THE MODELLING OF FIRST-PASS DATA IN MRI MEASUREMENTS

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Abstract: The paper presents five models of first-pass data in MRI measurements. The models are both parametric and non-parametric. The aim is to choose the most appropriate description of the data. The model of choice is the one which satisfies the adopted criteria of model quality (parameter accuracy, AIC index and physiological plausibility). The weighted residual sum of squares (WRSS) was used for parameter estimation of the models. It emerges from the calculations that the models considered show a similar ability to mimic the data. The parameter estimate accuracy and model quality used for description of the phenomena depend on the complexity of the model, in other words on parameter number. Better results are obtainable for less complex models. Parametric modelling gives insight into the functioning of the system, while the non-parametric does not.

Introduction

Magnetic resonance imaging (MRI) techniques are used for measuring cerebral blood flow (CBF). The most successful approach is based on dynamic tracking of a bolus of a paramagnetic contrast agent, referred to as "dynamic susceptibility contrast". The goal is to design a non-invasive method of mapping CBF with high temporal and spatial resolution over the range of blood flow that is of interest. The technique using dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) is non-invasive for a lower dosage of a contrast agent. At a higher dosage of the contrast the DSC-MRI technique is toxic.

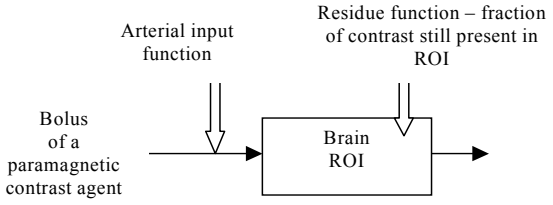

Figure 1: Symbolic representation of MRI measurements with a paramagnetic contrast agent.

A bolus of paramagnetic, as it passes through a region of interest (ROI) in the brain (Figure 1), undergo the dispersion. In modelling MRI measurements of dispersion both non-parametric and parametric models are employed.

Typical data observed during the passage of a bolus of a contrast agent in MRI techniques are shown in Figure 2. The transit time of a bolus through the tissue is only a few seconds. High temporal resolution imaging is therefore required to obtain the sequence of images during the flow in and out of the contrast material. Echo planar imaging (EPI), the fast imaging technique, enables the most interesting first-pass of a bolus to be measured.

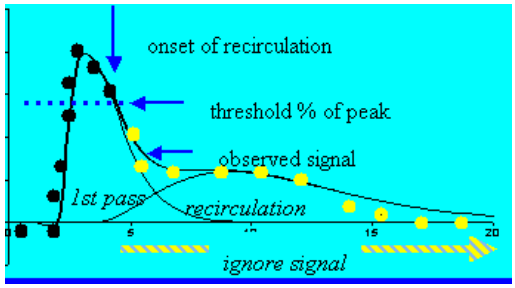

Figure 2: Three regions are shown [7], which can be distinguished in the time course. These represent the baseline (before the arrival of the bolus), the first-pass of the bolus and the recirculation (a second, smaller peak).

Models used for perfusion quantification are based on tracer kinetics and rely on the assumption that the blood-brain barrier (BBB) is intact and, therefore, that the contrast material remains intravascular.

The construction of block diagrams helps in modelling to clarify what key variables best represent the system under study. It also allows observation and intuition to be formalised. The block diagram represents a conceptual model of the process under study but it has limited ability to bring us closer to an understanding of the process described as it gives only a qualitative description of the phenomenon. An example of a model in the form of a block diagram is the symbolic representation of MRI measurements, shown in Figure 1.

