

*PET, parametric imaging, dynamic imaging,  
image processing*

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## **PARAMETRIC IMAGING IN DYNAMIC GLUCOSE METABOLISM STUDIES IN BRAIN**

Parametric imaging is more and more popular in dynamic brain studies. It enables to quantitatively or semi-quantitatively estimate physiological state and processes in brain. This work analyse the dynamic 18FDG-PET studies for estimation of brain glucose metabolism. The influence of the signal noise is analysed to estimate its influence on the final glucose metabolism parameter values. The LCMRGlc parameter is under investigation. It is based on three compartmental model proposed by Phelps. Using different 18FDG-PET data series obtained from independent sources the Gaussian noise was introduced (with different variance). Then the quality of the model fitting results were estimated. The final results clearly indicates than the noise is highly compensated in microparameter used in calculation of LCMRGlc. Concluding, it is possible to estimate the LCMRGlc parameter value even in the presence of noise.

### 1. INTRODUCTION

The application of positron emitting glucose 18FDG with Positron Emission Tomography enables to analyse regional glucose metabolism. This study is focus on brain tissue metabolism. The isotope activity measured by PET scanner enables to calculate its spatial distribution and present it as an image. However, it is also possible to measure a series of images in time and generate a set of one dimensional signals. Those signals represents 18FDG kinetics, as a response on excitation. Using mathematical model it is then possible to estimate a tissue fractional uptake of 18FDG and later a regional metabolic rate of glucose. Model micro or macro parameters (as well as derived parameters) may be used to construct parametric images. Those image represent spatial distribution of a parameter values, and can be used as a valuable information in diagnosis.

The goal of this work is to analyse the influence of noise in estimation of semi-quantitative value of a regional metabolic rate of glucose parameter.

#### 1.1. MODEL

In 18FDG-PET studies the most popular mathematical modelling uses three compartmental model [3][1]. Our studies are based on four rate constants model (fig. 1).

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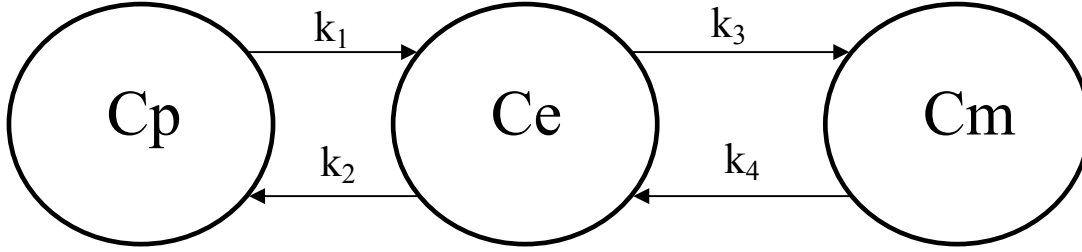


Fig. 1. Three compartment, four rate constant model of the 18FDG metabolism in a brain

The compartmental model represents: concentration of 18FDG in plasma –  $C_p$ , concentration of 18FDG in tissue –  $C_e$  and concentration of 18FDG-6-P (Fluorodeoxyglucose-6-phosphate) in tissue -  $C_m$ . The rate constants describe:  $k_1$ (ml/min/g) – 18FDG transport rate from plasma through brain-blood barrier (BBB) to brain tissue,  $k_2$ (1/min) – reverse rate (to  $k_1$ ),  $k_3$ (1/min) – phosphorylation rate,  $k_4$ (1/min) - de phosphorylation rate. Radioactivity measured by PET scanner  $C_t$  can be described as:

$$C_t = C_e + C_m + V_p C_p \quad (1)$$

where:

$V_p$  (ml/g) – fractional volume of plasma in vessel;

$C_p, C_e, C_m$  as above.

