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Measurement of Cerebral Metabolic Rates of Glucose CMR_{glc} with [^{18}F]FDG PET

A Practical Introduction with References

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Background: the Irreversible Model for Deoxyglucose

- Sokoloff, L.; Reivich, M.; Kennedy, C.; Des Rosiers, M.H.; Patlak, C.S.; Pettigrew, K.D.; Sakurada, O.; Shinohara, M. The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J. Neurochem. 28 (1977), 897 - 916.
- Reivich, M.; Kuhl, D.; Wolf, A.; Greenberg, J.; Phelps, M.; Ido, T.; Casella, V.; Fowler, J.; Hoffman, E.; Alavi, A.; Som, P.; Sokoloff, L. The [^{18}F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. Circ. Res. 44 (1979), 127 - 137.

Combined Forward Rate Constant $$K_I = \frac{K_1 \cdot k_3}{k_2 + k_3}$$

Cerebral Metabolic Rate of Glucose $$CMR_{glc} = \frac{C_p}{LC} \cdot K_I$$

Value of the Lumped Constant $$LC = 0.48$$

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‘Gold Standard’ Measurement of CMR_{glc} for Clinical Research

- Hu, M.T.M.; Taylor-Robinson, S.D.; Ray Chaudhuri, K.; Bell, J.D.; Labbé, C.; Cunningham, V.J.; Koepp, M.J.; Hammers, A.; Morris, R.G.; Turjanski, N.; Brooks, D.J. Cortical dysfunction in non-demented Parkinson's disease patients: A combined ^{31}P-MRS and ^{18}FDG-PET study. Brain 123 (2000), 340 - 352.
- Edison, P.; Archer, H.A.; Hinz, R.; Hammers, A.; Pavese, N.; Tai, Y.F.; Hotton, G.; Cutler, D.; Fox, N.; Kennedy, A.; Rossor, M.; Brooks, D.J. Amyloid, hypometabolism, and cognition in Alzheimer disease. An [^{11}C]PIB and [^{18}F]FDG PET study. Neurology 68 (2007), 501 - 508.

Protocol used

1. 60 min dynamic acquisition following intravenous bolus administration of [^{18}F]FDG.
2. Continuous monitoring of the arterial whole blood activity concentration with high temporal resolution.
3. On a set of discrete blood samples: measurement of the blood and plasma activity concentration and assay of the plasma glucose concentration.

Analysis performed

1. Generation of the [^{18}F]FDG arterial plasma input function.
2. Calculation of parametric maps of K_I using Spectral Analysis.
3. Conversion of the K_I images into CMR_{glc} images.

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The Use of a Standard Input Function

- Takikawa, S.; Dhawan, V.; Spetsieris, P.; Robeson, W.; Chaly, T.; Dahl, R.; Margouleff, D.; Eidelberg, D. Noninvasive quantitative fluorodeoxyglucose PET studies with an estimated input function derived from a population-based arterial blood curve. Radiology 188 (1993), 131 - 136.
- Shiozaki, T.; Sadato, N.; Senda, M.; Ishii, K.; Tsuchida, T.; Yonekura, Y.; Fukuda, H.; Konishi, J. Noninvasive estimation of FDG input function for quantification of cerebral metabolic rate of glucose: optimization and multicenter evaluation. J. Nucl. Med. 41 (2000), 1612 - 1618.
- Lewis, J.; Asselin, M.-C.; Herholz, K.; Hinz, R. Assessment of standard input functions for dynamic FDG brain PET. University of Manchester Biomedical Imaging Institute 3rd Annual Showcase, 8th Nov 2011, Poster 13.

