};

In[ ]:= Plot[qMultiple[inputs, {u[t], t}, t1], {t1, 0, 150},
  PlotRange -> {0, 10}, ExclusionsStyle -> {Blue, Blue}, ImageSize -> Large]

```



## Incorporación constante.

```

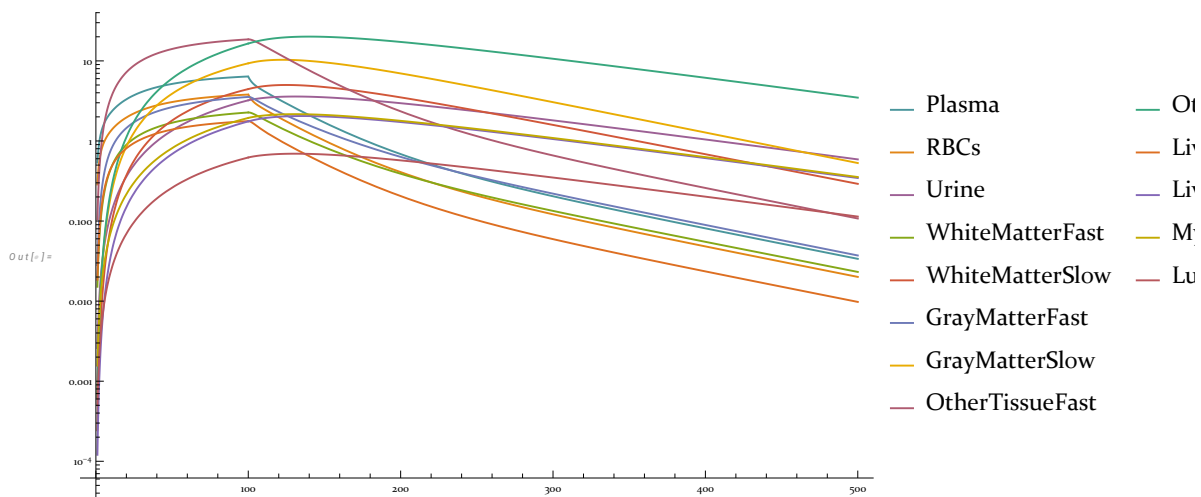
In[ ]:= compf = {"Plasma", "RBCs", "Urine", "WhiteMatterFast",
  "WhiteMatterSlow", "GrayMatterFast", "GrayMatterSlow",
  "OtherTissueFast", "OtherTissueSlow",
  "LiverFast", "LiverSlow", "Myocardium", "Lungs"};

```

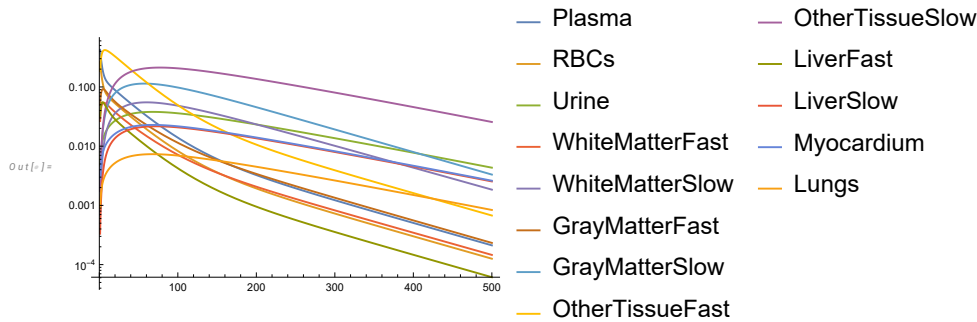
```

In[ ]:= LogPlot[Evaluate[qF18InjectionCte[t, 100]],
  {t, 1, 500}, PlotRange → All, PlotLegends → compf]

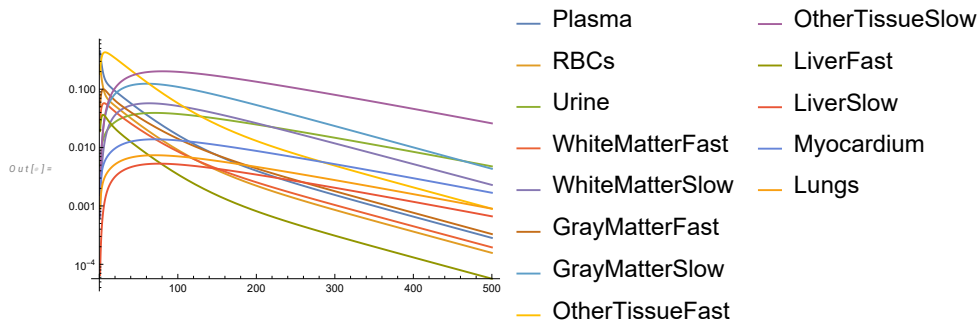
```



```
in[*]:= ResponseReport["Fluorine", "Injection",
    "Acute", "AritmeticMean", "GraphicsReport", {1, 500}]
```