Based on the assumed compartmental model we can describe the measured signal as [3]

$$C_t = \frac{k_1}{(a_2 - a_1)} \left[ (k_3 + k_4 - a_1) e^{-a_1 t} + (a_2 - k_3 - k_4) e^{-a_2 t} \right] \otimes C_p(t) + V_p C_p(t) \quad (2)$$

where:

$\otimes$  - convolution operator,

$a_1$  and  $a_2$  are given by:

$$a_1 = [k_2 + k_3 + k_4 - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4}] / 2 \quad (3)$$

$$a_2 = [k_2 + k_3 + k_4 + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4}] / 2 \quad (4)$$

In the parametric imaging using 18FDG-PET the target parameter is  $LCMRGlc$

$$LCMRGlc = \frac{C_{pg}}{LC} K, \quad (5)$$

where:

$C_{pg}$  – glucose concentration in blood,

$LC$  – lumped constant, a scale constant between glucose and its analogue – 18FDG (typical value 0.4-0.5 [2]).

Using three compartmental model and its fitting to measured data it is possible to estimate the fractional uptake of 18FDG [5]:

$$K = \frac{k_1 k_3}{(k_2 + k_3)} \quad (6)$$

The LCMRGlc parameter depends on K which depends on rate constants. The goal of this work was to evaluate: the influence of noise on rate constants; the influence of noise on the fractional uptake of 18FDG (K) and thus on target parameter (LCMRGlc).

## 1.2. MATERIAL

The 18FDG-PET dynamic data from different brain studies were used. Most of them based on data sets used in literature [3][7][6] and by referential software EPICA [4]. The artificial, software-based phantom (Fig.2) was build with the set of previously described segments. The signals in those segments were artificially generated using data sets modified by introducing of noise. The 18FDG-PET data originally measured with different procedures (e.g. 6 images every 1/6 min, 3 \* 0.5 min, 5 \* 1 min, 5 \* 2.5 min, 8 \* 5 min) were interpolated to generate a data sets build with 120 samples. We used MATLAB (The MathWorks Inc.) software performing linear interpolation.



Fig. 2. An example of the software phantom.

## 2. METHOD

Model fitting procedure was implemented using Levenberg-Marquardt method. We used Java programming language (Java JDK 1.5, Sun Microsystems) for model fitting implementation and for noise generation. Tests were performed using seven original data series. First two data series (white and grey matter) were described by the following parameters  $[k_1, k_2, k_3, V_p]$ :  $[0.04; 0.08; 0.029; 0.03]$ ,  $[0.102; 0.13; 0.062; 0.050]$ ; assuming a constant phosphorylation rate, i.e.  $k_4=0,004$  (1/min). Other five series were set as following (scalp ( $c_1$ ), white matter ( $c_2$ ), white and grey matter ( $c_3$ ), grey matter ( $c_4$ ) and sinus ( $c_5$ )):  $[0.032; 0.151; 0.036; 0.031]$ ,  $[0.030; 0.047; 0.036; 0.048]$ ,  $[0.087; 0.321; 0.146; 0.027]$ ,  $[0.103; 0.216; 0.168; 0.056]$ ,  $[0.030; 0.065; 0.032; 0.0332]$ .

Tests were performed using a maximum iteration number equal to 100 with 50 repetitions to calculate a mean error. Two different method were used to introduce a noise: additive and multiplicative. The following scale factors for noise levels were used: 0; 0.1; 0.25; 0.5; 1; 2; 4; 6; 8; 10. These factors were multiplied by expectation value of appropriate data series. The calculated noise levels represent standard deviations of normal distribution used as a representation of noise. Expectation values used in the study are presented in table 1.

Table 1. Description in the text

<i>Data set 1</i>		<i>Data set 2</i>				
$c_2$	$c_4$	$c_1$	$c_2$	$c_3$	$c_4$	$c_5$
0.0013	0.00053	0.00029	0.00056	0.00092	0.0015	0.00046

Each data set were used in the model fitting algorithm producing a set of constant rates. The calculated values are compared to original (i.e., unmodified values of rates for every data series) values of parameters. Comparison of parameter errors can be performed based on error measures. In our studies we used root mean square error (RMSE in percents) and bias (in percents) given as:

$$RMSE\% = \frac{1}{p} \sqrt{\frac{\sum_{i=1}^N (p_i - p)^2}{N - 1}}, \quad (7)$$

$$Bias\% = \frac{1}{p} \sum_{i=1}^N \frac{(p_i - p)}{N} \quad (8)$$

where:

$p$  – true parameter value,

$p_i$  – estimated parameter value at  $i$ -th step (total number – N).