See previous presentation *Input functions in PET* at

http://personalpages.manchester.ac.uk/staff/Rainer.Hinz/material/petif06.html

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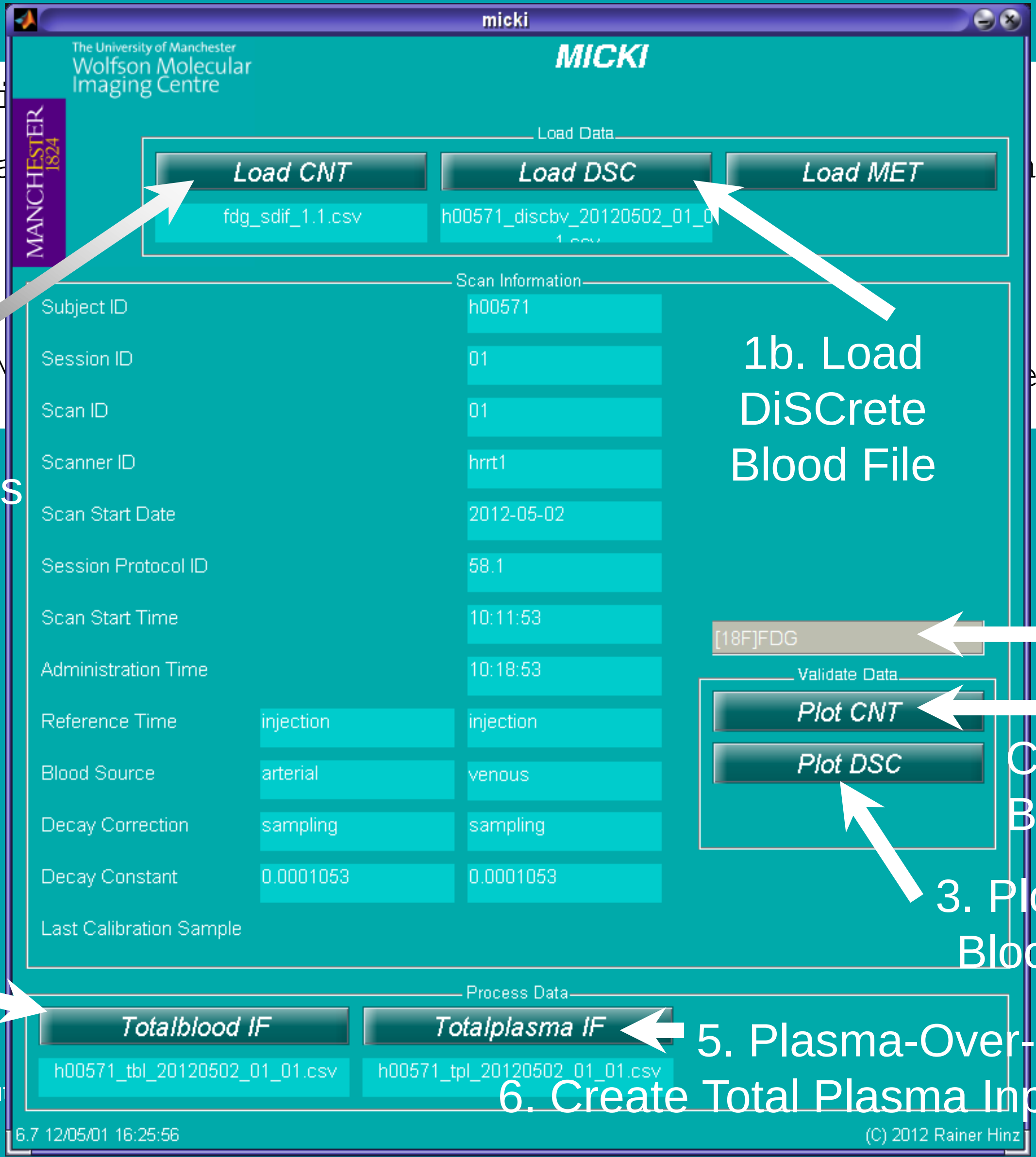
Step 1: Invoke MICKI and Load Data

For Solaris/Li

mmic-sun2:~/da … /micki &

For Windows:

S:\rhinz\data\ … exe



1a. Load CoNTinuous Blood File

1b. Load DiSCrete Blood File

1c. Select $[^{18}F]FDG$

2. Plot CoNTinuous Blood Curve

3. Plot DiSCrete Blood Samples

4. Create Whole Blood Input Function

5. Plasma-Over-Blood Ratio

6. Create Total Plasma Input Function

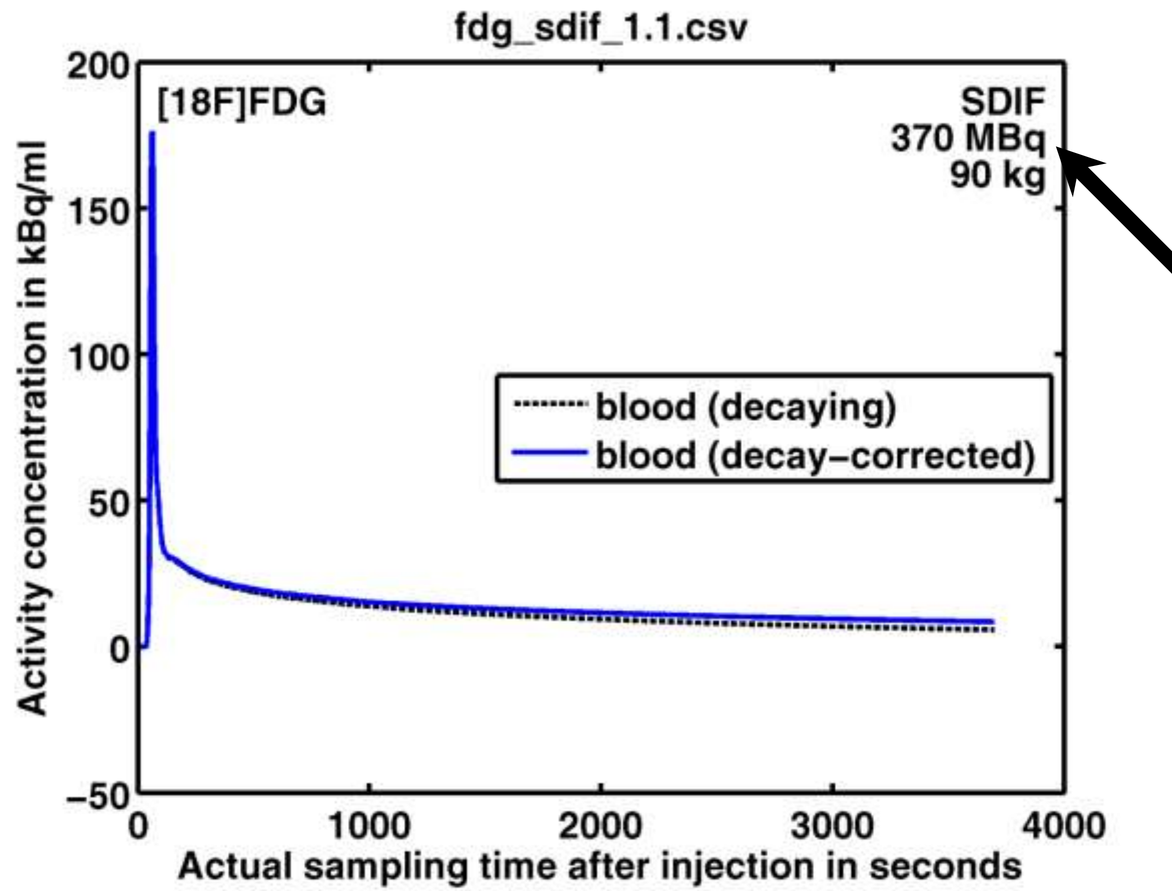
Step 2: Plot Continuous Blood Curve

```
{
# system identification
software_name        = micki.m
software_version     = 6.7
matlab_version       = 7.9.1.671 (R2009b) Service Pack 1 - deployed
                                                  c-sun2 (SunOS 5.10

                                                  Inc. Java HotSpot(TM) 64-Bit

                                                  /fdg/h00571

                                                  .1.csv" read.
                                                  iscbv_20120502_01_01.csv" read.
```