```
in[*]:= ResponseReport["Fluorine", "Injection",
    "Acute", "GeometricMean", "GraphicsReport", {1, 500}]
```



## Time integrated activity coefficients (TIAC)

```
in[*]:= ResponseReport["Fluorine", "Injection",
    "Acute", "AritmeticMean", "ResponseFunction", t] // Chop // Short
```

```
Out[*]//Short=
{ x1[t] -> 0.395683 e-13.1132 t + 0.430092 e-0.51053 t + <<4>> + 0.000262063 e-0.0105465 t +
  0.0161431 e-0.00868373 t, <<11>>, x13[t] -> <<15>> + <<21>> e<<1>> }
```

```
in[*]:= ResponseReport["Fluorine", "Injection",
    "Acute", "GeometricMean", "ResponseFunction", t] // Chop // Short
```

```
Out[*]//Short=
{ <<1>> }
```

```
in[*]:= ResponseReport["Fluorine", "Injection",
    "Acute", "AritmeticandGeometricMean", "TIAC", 1000]
```

```
Out[*]=
{ Plasma    RBCs    Urine    WhiteMatterFast  WhiteMatterSlow  GrayMatterFast  GrayMatterSlow  OtherTi
  0.123683  0.0735088  0.17182   0.0481276       0.178739         0.0759195       0.358863        0.36
  0.123683  0.0735088  0.17182   0.0481276       0.178739         0.0759195       0.358863        0.36 }
```

Se han integrado en BIOKMOD

<http://oed.usal.es/webMathematica/Biokmod/biokmod13fluor.jsp>

O

<http://oed.usal.es/webMathematica/Biokmod/index.html>.

Here is the BIOKMODWEB site. It can be used for solving yourself compartmental models or to make use of the ICRP biokinetic models (including the new ICRP 130/134/137 models). It can be applied in internal dosimetry, bioassay evaluations, nuclear medicine, pharmacokinetic, and more. It have been developed using the Wolfram Language [Mathematica](#) and [Java](#).

**BIOKMODWEB** uses the [Mathematica](#) toolbox: **BIOKMOD**. The most usual features of BIOKMOD are available here (use the left side menu). It runs entirely within your web browser.

What things you can do with BIOKMOD?

It can be used to solve systems of differential equations, to fit coefficients, convolution, and more, with application for modeling Linear and Nonlinear Biokinetic Systems. Most of the ICRP biokinetic models are included and they can be applied in internal dosimetry and bioassay evaluations.

(i) The user can build and solve its own compartmental model (constant and variable coefficients can be used).

(ii) All ICRP30/66/78 are solved for most isotopes (including some specific options for Lung and Respiratory Tract) obtaining the Intake Retention Fractions (IRF), their analytical expressions (intake retention functions), the compartmental contents and the graphic representations. Acute, constant - chronic, continuous (variable in the time) and multi-inputs, even random, intakes can be used. One can accept the default parameters or introduce specific values. They can be used for bioassay evaluations and for research and education purposes.

(iii) (New) The new ICRP 130/134/137 models for Co, I, Cs, U and F-18 have been added. They can be applied for bioassay evaluations.

(iv) An optimal design function is included. It can be used to establish the best moment for experimental sample or bioassay.

(v) Fitting functions for non linear fitting.

(vi) A function for evaluating uncertainties analytically.

If you have any comment send me an e-mail: [guillermo2046\(at\)gmail.com](mailto:guillermo2046(at)gmail.com).

Some papers have been published where BIOKMOD has been used (below are referenced some of them). For additional information visit: [BIOKMOD](#).

Guillermo Sánchez-León, María Antonia López, Montserrat Moraleda, Juan M. Rodríguez-Díaz; "Bioassays in workers exposed to long time random intakes" Radiation and Applied Radiation and Isotopes (180) 2022. <https://doi.org/10.1016/j.apradiso.2021.110057>

Rodríguez-Díaz Juan M. ; Sánchez-León Guillermo; "Efficient parameter estimation in multiresponse models measuring radioactivity retention" Radiation and Environmental Biophysics 2019 <https://doi.org/10.1007/s00411-019-00780-7>

Lopez-Fidalgo J, Sánchez-León Guillermo; "Optimal bioassay time allocations for multiple accidental chronic intakes of radioactive particles". Stochastic Environmental Research and Risk Assessment. <https://doi.org/10.1007/s00477-019-01668-0>

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

## Referencias

<https://diarium.usal.es/guillermo/biokmod/>