### 3. RESULTS

All experiments produce 1540 values, however only a subset of those values are presented below. Presented results are good representative of all calculated values ad are used to formulate final conclusions.

Presented results in tables 2-5 represents only the calculated RMSE values. Tables 2/3 presents results for data series corrupted by additive noise, while tables 4/5 presents results for multiplicative noise. Table 2 and 4 represents value for the first data set used in our studies (only white and grey matter); table 3 and 5 for the second data set. Every RMSE value represents the maximal error value calculated in experiments (repetitions). Additionally a total sum of RMSE values for all parameters [ $k_1, k_2, k_3, V_p$ ] was calculated. It is very important to analyze which parameter introduce the highest error value. Tables 2-5 present additional measure (PUS) defined as percentage presence of the particular parameter error in the total sum of RMSE values for an analyzed brain segment (e.g., white matter). The last parameter used to compare results is the particular parameters (i.e., all analyzed) error in the total sum of RMSE values for an analyzed data set (PUZ).

Table 2. Results for data set 1 (additive noise)

	$c_2$ [%]	PUS [%]	$c_4$ [%]	PUS [%]	PUZ [%]
$k_1$	0.01	8.20	0.018	10.43	9.51
$k_2$	0.02	16.39	0.035	20.29	18.68
$k_3$	0.016	13.11	0.016	9.28	10.87

**DECISION MODELLING SYSTEMS**

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<b>V<sub>p</sub></b>	0.07	57.38	0.1	57.97	57.72
<b>K</b>	0.006	4.92	0.0035	2.03	3.23
<b>Sum</b>	0.122		0.1725		

Table 3. Results for data set 2 (additive noise)

	<b>c1 [%]</b>	<b>PUS [%]</b>	<b>c2 [%]</b>	<b>PUS [%]</b>	<b>c3 [%]</b>	<b>PUS [%]</b>	<b>c4 [%]</b>	<b>PUS [%]</b>	<b>c5 [%]</b>	<b>PUS [%]</b>	<b>PUZ [%]</b>
<b>k<sub>1</sub></b>	0.012	14.94	0.0098	8.52	0.041	13.79	0.017	9.79	0.011	0.012	12.42
<b>k<sub>2</sub></b>	0.018	22.42	0.032	27.83	0.065	21.86	0.034	19.58	0.023	0.018	23.52
<b>k<sub>3</sub></b>	0.0096	11.96	0.029	25.22	0.019	6.39	0.016	9.21	0.019	0.0096	12.66
<b>V<sub>p</sub></b>	0.037	46.08	0.037	32.17	0.17	57.18	0.103	59.31	0.0053	0.037	48.18
<b>K</b>	0.0037	4.61	0.0072	6.26	0.0023	0.77	0.0036	2.10	0.0066	0.0037	3.21
<b>Sum</b>	0.0803		0.115		0.2973		0.1736		0.0649		

Table 4. Results for data set 1 (multiplicative noise)

	<b>c2 [%]</b>	<b>PUS [%]</b>	<b>c4 [%]</b>	<b>PUS [%]</b>	<b>PUZ [%]</b>
<b>k<sub>1</sub></b>	0.36	9	1.3	11.21	10.64
<b>k<sub>2</sub></b>	0.79	19.75	2.65	22.84	22.05
<b>k<sub>3</sub></b>	0.78	19.5	1.55	13.36	14.94
<b>V<sub>p</sub></b>	1.76	44	5.71	49.22	47.88
<b>K</b>	0.31	7.75	0.39	3.36	4.49
<b>Sum</b>	4		11.6		