1. Enter dose from protocol
2. Enter body weight of subject scanned

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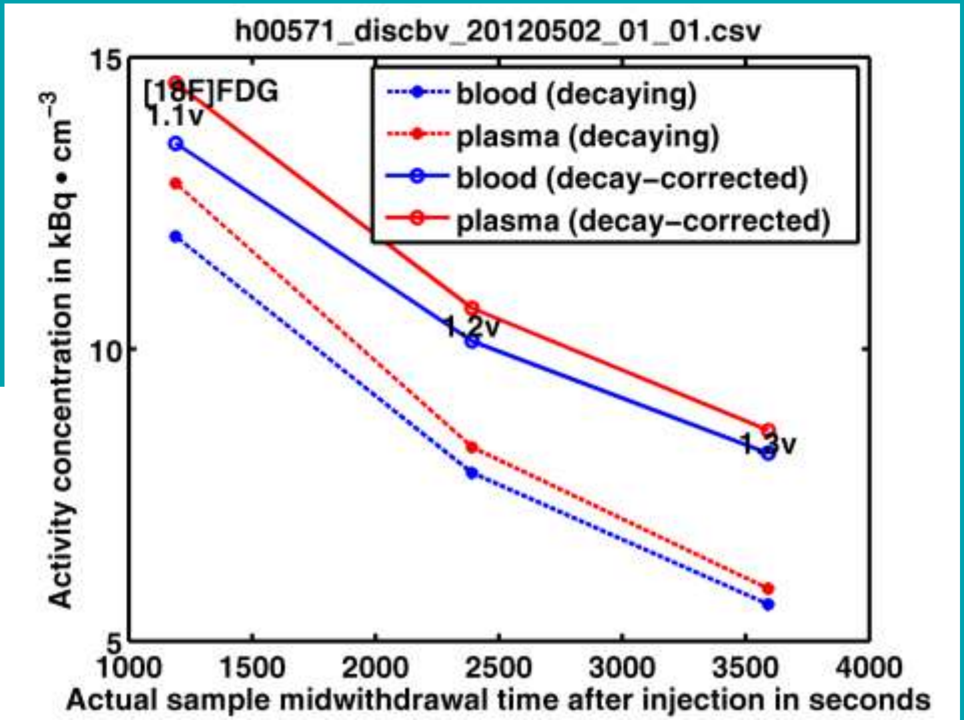
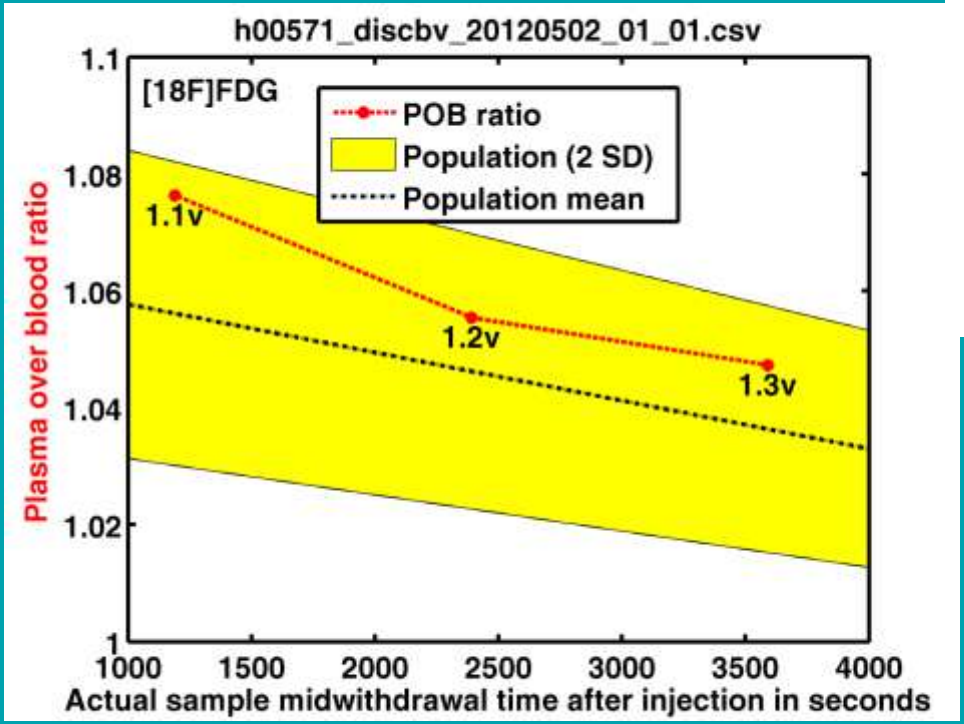
Step 3: Plot Discrete Blood Samples

