

# The Optdesign package

Last version available at <http://web.usal.es/guillermo/biokmod>

Updated a 2006-04-15

## ■ Inicialization

## ■ D-optimal designs

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

The procedure used is the following:

1.- It is defined a model  $r(t, \beta)$

As a example we will suppose this model and unknown parameters.

```
In[7]:= r = inp  $\left( \frac{1}{1 + 0.2 k + 0.3 k^2} e^{-(0.1 + 0.2 k) t} \right) e^{-0.02 t + 0.2 p};$ 
```

```
In[8]:=  $\beta = \{inp, k, p\};$ 
```

2.- Now it is computed  $\nabla(r(t), \beta) = \left\{ \frac{dr(t)}{d\beta_1}, \dots, \frac{dr(t)}{d\beta_p} \right\}$ ,

```
In[9]:= grad[s_, vars_List] := Map[Function[{v}, D[s, v]], vars]
```

In our example

```
In[10]:= g[t_] = grad[r,  $\beta$ ]
```

```
Out[10]=  $\left\{ \frac{e^{0.2 p - 0.02 t + (-0.1 - 0.2 k) t}}{1 + 0.2 k + 0.3 k^2}, \right.$   

 $-\frac{e^{0.2 p - 0.02 t + (-0.1 - 0.2 k) t} inp (0.2 + 0.6 k)}{(1 + 0.2 k + 0.3 k^2)^2} - \frac{0.2 e^{0.2 p - 0.02 t + (-0.1 - 0.2 k) t} inp t}{1 + 0.2 k + 0.3 k^2},$   

 $\left. \frac{0.2 e^{0.2 p - 0.02 t + (-0.1 - 0.2 k) t} inp}{1 + 0.2 k + 0.3 k^2} \right\}$ 
```

4.- Here is defined the number of points to be used in the optimal design

We suppose a 3-points design

```
In[11]:= n = 2;
```

```
In[12]:= tt = Table[t_i, {i, 0, n}]
```

```
Out[12]= {t_0, t_1, t_2}
```

For computational purpose we have found more appropriate to use the distance  $d_i = t_i - t_{i-1}$ , instead of  $t_i$ , then  $t_i = \sum_i d_i$  being  $d_0 = t_0$

```
In[13]:= dd = Table[di, {i, n}]
```

```
Out[13]= {d1, d2}
```

```
In[14]:= ddd = FoldList[Plus, Subscript[d, 0], dd]
```

```
Out[14]= {d0, d0 + d1, d0 + d1 + d2}
```

5.- It is evaluated  $\nabla(r(t), \beta)$  at points  $t: \{t_0, \dots, t_n\}$ , obtaining  $X = \{X_1, \dots, X_p\}$  with  $X_1 = \left\{ \frac{dr(t_0)}{d\beta_1}, \dots, \frac{dr(t_n)}{d\beta_1} \right\}$ , ...,  $X_p = \left\{ \frac{dr(t_0)}{d\beta_p}, \dots, \frac{dr(t_n)}{d\beta_p} \right\}$

```
In[15]:= X = g[ddd];
```

$\tilde{A} = (l_{ij})$  with  $l_{ij} = \exp(-\tilde{\eta}|t_j - t_i|)$ , meaning that the relationship between samples decays exponentially with increasing time-distance between them

6.- A typical election for compute the covariance matrix is assumed that that the relationship between samples decays exponentially with increasing time-distance between them, that is  $\Gamma = \{l_{ij}\}$  with  $l_{ij} = \exp\{\rho|t_j - t_i|\}$

$\Gamma$  where

$$\Gamma = \begin{pmatrix} 1 & e^{-\rho|t_0-t_1|} & e^{-\rho|t_0-t_2|} & \dots & e^{-\rho|t_0-t_n|} \\ e^{-\rho|t_0-t_1|} & 1 & e^{-\rho|t_1-t_2|} & \dots & e^{-\rho|t_1-t_n|} \\ e^{-\rho|t_0-t_2|} & e^{-\rho|t_1-t_2|} & 1 & \dots & e^{-\rho|t_2-t_n|} \\ \dots & \dots & \dots & \dots & \dots \\ e^{-\rho|t_0-t_n|} & e^{-\rho|t_1-t_n|} & e^{-\rho|t_n-t_2|} & \dots & 1 \end{pmatrix}$$

that is

$$a_{ij} = 1 \text{ if } i = j \text{ and } a_{ij} = e^{-\rho|t_i - t_j|} \text{ if } i \neq j$$

replacing (for computational purpose)  $t_i$  for  $d_i$

$$\text{For } i < j \quad |t_i - t_j| = d_{i+1} + d_{i+2} + \dots + d_j$$

$$\text{For } i > j \quad |t_i - t_j| = d_{j+1} + d_{j+2} + \dots + d_i$$

```
In[16]:= ff[i_, j_] := Which[i == j, 1, i < j, e-ρ Σk=ij-1 dk, i > j, e-ρ Σk=ji-1 dk];
```

```
In[17]:= Γ = Array[ff, {n + 1, n + 1}];
```

6.- Now it is computed the covariance matrix  $\Sigma = \sigma^2 \Gamma$

```
In[18]:= Σ = σ2 * Γ;
```

```
In[19]:= Σ // MatrixForm
```

```
Out[19]//MatrixForm=
```

$$\begin{pmatrix} \sigma^2 & e^{-\rho d_1} \sigma^2 & e^{-\rho (d_1+d_2)} \sigma^2 \\ e^{-\rho d_1} \sigma^2 & \sigma^2 & e^{-\rho d_2} \sigma^2 \\ e^{-\rho (d_1+d_2)} \sigma^2 & e^{-\rho d_2} \sigma^2 & \sigma^2 \end{pmatrix}$$

```
In[20]:= ρ = 1;
```

We will also need give the initial values for the  $\beta$  parameters and the standard deviation of the measures. The first measured should be take at  $t_0 > 0$  as soon as possible (for urine or fecal excretion we usually collect the accumulate quantities during the first 24 h)

```
In[21]:= d0 = t0 = 0.5; inp = i0 = 100; k = k0 = 0.5; p = 5; σ = 2;
```