Table 5. Results for data set 2 (multiplicative noise)

	c1 [%]	PUS [%]	c2 [%]	PUS [%]	c3 [%]	PUS [%]	c4 [%]	PUS [%]	c5 [%]	PUS [%]	PUZ [%]
<b>k<sub>1</sub></b>	0.35	16.36	0.39	8.59	2.77	15.98	1.32	11.36	0.72	17.45	13.96
<b>k<sub>2</sub></b>	0.51	23.83	1.38	30.40	4.45	25.68	2.65	22.81	1.51	36.61	26.41
<b>k<sub>3</sub></b>	0.25	11.68	1.41	31.06	1.12	6.46	1.55	13.34	1.11	26.91	13.68
<b>V<sub>p</sub></b>	0.92	42.99	0.98	21.59	8.79	50.72	5.71	49.14	0.41	9.94	42.28
<b>K</b>	0.11	5.14	0.38	8.37	0.2	1.15	0.39	3.36	0.375	9.09	3.66
<b>Sum</b>	2.14		4.54		17.33		11.62		4.125		

#### 4. DISCUSSION AND CONCLUSION

The main goal of this discussion is to analyze the results and to find in which extend the generated noise contributes to mathematical model parameter values and thus on parametric images.

The first possible results classification is to find which parameters:

- are highly sensitive to noise (C1),
- are moderate sensitive to noise (C2),
- are lowly sensitive to noise (C3).

Based on all obtained results (not only those presented in the upper tables) it could be concluded that the parameter V<sub>p</sub> belongs to the group C1, parameters k<sub>1</sub>, k<sub>2</sub>, k<sub>3</sub> belongs to the group C2 and derived parameter K (fractional uptake) belongs to the group C3. Such results are very promising because the target parameter LCMRGlc depends only on K, so even in the presence of noise it is possible to estimate the LCMRGlc.

Analyzing the influence of particular parameter errors on aggregate error (sum of all errors – PUZ) it could be concluded that the V<sub>p</sub> parameter is highly sensitive (~50%) in case of all data sets, segments and noise introduction method. Taking the same conditions the K parameter errors (i.e., PUZ) is almost in the same range 3%. Other parameters are characterized by PUZ values in the range of 10-25%. This characteristic describes all data sets and experiments. However it is also interesting to analyze errors for particular brain segments, starting from the first data set: white and gray matter. In this case the results show that additive noise leads to lower errors than multiplicative noise. Average difference between errors is about 50 times. Those relations are similar for RMSE (7) and BIAS (8). Finally the BIAS error is about 6 times lower than for RMSE. What is really important the implemented model fitting algorithm is able to accurately find parameters even in the presence of high additive noise (typically used to model a signal corruption). The maximum error was observed at the range of 0.1 % (RMSE%) which is fully acceptable (PET measurement accuracy is usually low). In case of multiplicative noise the maximum error is much higher ~ 6% (RMSE%). Additionally it could be say that parameters for grey matter are more sensitive than for white matter. This is more visible for multiplicative noise.