1. Measured Activity Concentrations





2. Plasma-Over-Blood Ratios on top of a historic data base from 69 scans (mostly arterial samples)

Step 4: Create Whole Blood Input Function

****************** STANDARD INPUT FUNCTION SCALE FACTORS *******************

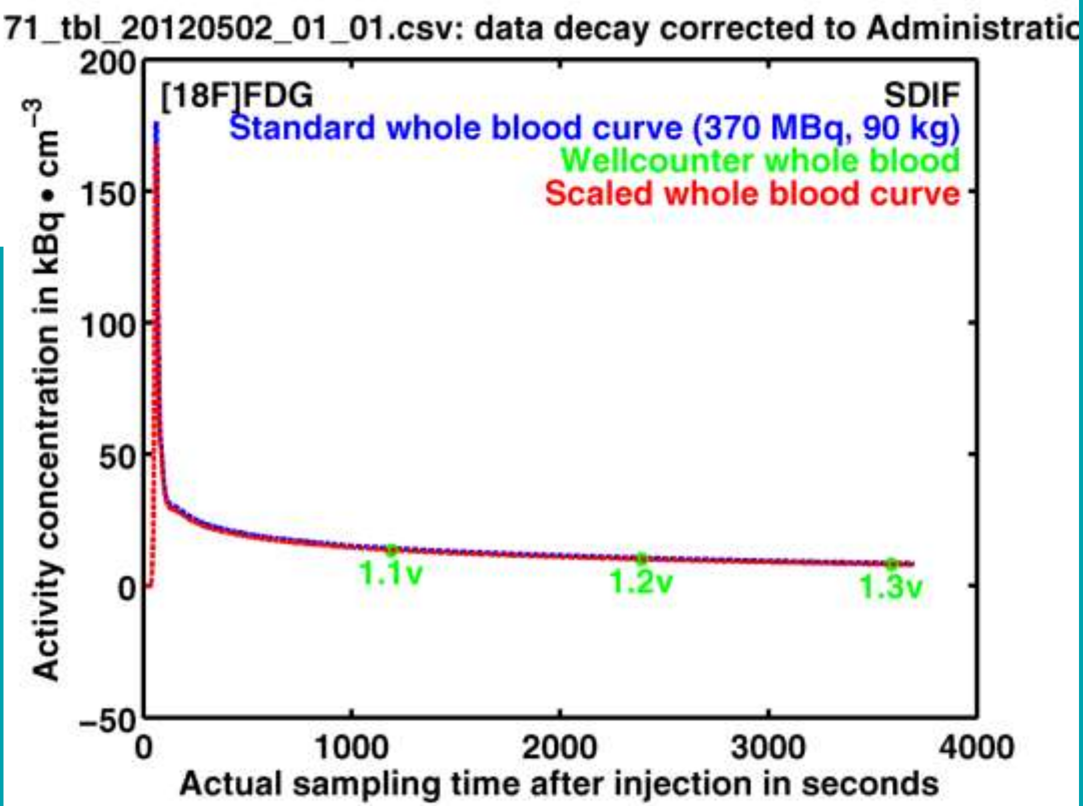
wc.time	wc.blood	time	blood	sf_wb	c
1189.5	13.5235	1189	14.3317	0.943607	0
2390.5	10.1368	2390	10.6707	0.949965	1
3590.5	8.21679	3590	8.63504	0.951564	1

NOTE: code= 1 stands for data points selected for fitting

==============================

Scale factor whole bl.: 0.950765

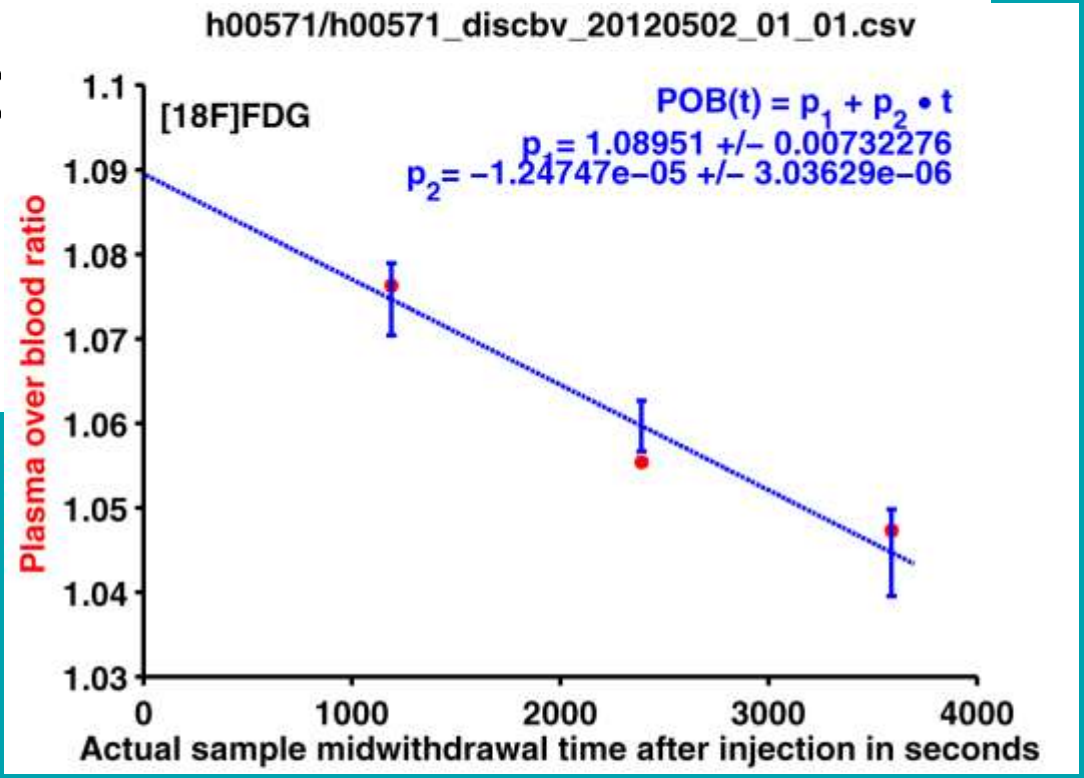
==============================



1. Blue curve: scaled using injected dose and body weight only (Shiozaki et a., 2000)
2. Red curve: scaled using the discrete whole blood activity measurements from 37.5 min p.i. onwards (Takikawa et al., 1993)