7.- Then we can obtain the information matrix

$$M = X^T \Sigma^{-1} X$$

```
In[22]:= m = X . Inverse[Σ] . Transpose[X];
```

8.- A D-optimal design will be a design that leads the determinant of the information matrix  $\det[M]$  to a maximum. It can be done as it follows

```
In[23]:= deter[x_? (VectorQ[#, NumberQ] &)] := Det[m /. Thread[dd -> x]];
```

```
In[24]:= bb = NMaximize[{deter[dd], Thread[dd > 1]}, dd];
           {bb[[1]], Thread[tt -> ddd /. Last[bb]]}
```

```
Out[25]= {3.25606 × 10-10, {t0 -> 0.5, t1 -> 3.02475, t2 -> 5.25831}}
```

```
In[26]:= Clear[Σ, m, deter, bb]
```

If it is assumed that all samples are independent then

```
In[27]:= Σ = σ2 * IdentityMatrix[n + 1];
```

```
In[28]:= m = X . Inverse[Σ] . Transpose[X];
```

```
In[29]:= deter[x_? (VectorQ[#, NumberQ] &)] := Det[m /. Thread[dd -> x]];
```

```
In[30]:= bb = NMaximize[{deter[dd], Thread[dd > 1]}, dd];
           {bb[[1]], Thread[tt -> ddd /. Last[bb]]}
```

```
Out[31]= {5.0931 × 10-10, {t0 -> 0.5, t1 -> 1.57182, t2 -> 3.83282}}
```

```
In[32]:= Clear[r, β, grad, g, n, tt, ff, Γ, Σ, ρ, d, m, deter, bb]
```

## ■ The package functions

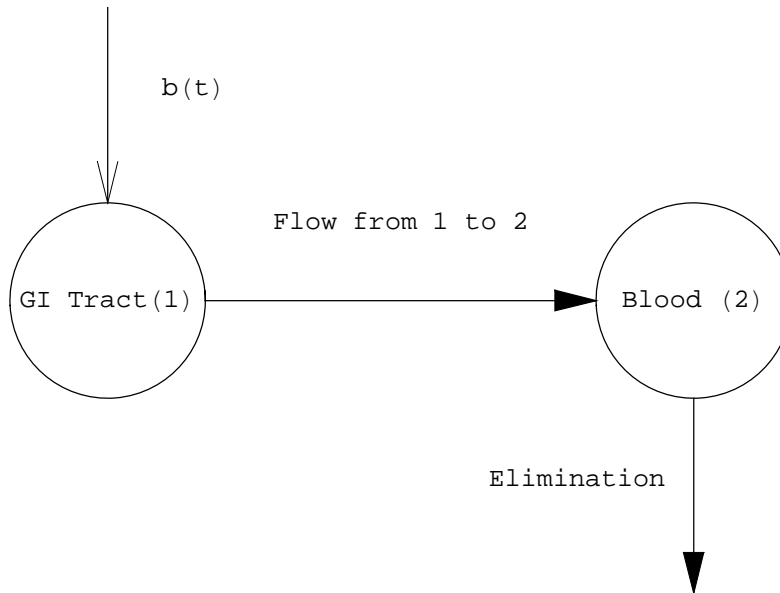
The procedure before described has been implemented at the function **DOptimize** includes in the package **Optdesign**.

DOptize[ R[t,  $\beta_1, \dots, \beta_p$ ], t, {{ $\beta_1, \beta_{10}$ }, ..., { $\beta_p, \beta_{p0}$ }}, t<sub>0</sub>, ρ, σ, n, opts] being  $\beta_1, \dots, \beta_p$  the unknown parameters and  $\beta_{10}, \dots, \beta_{p0}$  their the initial values, t<sub>0</sub> is the point were is takes the first measured, ρ (*relationship between samples that decays exponential*), usually will be used ρ=1 (it is assumed that there not correlation between samples will be written "NoCorrelation"); σ is the standard deviation of the measures, n is the number of the point (additional at t<sub>0</sub>) where we want to take measured; *opts* is a option to close the maximization method (The are the same that used by NMaximize). The function will give the values for {t<sub>0</sub>, ..., t<sub>i</sub>, ... t<sub>n</sub>}.

```
In[33]:= ? "Biokmod`Optdesign`"
```

## ■ Example

This Figure is represented an easy example of a two compartmental system. 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. It is suppose that  $b(t) = 2.1 \text{Exp}[-0.2 t]$ , with  $t$  en h. The rate transfers  $k_{12}$  and  $k_{20}$  are unknown. We wish to estimate  $k_{12}$  and  $k_{20}$  measuring the concentration in the compartment (2). It is assumed that the it will be taken 6 samples, the first at  $t_0 = 0.5$  h, and  $\sigma = 2$ .



```
In[34]:= Clear[x2, sol]
```

```
In[35]:= x2[t_, k12_, k20_] =
  x2[t] /. SystemDSolve[CompartmentMatrix[2, {{1, 2, k12}, {2, 0, k20}}],
    {0, 0}, {2.1 Exp[-0.2 t], 0}, t, t, x, Method -> "DSolve"] // Simplify;
```

Here it is used  $\rho = 1$ .

```
In[36]:= sol = DOptimize[x2[t, k12, k20], t, {{k12, 2}, {k20, 0.3}}, 0.5, 1, 2, 5]
Out[36]= {1.01445, {t0 -> 0.5, t1 -> 1.5, t2 -> 2.64805, t3 -> 6.44024, t4 -> 8.84565, t5 -> 11.4743}}
```

Here is assumed no correlation between samples

```
In[37]:= DOptimize[x2[t, k12, k20], t, {{k12, 2}, {k20, 0.3}}, 0.5, "NoCorrelation", 2, 5]
Out[37]= {1.88609, {t0 -> 0.5, t1 -> 1.5, t2 -> 2.5, t3 -> 7.36005, t4 -> 8.36005, t5 -> 9.36005}}
```

## Simulation

We are going to simulate the blood (compartment 2) measures in the moments predicted by the optimal design. It will be assumed that the real values of the "unknown" parameters are  $k_{12} = 2.3$  and  $k_{20} = 0.25$ .

```
In[38]:= gg[i_, j_] := Exp[-rho Abs[tj-1 - ti-1]]
```

```
In[39]:=  $\rho = 1$ ;  $\sigma = 2$ ;  $n = 5$ ;
```

```
In[40]:= covMatrix =  $\sigma^2$  Array[gg, {n + 1, n + 1}] /. sol[[2]];
```

---

The predicted  $x_2(t)$  in the moments  $\{t_0, \dots, t_n\}$  are

```
In[41]:= measuretime = Table[ti, {i, 0, n}] /. sol[[2]];
```

```
In[42]:= means = x2[measuretime, 2.3, 0.25]
```

```
Out[42]= {0.392796, 1.72684, 2.78285, 3.26867, 2.68012, 1.96011}
```

```
In[43]:= SeedRandom[10]
```