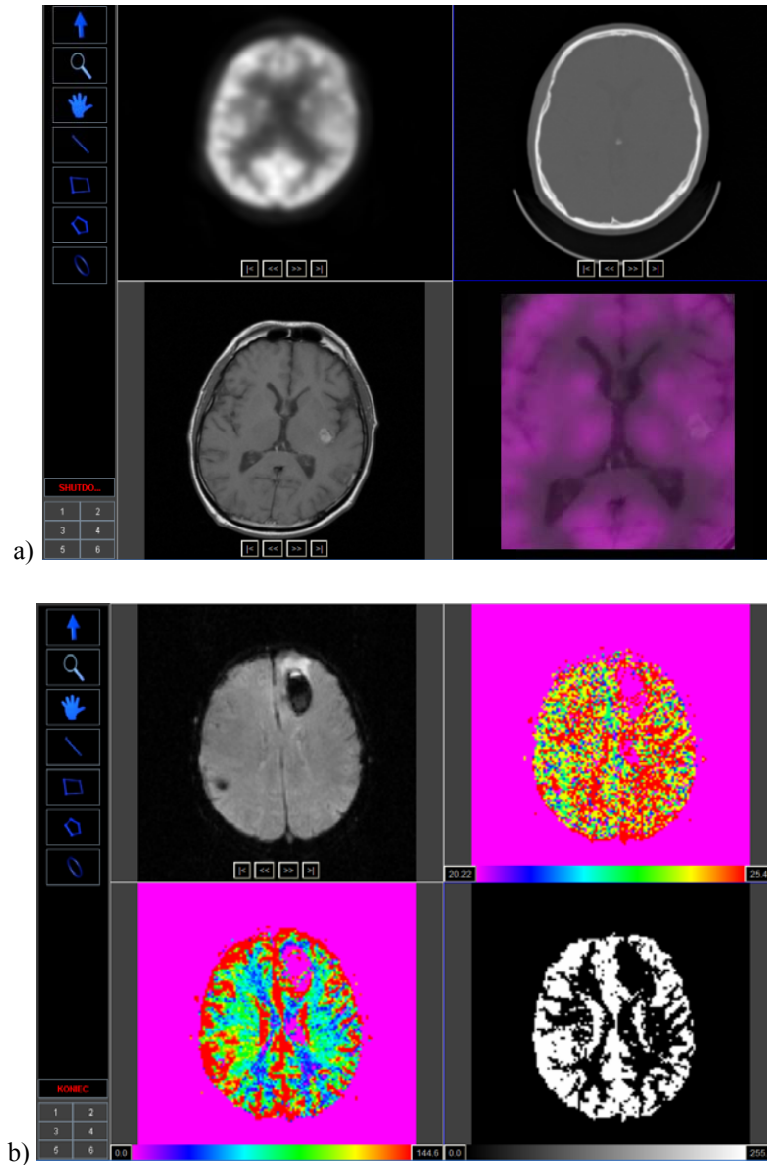


Fig. 3. Examples of the integrated parametric imaging package: a) PET, CT, MRI and co-registered PET to MRI images; b) dynamic MRI imaging and some parametric images (Bolus Arrival Time, Cerebral Blood Volume, Arterial Input Function Mask)

The same analysis can be performed for the second data set. General conclusions are the same as for the first data set. Additive noise introduces lower errors than multiplicative noise. Additionally it can be observed that results for the first and the second data sets are correlated. Scaling the results for the first data set by the factor 5/2 (ration of analyzed segments number) obtained errors are in the same range. This leads to conclusion that mean errors for both data sets are similar (thus the conclusions too). However in the second data set more different brain segments are analyzed so it is worth to discussed the results. The most sensitive on noise is the  $c_3$  segment (white and grey matter) with the average contribution in the total error (sum) equal to 38%. The next sensitive segment is a grey matter – 27%. Other segments are not so sensitive on noise. It can be concluded that grey matter signal is usually characterized by higher differences in the measured isotope activity ( $C_t$ ) - higher presence of vessels than for other segments. Taking it into account the target parameter  $LCMRGlc$  could be sensitive on noise in the grey matter area. Fortunately  $LCMRGlc$  depends only on fractional uptake parameter  $K$ , which compensates particular parameters errors. Also in the second data set the  $K$  parameter is almost not sensitive on noise (i.e.,

in the measured range of noise). The most sensitive parameter is  $V_p$ , as it was for the first data set. There is a difference between distribution of particular parameters in the total error, however in all cases the K parameter the smallest or very small.

Concluding the application of three compartmental model of  $^{18}\text{F}$ FDG distribution and its implementation in Java programming language gives very interesting results. Even in case of a high noise it is possible to accurately calculate LCMRGlc parameter values, so parametric imaging could be (taking into account the scaling factor LC) quantitative and repeatable. This is extremely important since the glucose metabolism is a strong factor in the diagnosis of cancer tissues, which usually are characterize by higher metabolism.

Described methodology and software are implemented as a part of the parametric imaging framework for brain studies. The target software package is prepared to analyzed dynamic MRI and PET data, to combine them in one common view, especially in case of parameter images which describes dynamic changes in brain. In fig. 3 the example of the graphical user interface is presented with brain images.

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