Step 5: Plasma-Over-Blood Ratio

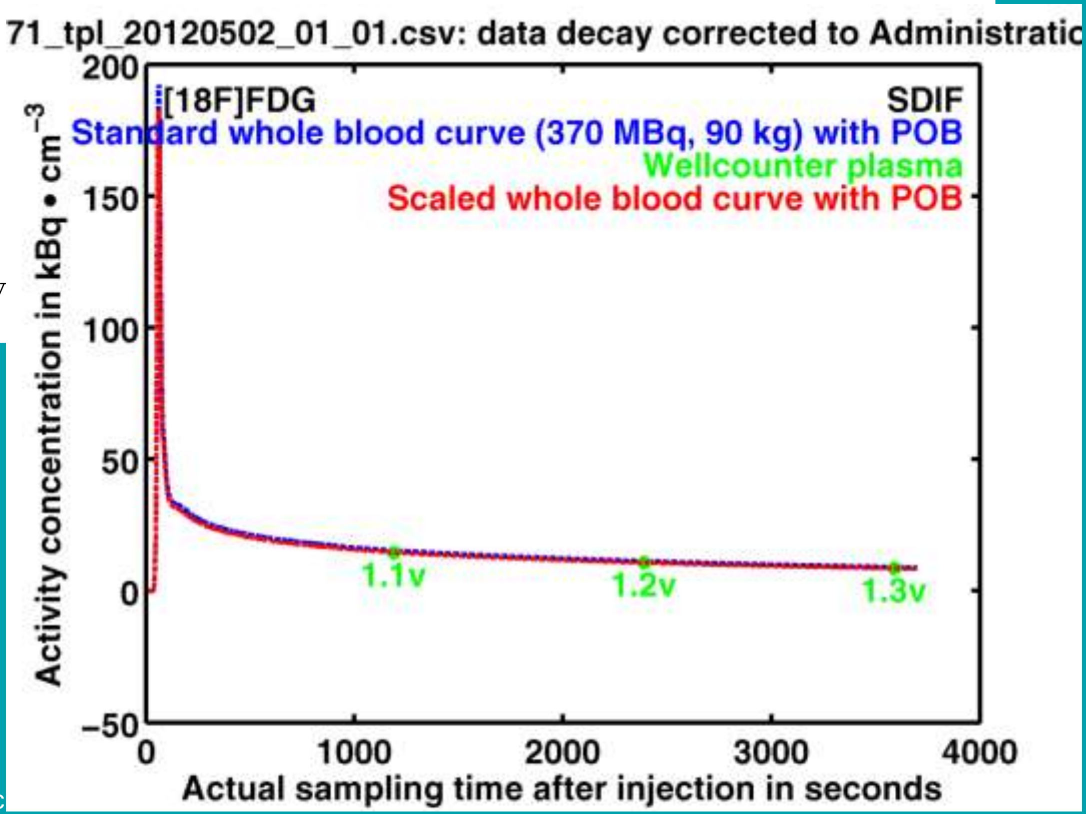
```
**************************    PLASMA-OVER-BLOOD MODEL    **************************

         i           d           w  c
    1189.5     1.07631     6.05143  2
    2390.5     1.05543     4.67271  2
    3590.5     1.04731     3.83214  2

   NOTE: code= 2 stands for data points selected for fitting

 ==============================

 res sum squares...... 1.2683016599
 res mean square...... 1.2683016599
 degrees freedom...... 1

 ==============================

  0 --- 1.0895071332210E+00   +/-
  1 --- -1.2474694722886E-05   +/-
```



Straight line fit of all measured samples: slope ≈ $-1 \cdot 10^{-5}\ s^{-1}$

Step 6: Create Total Plasma Input Function


```
Agreement between the discrete plasma samples and the plasma input function

     wc.time       wc.plasma     inpfn.time   inpfn.plasma   wc.plasma/inpfn.plasma
      1189.5         14.5555           1189        14.6436        0.993984
      2390.5         10.6987           2390        10.7509         0.99514
      3590.5         8.60556           3590        8.57706         1.00332


Administration Time (DSC)  -  Scan Start Time (DSC) = 420.000 s
"h00571_tpl_20120502_01_01.csv" written.
"h00571_01_01_cnt.fig" saved.
"h00571_01_01_dsc.fig" saved.
"h00571_01_01_pob.fig" saved.
"h00571_01_01_tbl.fig" saved.
"h00571_01_01_pobfit.fig" saved.
"h00571_01_01_tpl.fig" saved.

Plain text file "micki_6.7.log" sav
```