---

It is simulated 100 times the measures of  $x_2(t)$  at  $\{t_0, \dots, t_n\}$ . We will use the average of this values

```
In[44]:= sampledata = Transpose[{measuretime,
    Mean[RandomArray[MultinormalDistribution[means, covMatrix], 100]]}]
```

```
Out[44]= {{0.5, 0.510514}, {1.5, 1.7231}, {2.64805, 2.74308},
    {6.44024, 3.58085}, {8.84565, 2.61859}, {11.4743, 2.2243}}
```

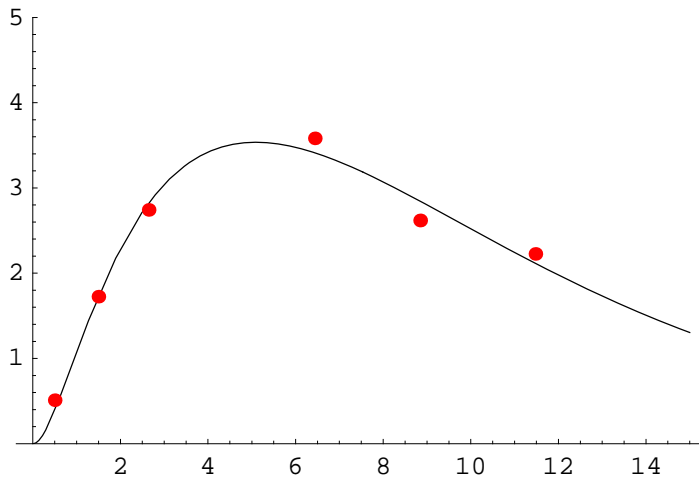
---

The best fit parameters are

```
In[45]:= fittedparameters =
    NonlinearRegress[sampledata, x2[t, k12, k20], {t}, {{k12, 1, 5}, {k20, 0.1, 0.5}}]
```

```
Out[45]= {BestFitParameters -> {k12 -> 2.26474, k20 -> 0.235025},
    ParameterCITable -> k12      Estimate      Asymptotic SE      CI
                             k20      0.235025      0.00891941        {0.210261, 0.25979}
    EstimatedVariance -> 0.0280586,
    ANOVATable -> Error      DF      SumOfSq      MeanSq
    Model      2      35.269      17.6345
    Uncorrected Total      6      35.3812
    Corrected Total      5      5.45259
    AsymptoticCorrelationMatrix -> ( 1.      -0.0955468
    -0.0955468  1. ),
    FitCurvatureTable -> Max Intrinsic      Curvature
    Max Parameter-Effects      0.155366
    95. % Confidence Region      0.560101
    0.379478
```

```
In[46]:= Plot[Evaluate[x2[t, k12, k20] /. fittedparameters[[1, 2]]], {t, 0, 15},
  Epilog -> {Hue[0.], PointSize[0.02], Map[Point, sampledata]}, PlotRange -> {0, 5}]
```



```
Out[46]= - Graphics -
```

```
In[47]:= Quit[]
```

# OPTIMAL DESIGNS TO STABLISH A BIOASSAY PROGRAM FOR PARAMETER ESTIMATIONS

Last version available at <http://web.usal.es/guillermo/biokmod>

Updated a 2006-04-15

*ICRP models describing the evolution of radioactive particles in the human body as function of some parameters are solved and studied for the case of both inhalation and ingestion intake . A general method is developed for the main situations. Optimal designs for the estimation of the unknown parameters are computed for such models. The goodness of the design will depend on the number of samples and the measurement accuracy, thus designs with support in different number of points are shown for some examples. Several computer routines are implemented and enclosed in a program called Optdesign.*

## ■ Inicialization

```
In[1]:= Needs["Statistics`ContinuousDistributions`"]
```

```

In[2]:= Needs["Biokmod`Biokdata`"]

Respract 1.2 b1 2005-05-16

SysModel, version 1.3. 2006-01-02

Humorap 3.3 b1 2005-06-17

Biokdata 1.2.2 2004-09-3

In[3]:= DOptimize[r_, t_, params_List, t0_, ρ_?NumericQ, sig_, n_, opts___] :=
Module[{β, initial, grad, s, vars, v, g, t1, d, tt, i, j, k, dd,
  ddd, X, ff, Γ, Σ, m, deter, bb}, {β, initial} = Transpose[params];
grad[s_, vars_List] := Function[{v}, D[s, v]] /@vars;
g[t1_] = grad[r, β] /. Thread[β → initial] /. t → t1 // ExpandAll
(*Reduce enormemente el tiempo de calculo*);
tt = Table[Subscript[t, i], {i, 0, n}];
dd = Table[Subscript[d, i], {i, n}]; Subscript[d, 0] = t0;
ddd = FoldList[Plus, Subscript[d, 0], dd];
X = g[ddd];
ff[i_, j_] := Which[i == j, 1, i < j, E^((-ρ) * Sum[Subscript[d, k], {k, i, j - 1}]),
  i > j, E^((-ρ) * Sum[Subscript[d, k], {k, j, i - 1}]);
Γ = Array[ff, {n + 1, n + 1}]; Σ = sig^2 * Γ;
m = X.Inverse[Σ].Transpose[X];
deter[(x_)? (VectorQ[#1, NumberQ] &)] := Det[m /. Thread[dd → x]];
bb = NMaximize[{deter[dd], Thread[dd > 1]}, dd, opts];
{bb[[1]], Thread[tt → ddd /. Last[bb]]}]

In[4]:= DOptimize[r_, t_, params_List, t0_, "NoCorrelation", sig_, n_, opts___] :=
Module[{β, initial, grad, s, vars, v, g, t1, d, tt, i, j, k, dd,
  ddd, X, ff, Γ, Σ, m, deter, bb}, {β, initial} = Transpose[params];
grad[s_, vars_List] := Function[{v}, D[s, v]] /@vars;
g[t1_] = grad[r, β] /. Thread[β → initial] /. t → t1 // ExpandAll
(*Reduce enormemente el tiempo de calculo*);
tt = Table[Subscript[t, i], {i, 0, n}];
dd = Table[Subscript[d, i], {i, n}]; Subscript[d, 0] = t0;
ddd = FoldList[Plus, Subscript[d, 0], dd];
X = g[ddd];
Σ = sig^2 * IdentityMatrix[n + 1];
m = X.Inverse[Σ].Transpose[X];
deter[(x_)? (VectorQ[#1, NumberQ] &)] := Det[m /. Thread[dd → x]];
bb = NMaximize[{deter[dd], Thread[dd > 1]}, dd, opts];
{bb[[1]], Thread[tt → ddd /. Last[bb]]}]

```

Needs["Biokmod`Optdesign`"] (\*DOptimize will be included in the package Optdesign\*)

## ■ Solving ICRP model as function of AMAD $p$ or a rate transfer factor $k$ .

In occasions after an accidental intake  $I$  of radioactive particles we need to estimate some parameters of the particles intaken (AMAD,  $f_1$ , etc). It can be made taken bioassay measures. **Optdesign** can be applied to establish the best moments where the bioassay measures should be taken. We will need known the  $R_m(I, k_1, \dots, k_p, t) = I r_m(I, k_1, \dots, k_p, t)$  as function of the parameters unknown. In the practical situations the typical parameters unknown are  $I$  and AMAD or  $f_1$ . In this cases we will need find the analytical solutions of the ICRP models as function of this parameters.

The predicted value  $r_m(t)$  of the retention function for a kind of bioassay  $m$  after an acute input  $I = "1"$  at  $t = 0$  is obtained by the sum of the content of one or several compartments. It will also a sum of exponentials. It can be shown in the following examples

### ICRP model solution as function of AMAD $p$

To obtain the solution as function of AMAD  $p$  we will use an approximation of the Initial Deposition Factor (IDF). The  $IDF_j(p)$  may be either calculated following the procedure described in ICRP 66 (1994) or obtained from Annex F of ICRP 66 (1994). ICRP 66 already gives the procedure to obtain what we call the Initial Deposition Derivate Factor or  $IDDF_k(p)$ .

#### Relation IDDF vs IDF

$$\begin{aligned}
 IDF_1(p) &= 0.3 IDDF_{AI}(p); \\
 IDF_2(p) &= 0.6 IDDF_{AI}(p) \\
 IDF_3(p) &= 0.1 IDDF_{AI}(p) \\
 IDF_4(p) &= 0.993 IDDF_{bb(\text{fast+sec})}(p) - 0.007 IDDF_{bb(\text{slow})}(p) \\
 IDF_5(p) &= IDDF_{bb(\text{slow})}(p) \\
 IDF_6(p) &= 0.007 IDDF_{bb(\text{fast+sec})}(p) + IDDF_{bb(\text{slow})}(p) \\
 IDF_7(p) &= 0.993 IDDF_{BB(\text{fast+sec})}(p) - 0.007 IDDF_{BB(\text{slow})}(p) \\
 IDF_8(p) &= IDDF_{BB(\text{slow})}(p) \\
 IDF_9(p) &= 0.007 IDDF_{BB(\text{fast+sec})}(p) + IDDF_{BB(\text{slow})}(p) \\
 IDF_{10}(p) &= 0.9995 IDDF_{ET2}(p) \\
 ET_{seq} IDF_{11}(p) &= 0.0005 IDDF_{ET2}(p) \\
 IDF_{12}(p) &= IDDF_{ET1}(p)
 \end{aligned}$$

We have found that the  $IDDF$  parameters in the range of interest of AMAD  $p$ , [0.5  $\mu\text{m}$ , 20  $\mu\text{m}$ ], for standard workers may be fitted using least squared estimators. This approximation is used by **AMADfit[p]**

```
In[5]:= {IDDFAI, IDDFbb(fast+seq), IDDFbbslow,
          IDDFBB(fast+seq), IDDFBBslow, IDDET2, IDDET1} = AMADfit[p];
```

```
In[6]:= IDDFAI
```

```
Out[6]= 0.128187 e-0.170111 p
```

Here it is shown the lung retention for an Adult worker as function of  $I$  and the AMAD  $p$  (type S and  $\lambda_R \rightarrow 0$ ), after an acute intake  $I$  at  $t=0$ . It will be used in example 1.

```
In[7]:= LungRetention[1, AMADfit[p], s, t, 0] // Chop
```

```
Out[7]= -2.67441 × 10-8 e-4.35327 p-110.1 t + 7.74325 × 10-8 e-1.11147 p-110.1 t -
0.0000170195 e-0.566783 p-110.1 t + 2.11792 × 10-8 e-0.170111 p-110.1 t -
1.15724 × 10-8 e-0.147244 p-110.1 t - 7.74325 × 10-8 e-0.123578 p-110.1 t -
2.4958 × 10-6 e-0.0878945 p-110.1 t + 0.0000170195 e-0.0577835 p-110.1 t -
1.85867 × 10-7 e-4.35327 p-102.1 t - 5.33384 × 10-7 e-0.170111 p-102.1 t -
8.04258 × 10-8 e-0.147244 p-102.1 t + 0.000012479 e-0.0878945 p-102.1 t +
0.0000213058 e-4.35327 p-100.13 t - 0.0000110618 e-1.11147 p-100.13 t +
9.21917 × 10-6 e-0.147244 p-100.13 t + 0.0000110618 e-0.123578 p-100.13 t +
0.0000388446 e-0.170111 p-100.12 t + 0.0000768046 e-0.170111 p-100.101 t +
0.0000106617 e-0.170111 p-100.1 t + 1.48693 × 10-7 e-4.35327 p-100.1 t -
7.74325 × 10-8 e-1.11147 p-100.1 t - 1.19977 × 10-7 e-0.566783 p-100.1 t +
2.13218 × 10-6 e-0.170111 p-100.1 t + 6.43406 × 10-8 e-0.147244 p-100.1 t +
7.74325 × 10-8 e-0.123578 p-100.1 t + 7.03752 × 10-8 e-0.0878945 p-100.1 t +
1.19977 × 10-7 e-0.0577835 p-100.1 t - 0.0000267709 e-4.35327 p-10.0001 t +
0.00007751 e-1.11147 p-10.0001 t - 0.0170366 e-0.566783 p-10.0001 t + 0.0000212004 e-0.170111 p-10.0001 t -
0.000011584 e-0.147244 p-10.0001 t - 0.00007751 e-0.123578 p-10.0001 t -
0.0024983 e-0.0878945 p-10.0001 t + 0.0170366 e-0.0577835 p-10.0001 t - 0.000186053 e-4.35327 p-2.0001 t -
0.000533918 e-0.170111 p-2.0001 t - 0.0000805063 e-0.147244 p-2.0001 t +
0.0124915 e-0.0878945 p-2.0001 t + 0.0213271 e-4.35327 p-0.0301 t - 0.0110729 e-1.11147 p-0.0301 t +
0.0092284 e-0.147244 p-0.0301 t + 0.0110729 e-0.123578 p-0.0301 t + 0.0388835 e-0.170111 p-0.0201 t +
0.0768815 e-0.170111 p-0.0011 t + 0.0106723 e-0.170111 p-0.00022 t + 0.000148842 e-4.35327 p-0.0001 t -
0.00007751 e-1.11147 p-0.0001 t - 0.000120097 e-0.566783 p-0.0001 t + 0.00213432 e-0.170111 p-0.0001 t +
0.000064405 e-0.147244 p-0.0001 t + 0.00007751 e-0.123578 p-0.0001 t +
0.0000704456 e-0.0878945 p-0.0001 t + 0.000120097 e-0.0577835 p-0.0001 t
```