1. Blue curve: scaled using injected dose and body weight only (Shiozaki et a., 2000)
2. Red curve: scaled using the discrete samples (Takikawa et al., 1993) – double that check plasma scale factors are 0.99 … 1.01

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The Estimation of the Combined Forward Rate Constant

In the first instance, developed for region of interest (ROI) analysis

- Gjedde, A. High- and low-affinity transport of D-glucose from blood to brain. J. Neurochem. 36 (1981), 1463 - 1471.
- Patlak, C.S.; Blasberg, R.G.; Fenstermacher, J.D. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J. Cereb. Blood Flow Metab. 3 (1983), 1 - 7.
- Patlak, C.S.; Blasberg, R.G. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J. Cereb. Blood Flow Metab 5 (1985), 584 - 590.
- Wong, D.F.; Gjedde, A.; Wagner, H.N. Jr. Quantification of neuroreceptors in the living human brain. I. Irreversible binding of ligands. J. Cereb. Blood Flow Metab. 6 (1986), 137 - 146.
- Cunningham, V.J.; Jones, T. Spectral analysis of dynamic PET Studies. J. Cereb. Blood Flow Metabol. 13 (1993), 15 - 23.
- Turkheimer, F.; Moresco, R.M.; Lucignani, G.; Sokoloff, L.; Fazio, F.; Schmidt, K. The use of spectral analysis to determine regional cerebral glucose utilization with positron emission tomography and [^{18}F]fluorodeoxyglucose: theory, implementation, and optimization procedures J. Cereb. Blood Flow Metab. 14 (1994), 406 - 422.

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The Estimation of the Combined Forward Rate Constant

Modifications and extensions for the generation of parametric images of K_I

- Blomqvist, G. On the construction of functional maps in positron emission tomography. J. Cereb. Blood Flow Metab. 4 (1984), 629 - 632.
- Tadokoro, M.; Jones, A.K.P.; Cunningham, V.J.; Sashin, D.; Grootoonk, S.; Ashburner, J.; Jones, T. Parametric images of ^{11}C-diprenorphine binding using spectral analysis of dynamic PET images acquired in 3D. *In*: Quantification of Brain Function: Tracer Kinetics and Image Analysis in Brain PET (Uemura K, Jones T, Lassen NA, Kanno I, eds), New York: Excerpta Medica, 289 - 294.
- Turkheimer, F.E.; Aston, J.A.D.; Asselin, M.-C., Hinz, R. Multi-resolution Bayesian regression in PET dynamic studies using wavelets. Neuroimage 32 (2006), 111 - 121.
- Hinz, R.; Edison, P.; Brooks, D.J.; Turkheimer, F.E. Multi-resolution Bayesian regression for parametric imaging of [^{18}F]FDG brain studies. J. Cereb. Blood Flow Metab. 27 (2007), Supplement 1, PO04-04U.

See full presentation *Multi-resolution Bayesian regression for parametric imaging of [^{18}F]FDG brain studies* at