### Biokinetic model for elements using ICRP 30 metabolic model structure

We will need the analytical expression of  $R_m(I, k, t)$ , where  $k$  represents any parameter of the model, is only possible in particular cases. However they are many practical situations in which it is feasible, in particular it can be obtained for models that do not involve recycling. This condition is verified for many ICRP models (ICRP 2001), all of them where is still applicable the ICRP 30 (1981) metabolic model structure represented in fig. 1.

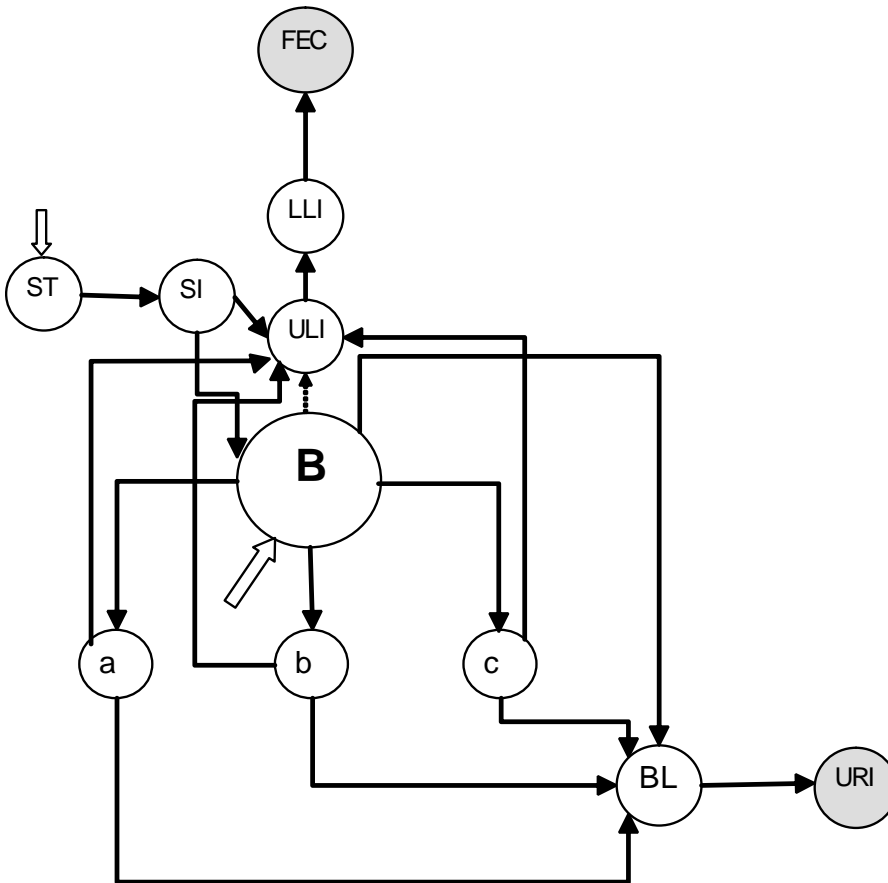


Fig 1 represents a diagram flow where are included all ICRP 30 elements. All elements have compartments B, LLI, ULI, BL and URI however the number of systemic compartments change (the maximum is three: a, b and c) depending on the element. The same happen of the flow.

Compartments numbers: Blood (1), **a** or SysA (2), **b** or SysB (3), **c** or SysC (4), Bladder (5), URI (6), ULI (7), LLI(8) and FEC(9). If a element has only 2 systemic compartments the numbers (since bladder) will decrease in minus 1

$f_u$  = fraction from Sys i to BL

$f_f$  = fraction from Sys i to ULI

$T_i = \{T_a, T_b, T_c\}$  where  $T_i = \text{Log}(2)/k_i$  with  $i = \{\text{SysA}, \text{SysB}, \text{SysC}\}$

$f_i = \{f_{SYA}, f_{SYB}, f_{SYC}\}$  fraction from compartment B to compartment  $i$ .

$f_R$  = fraction from compartment B. It must be verified  $f_R + \sum f_i = 1 \rightarrow f_R = 1 - \sum f_i$  (for same elements  $f_R=0$ )

$T_B = \text{Log}[2] / k_B$  where  $k_B$  = total rate transfer from B.

The information of  $\{f_u, f_f, T_i, f_i, \text{ and } T_B\}$  are summarized in Potter CA, Health Phys 83:775-779 (table E3).; 2002. "Metabolic parameters for elements using ICRP 30 metabolic model structure". Not always these match with ICRP 78 (i.e Cf-252).

The examples 2 and 3 shown the solution for cobalt

## ■ Examples

These examples, including the information about the method of the measurements (minimum detectable activity, precision, etc) are based in the report: Direct Method for Measuring Radionuclides in the Human Body. IAEA Safety Series No. 114. Vienna 1996.

### EXAMPLE 1 .- Lung counter applied to estimate the uranium intake / by inhalation (being / and the AMAD $p$ unknown)

A worker has accidentally intaken by inhalation an unknown  $I$  quantity of  $\text{UO}_2$  enriched 4.4 %  $^{235}\text{U}$  being the AMAD  $p$  also unknown. We wish to estimate  $I$  measuring the uranium lung content using a lung body counter. It will be assumed that the worker has not previously been exposed to significant uranium intakes.

*Note.- The enriched uranium is composed of  $^{234}\text{U}$ ,  $^{235}\text{U}$  and  $^{238}\text{U}$ . The lung counters usually measure only the  $^{235}\text{U}$  content. However, given that the isotopic composition is usually known then  $^{234}\text{U}$  and  $^{238}\text{U}$  can be derivated from the  $^{235}\text{U}$  measured. So for the enriched 4.4 %  $^{235}\text{U}$ , the activity for  $^{235}\text{U}$  is 3.5% this means that if it 3.5 Bq of  $^{235}\text{U}$  is measured with the lung counter then the uranium content will be 100 Bq. Also, the disintegration constants can be assumed "0" for all uranium isotopes because their half-live are too long*

The minimum detectable activity (MDA), according IAEA 1996 (VIII-5) of  $^{235}\text{U}$  is 7 – 14 Bq with phoswich detector and 4 – 6 Bq with array germanium detectors. Based in  $\text{MDA} = 3.3 \sigma$ , therefore that is  $\sigma$ : 1.2 – 1.8 Bq . We will assumed  $\sigma = 2$ .

To define the optimal design the first step to obtain the lung retention function  $R_{\text{Lung}}(I, p, t) = I r_{\text{Lung}}(t, p)$  for these kind of radioactive aerosols.

```
In[8]:= rlung[t_, p_] = LungsRetention[1, AMADfit[p], S, t, 0] // Chop
Out[8]= -2.67441 × 10-8 e-4.35327 p-110.1 t + 7.74325 × 10-8 e-1.11147 p-110.1 t -
0.0000170195 e-0.566783 p-110.1 t + 2.11792 × 10-8 e-0.170111 p-110.1 t -
1.15724 × 10-8 e-0.147244 p-110.1 t - 7.74325 × 10-8 e-0.123578 p-110.1 t -
2.4958 × 10-6 e-0.0878945 p-110.1 t + 0.0000170195 e-0.0577835 p-110.1 t -
1.85867 × 10-7 e-4.35327 p-102.1 t - 5.33384 × 10-7 e-0.170111 p-102.1 t -
8.04258 × 10-8 e-0.147244 p-102.1 t + 0.000012479 e-0.0878945 p-102.1 t +
0.0000213058 e-4.35327 p-100.13 t - 0.0000110618 e-1.11147 p-100.13 t +
9.21917 × 10-6 e-0.147244 p-100.13 t + 0.0000110618 e-0.123578 p-100.13 t +
0.0000388446 e-0.170111 p-100.12 t + 0.0000768046 e-0.170111 p-100.101 t +
0.0000106617 e-0.170111 p-100.1 t + 1.48693 × 10-7 e-4.35327 p-100.1 t -
7.74325 × 10-8 e-1.11147 p-100.1 t - 1.19977 × 10-7 e-0.566783 p-100.1 t +
2.13218 × 10-6 e-0.170111 p-100.1 t + 6.43406 × 10-8 e-0.147244 p-100.1 t +
7.74325 × 10-8 e-0.123578 p-100.1 t + 7.03752 × 10-8 e-0.0878945 p-100.1 t +
1.19977 × 10-7 e-0.0577835 p-100.1 t - 0.0000267709 e-4.35327 p-10.0001 t +
0.00007751 e-1.11147 p-10.0001 t - 0.0170366 e-0.566783 p-10.0001 t + 0.0000212004 e-0.170111 p-10.0001 t -
0.000011584 e-0.147244 p-10.0001 t - 0.00007751 e-0.123578 p-10.0001 t -
0.0024983 e-0.0878945 p-10.0001 t + 0.0170366 e-0.0577835 p-10.0001 t - 0.000186053 e-4.35327 p-2.0001 t -
0.000533918 e-0.170111 p-2.0001 t - 0.0000805063 e-0.147244 p-2.0001 t +
0.0124915 e-0.0878945 p-2.0001 t + 0.0213271 e-4.35327 p-0.0301 t - 0.0110729 e-1.11147 p-0.0301 t +
0.0092284 e-0.147244 p-0.0301 t + 0.0110729 e-0.123578 p-0.0301 t + 0.0388835 e-0.170111 p-0.0201 t +
0.0768815 e-0.170111 p-0.0011 t + 0.0106723 e-0.170111 p-0.00022 t + 0.000148842 e-4.35327 p-0.0001 t -
0.00007751 e-1.11147 p-0.0001 t - 0.000120097 e-0.566783 p-0.0001 t + 0.00213432 e-0.170111 p-0.0001 t +
0.000064405 e-0.147244 p-0.0001 t + 0.00007751 e-0.123578 p-0.0001 t +
0.0000704456 e-0.0878945 p-0.0001 t + 0.000120097 e-0.0577835 p-0.0001 t
```

DOptimize is used to define an n-point design taken as initial values  $t_0=0.5$ ,  $I_0=1000$ ;  $p_0=5$ ,  $\rho=1$

DOptimize[ R[t, $\beta_1,\dots,\beta_p$ ], t, {{ $\beta_1,\beta_{10}$ },...,{ $\beta_p,\beta_0$ }},  $t_0$ ,  $\rho$ ,  $\sigma$ , n, opts] being  $\beta_1,\dots,\beta_p$  the unknown parameters and  $\beta_{10},\dots,\beta_{p0}$  their initial values,  $t_0$  is the point where it takes the first measured,  $\rho$  (relationship between samples that decays exponential), usually will be used  $\rho=1$  (it is assumed that there is not correlation between samples will be written "NoCorrelation");  $\sigma$  is the standard deviation of the measures, n is the number of the point (additional at  $t_0$ ) where we want to take measured; *opts* is an option to close the maximization method (The are the same that used by NMaximize). The function will give the values for  $\{t_0,\dots, t_i, \dots, t_n\}$ .