http://personalpages.manchester.ac.uk/staff/Rainer.Hinz/material/osaka07.html

Conversion of K_i images into CMRglc images

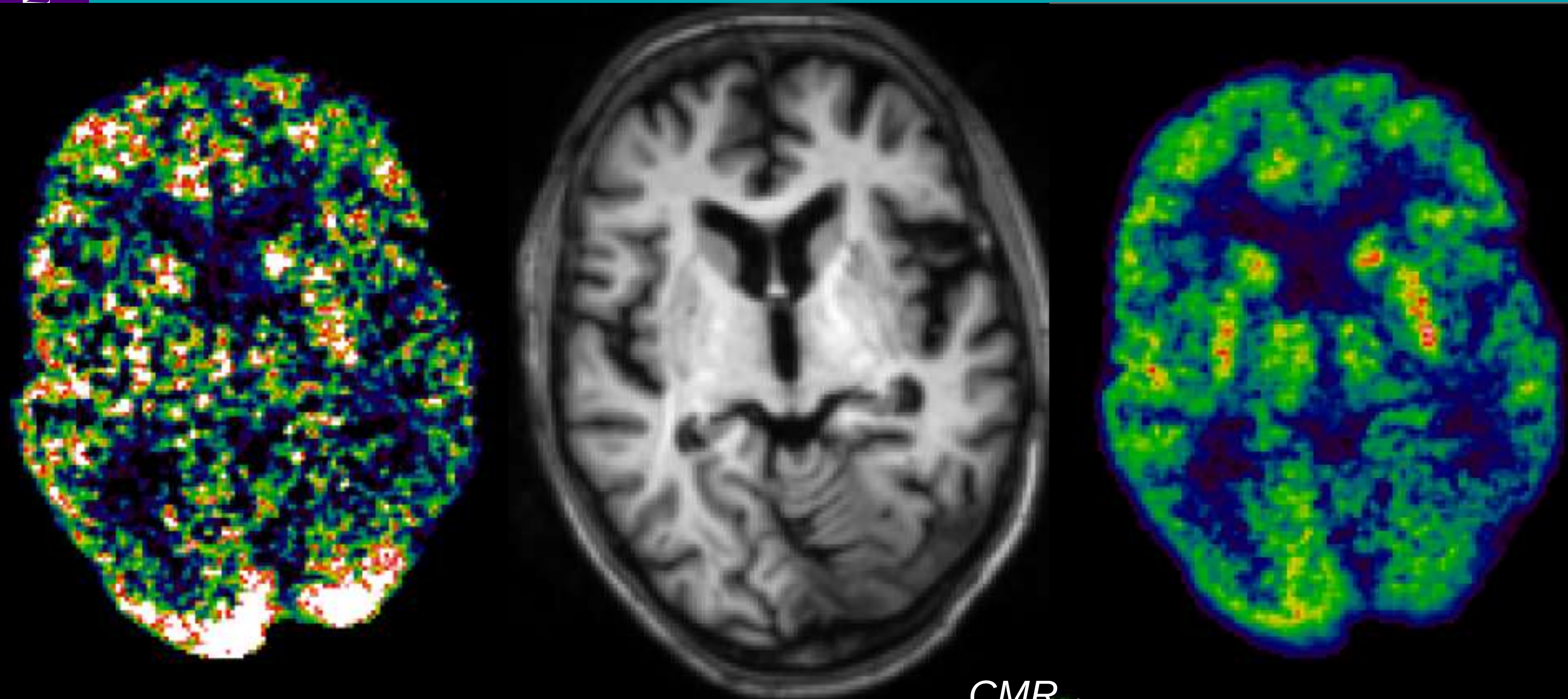
```
For Solaris/Linux:
mmic-sun2:~/data/fdg/t00321>  cmrgima t00321_45min.hdr

Input file     : "t00321_45min.hdr" (type 0)
  ROIScale     = 3.0592648e-08 = 0x330364f9 (single precision)
  cal_max      = 1.0024293e-03 = 0x3a8363f2 (single precision)

Enter Plasma Glucose Samples in Millimolar Units (concentration in mmol/l):
*** press Ctrl-D (^D) to finish input ***
   Sample 0    = 5.70
   Sample 1    = 5.54
   Sample 2    = 5.50
   Sample 3    = 5.36
   Sample 4    = 5.50
   Sample 5    = done.
    Mean       =  5.52000000000000e+00 mmol/l
    Lumped Con= 0.48
  Output Image= Input Image *  1.15000000000000e+01 * 60
  ROIScale     =  2.11089271200000e-05 (double precision)
  cal_max      =  6.91676217000000e-01 (double precision)

Output files   : "./t00321_45min_cmrg.img" -> written.
                 "./t00321_45min_cmrg.hdr" -> written.
  ROIScale     = 2.1108926e-05 = 0x37b11313 (single precision)
  cal_max      = 6.9167620e-01 = 0x3f3111b1 (single precision)
```

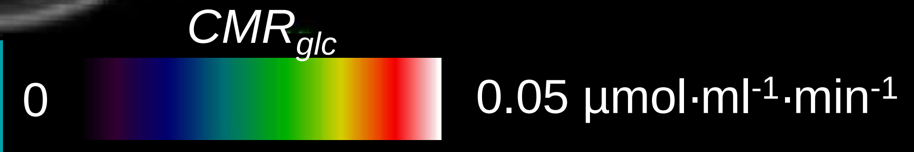
http://personalpages.manchester.ac.uk/staff/Rainer.Hinz/material/toolshelp.html#cmrgima

CMRglc measured on the HRRT in Manchester

Graphical Analysis (Gjedde-Patlak Plot), Slope
(5 frames: 35 min … 60 min, 5 % blood volume)

Spectral Analysis,
45 min Impulse Response Function (IRF)
(28 frames)





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