Here it is computed the design for different n-points using  $\rho=1$ .

```
In[9]:= opdEj1 =
      Table[{n, DOptimize[inprlung[t, p], t, {{inp, 1000}, {p, 5}}, 0.5, 1, 2, n]},
            {n, 1, 5}] // TableForm

Out[9]//TableForm=
1      0.0000348044
      t0 → 0.5      t1 → 68.8843
2      0.0000695412
      t0 → 0.5      t1 → 64.8287      t2 → 73.4339
3      0.000104202
      t0 → 0.5      t1 → 61.2132      t2 → 69.3803      t3 → 77.5147
4      0.0001388
      t0 → 0.5      t1 → 57.6447      t2 → 65.5745      t3 → 73.206      t4 → 81.1226
5      0.000187885
      t0 → 0.5      t1 → 4.91858      t2 → 69.0165      t3 → 76.6538      t4 → 84.0747      t5 → 91.8442
```

Here it is assumed that there are not correlations between samples.

```
In[10]:= Table[{n, DOptimize[inprlung[t, p], t, {{inp, 1000}, {p, 5}},
      0.5, "NoCorrelation", 2, n]}, {n, 1, 5}] // TableForm

Out[10]//TableForm=
1      0.0000348044
      t0 → 0.5      t1 → 68.8843
2      0.0000696075
      t0 → 0.5      t1 → 68.2079      t2 → 69.5319
3      0.00010441
      t0 → 0.5      t1 → 68.1543      t2 → 69.1543      t3 → 70.1545
4      0.000139211
      t0 → 0.5      t1 → 67.2135      t2 → 68.3628      t3 → 69.3628      t4 → 70.3677
5      0.000201858
      t0 → 0.5      t1 → 1.5      t2 → 76.3821      t3 → 77.384      t4 → 78.5255      t5 → 79.5256
```

## Simulation and fitting data

We simulate the lung measured in the moment predicted by the optimal design assuming an "unknown" intake of 850 Bq of  $^{235}\text{U}$  with AMAD  $7\ \mu\text{m}$  in  $t=0$  (a random noise  $N(\mu=0, \sigma=2)$  is included).

```
In[11]:= uraniumLungRet[t_, int_, p_] := LungsRetention[int, AMADAdultW[p], s, t, 0];
In[12]:= SeedRandom[110]
In[13]:= daymeasured = Table[ti, {i, 0, 5}] /. opdEj1[[1, 5, 2, 2]]
Out[13]= {0.5, 4.91858, 69.0165, 76.6538, 84.0747, 91.8442}
```

Here is simulated the uncertainty of the measured system (it only simulates the uncertainties of the measured system)

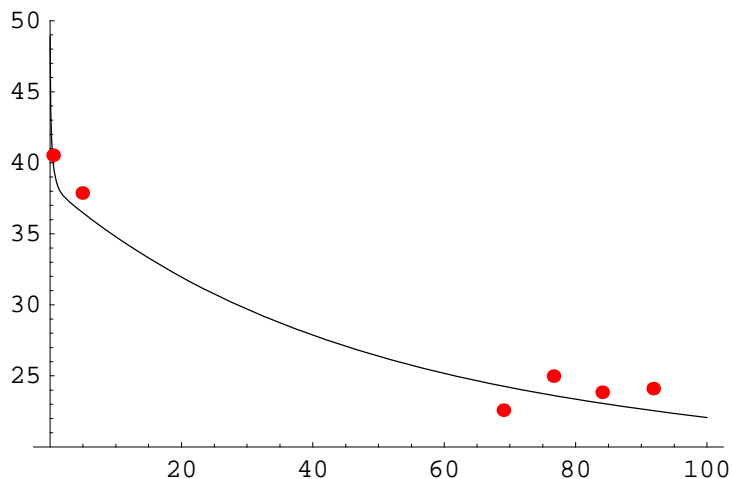
```
In[14]:= sampleLung = Map[
      {#, uraniumLungRet[#, 850, 7] + Random[NormalDistribution[0, 2]]} &, daymeasured]
Out[14]= {{0.5, 40.53}, {4.91858, 37.8725}, {69.0165, 22.579},
      {76.6538, 24.9874}, {84.0747, 23.8428}, {91.8442, 24.0999}}
```

The best fit parameters are

```
In[15]:= {inputAcute, pp} =
      {int, p} /. FindFit[sampleLung, int rlung[t, p], {{int, 500, 1000}, {p, 3, 10}}, t]
Out[15]= {571.787, 4.71393}
```

The agree between experimental and the fitted function is very good

```
In[16]:= Plot[Evaluate[uraniumLungRet[t, inputAcute, pp]], {t, 0, 100},
      Epilog -> {Hue[0.], PointSize[0.02], Map[Point, sampleLung]},
      PlotRange -> {20, 50}]
```



```
Out[16]= - Graphics -
```

### EXAMPLE 2 .- Whole body counter applied to estimation of $^{60}\text{Co}$ intake by ingestion (being $I$ and the AMAD $f_1$ unknown)

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

The minimum detectable activity (MDA), according IAEA 1996 (Table V-1) of  $^{60}\text{Co}$  is 28 Bq. Based in  $\text{MDA} = 3.3 \sigma$ , therefore that is  $\sigma = 8.5 \text{ Bq}$ . We will assumed  $\sigma^2 = 72$ .

#### Obtaining the whole body retention function

```
In[17]:= CompartNumbers[cobalt]
```

```
Out[17]//TableForm=
  1    Blood
  2    Systemic A
  3    Systemic B
  4    Systemic C
  5    Bladder
  6    Urine
  7    ULI
  8    LLI
  9    FEC
```

The GI compartments much be added

Bladder (n-4) to urine(n-3)	$k[n-4, n-3] \rightarrow$	12
ULI (n-2) to LLI(n-1)	$k[n-2, n-1] \rightarrow$	$k_{ULI}$
LLI (n-1) to FEC(n)	$k[n-1, n] \rightarrow$	$k_{LLI}$
SI (n+1) to ULI(n-2)	$k[n+1, n-2] \rightarrow$	$k_{SI}$
ST (n+2) to SI (n+1)	$k[n+2, n+1] \rightarrow$	$k_{ST}$
SI (n+1) to B(1)	$k[n+1, 1] \rightarrow$	$f_B k_{SI}$

Then the cobalt compartmental matrix is

```
In[18]:= cobaltextended =
  Join[icrp30Model[6/7, 1/7, {6, 60, 800}, {3/10, 1/10, 1/10}, 1/2],
  {{11, 10, kST}, {10, 1, fB kSI}, {10, 7, kSI}} /. Rationalize[Options[qGI]];
```

The content in each compartment, for  $I = 1$ , is given by

```
In[19]:= {q1[t_], q2[t_], q3[t_], q4[t_],
  q5[t_], q6[t_], q7[t_], q8[t_], q9[t_], q10[t_], q11[t_]} =
  MatrixExp[CompartMatrix[11, cobaltextended], t].{0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 1};
```

The whole body content as function of  $f_1$  and  $t$  is (note are obtained sum all compartment content except compartment 6 (urine) and 9 (fecal))

```
In[20]:= rWBCo[t_, fn1_] = Block[{f1 = fn1},
  Plus@@{q1[t], q2[t], q3[t], q4[t], q5[t], q7[t], q8[t], q10[t], q11[t]}];
```

DOptimize[{ $I r_{wb}(t, f_1)$ ,  $I, f_1, t$ },  $I_o, f_{10}, t_0, \rho, \sigma^2, n-1$ ] is used to define a  $n$ -point design taken as initial values  $t_0=0.5$ ,  $I_o=10000$  (this parameter can be modified and the solution will be the same);  $f_1 = 0.1$ ,  $\rho = 1$ , and  $\sigma = 10$ . It has been account that for  $^{60}\text{Co}$   $\lambda_R = \text{Log}[2]/(5.27*365.24)$ .

The 3-point D-optimal designs for values of  $f_j = \{0.05, 0.1, 0.15, 0.2\}$  are obtained proving that the optimal designs are very robust respect to the election of the initial value for parameter  $f_1$

Here it is computed 4-point D-optimal designs. The solution is very robust

```
In[21]:= opdEj2 = Table[{f1, DOptimize[inp rWBCo[t, fn1] Exp[-Log[2] / (5.27 * 365.24) t], t,
  {{inp, 10000}, {fn1, f1}}, 0.5, 1, 10, 3]}, {f1, 0.05, 0.2, 0.05}] // TableForm
```

```
Out[21]//TableForm=
```

0.05	2824.84	$t_0 \rightarrow 0.5$	$t_1 \rightarrow 3.69992$	$t_2 \rightarrow 6.17856$	$t_3 \rightarrow 9.34202$
	2829.56	$t_0 \rightarrow 0.5$	$t_1 \rightarrow 3.67219$	$t_2 \rightarrow 6.15028$	$t_3 \rightarrow 9.31308$
0.1	2835.39	$t_0 \rightarrow 0.5$	$t_1 \rightarrow 3.64437$	$t_2 \rightarrow 6.12189$	$t_3 \rightarrow 9.28403$
0.15	2842.37	$t_0 \rightarrow 0.5$	$t_1 \rightarrow 3.61649$	$t_2 \rightarrow 6.09345$	$t_3 \rightarrow 9.2549$
0.2					

## Fitting data

```
In[22]:= Clear[daymeasured, sampleWB, inputAcute, ff1]
```

---

We simulate the whole body measured in the moment predicted by the optimal design assuming an "unknown" intake of 25000 Bq of  $^{60}\text{Co}$  in  $t = 0$  with  $f_1 = 0.15$  (a random noise  $N(\mu=0, \sigma = 10)$  is included).

```
In[23]:= SeedRandom[110]
```

```
In[24]:= daymeasured = Table[t_i, {i, 0, 3}] /. opdEj2[[1, 4, 2, 2]]
```

```
Out[24]= {0.5, 3.61649, 6.09345, 9.2549}
```

---

Here is simulated the uncertainty of the measured system

```
In[25]:= sampleWB =
  Map[{-#, 25000 rWBCo[#, 0.15] + Random[NormalDistribution[0, 10]]} &, daymeasured]
```

```
Out[25]= {{0.5, 22926.5}, {3.61649, 3161.3}, {6.09345, 1497.38}, {9.2549, 1172.16}}
```

---

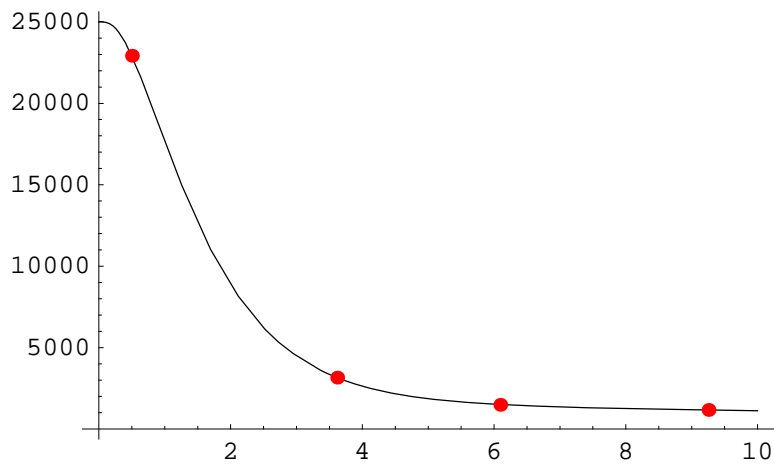
The best fit parameters are

```
In[26]:= {inputAcute, ff1} = {int, f1} /.
  FindFit[sampleWB, int rWBCo[t, f1], {{int, 1000, 5000}, {f1, 0.05, 0.2}}, t]
```

```
Out[26]= {24997.1, 0.149949}
```

The agree between experimental and the fitted function is very good

```
In[27]:= Plot[inputAcute rWBCo[t, ff1], {t, 0, 10},
  Epilog -> {Hue[0.], PointSize[0.02], Map[Point, sampleWB]}]
```



```
Out[27]= - Graphics -
```

### EXAMPLE 3 .- Whole body counter applied to estimation of $^{60}\text{Co}$ intake by inhalation (being $I$ and the AMAD $p$ unknown)

An operator has been exposed to an simple accidental intake by inhalation of  $^{60}\text{Co}$ , we wish estimate the intake  $I$  and the AMAD  $p$ , it is take  $f_1 = 0.1$ . A program of in-vivo monitoring using an whole body counter must be defined

The first step is get the whole body retention for  $^{60}\text{Co}$ , it can be do as it follows

```
In[28]:= cobaltwb[t_] = qWholebody[t] /.
  BiokdataReport[cobalt, "Inhalation", "Acute", "Automatic", 1, {AI, bbfast+seq,
  bbslow, BBfast+seq, BBslow, ET2, ET1}, S, 0.1, t, Log[2] / (5.27 * 365.24)];
```

```
In[29]:= {AI, bbfast+seq, bbslow, BBfast+seq, BBslow, ET2, ET1} = AMADfit[p];
```

```
In[30]:= coWB[t_, p_] = ExpandAll[cobaltwb[t]] // Chop;
```

Here it is to obtain a 5-points design. The first measure is taken at  $t = 0.5$  and  $\sigma = 10$  Bq

```
In[31]:= DOptimize[inp coWB[t, p], t, {{inp, 1000}, {p, 5}}, 0.5, 1, 10, 4]
```

```
Out[31]= {0.0156046, {t0 → 0.5, t1 → 4.2437, t2 → 8.05711, t3 → 12.2675, t4 → 17.165}}
```