The non-parametric model assumes no internal structure and has been referred to in the literature [1] as the *black-box* or *empirical* model. In this approach the output of a system is fitted to a chosen regression

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function $f(p_i,t)$ depending of the number of free parameters p_i it incorporates. Sometime we are able to form a hypothesis concerning the probable principle of system operation in the form of an algebraic differential or integral equation that relates the input to the output of the system under study. This type of model is said to possess internal structure and is termed [1] a *structural*, *parametric* or *grey-box* model. Parametric modelling brings us to better understanding of the system behaviour and is a more desirable approach then the non-parametric one. The paper presents parametric and non-parametric models describing a bolus passing through the brain ROI in dynamic MRI measurements. These are compared in terms of parameter accuracy and the Akaike criterion with respect to their ability to deliver a robust and sensitive candidate for parametric imaging (or mapping) of important physiological factors and macroscopic parameters such as CBF, CBV, MTT.

The state of the art. Black-box models. Regression function modelling

Linear interpolation

The most straightforward approach is to use linear interpolation between the points measured [2]. This kind of approximation follows point by point and does not round any of them. The disadvantage of the description is the large number of model parameters. The number is twice as great as the number of used linear sections; each of the linear sections fits two neighbouring measurements with two parameters.

Spline functions

A measured curve can be smoothed by piecewise short lengths, usually of cubic polynomials, that give the best fit to localised sections of data. The equations are joined together smoothly so they gave a single empirical regression function. Splines (not necessarily cubic but also quadratic or linear) are flexible and convenient for the empirical description of data but the price paid is the large number of parameters. For instance, in the case when four separate cubic sections are used, each with four parameters, the model fits the data with sixteen parameters.

The impulse response and linear convolution

The impulse response, $h(t)$, provides a complete characterisation of the dynamic behaviour of a linear system. Once $h(t)$ is known, the time response $y(t)$ to any arbitrary input $u(t)$ can be calculated by convolving $h(t)$ and $u(t)$: $y(t)=\int_0^\infty h(\tau)u(t-\tau)d\tau$.

Gamma Variate

The expression of Gamma Variate is [2]: $f(t)=t^\alpha e^{-t/\beta}/\beta^{(\alpha+1)}\Gamma(\alpha+1)$, where $\alpha>-1$ and β are parameters and $\Gamma(\alpha+1)$ is the gamma function defined as follows: $\Gamma(\alpha+1)=\int_0^\infty x^\alpha e^{-x}dx$.

The Gamma Variate is usually expressed as [6]:

$$f(t)=A(t-t_0)^\alpha\, exp(-(t-t_0)/\beta),\ \text{for}\ t>t_0 \qquad (1)$$

Time t_0 is the delay from $t=0$ to the point which begins the part of the Gamma Variate function used for perfusion modelling. For modelling first-pass data the part of the Gamma Variate function for $t>t_0$ is used. A,α,β are free parameters. An exemplary Gamma Variate function is presented in Figure 3.

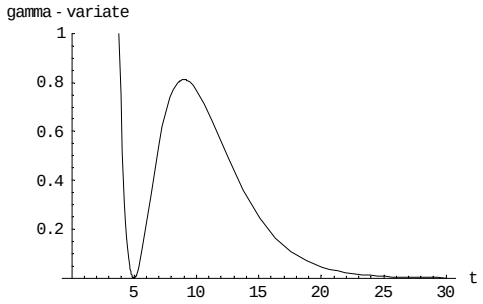

Figure 3: An exemplary Gamma Variate function ($t_0=5$). The part of the curve for $t>t_0$ is used for perfusion modelling.

The Gamma Variate function in the form (1) shows a number of difficulties in the identification procedures. This is because the parameters α and β are coupled. It can be shown that [6]:

$$\alpha\beta=t_{max},\ \text{where}\ t_{max}=arg\, f(t)=max \qquad (2)$$

A convenient approach is to adopt the Gamma Variate regression function in the form [7]:

$$f(t;t_0,\tau,\beta)=x_0+A\cdot\left(\frac{t-t_0}{\tau}\right)^\beta\cdot\exp^{-\left(\frac{t-t_0}{\tau}\right)};t>t_0, \qquad (3)$$

where x_0 – baseline, A – amplitude, t_0 – delay, τ – spread, β - superscript parameter. The baseline is not estimated but is measured. Thus there are four parameters of the Gamma Variate function to be estimated: A, t_0, τ and β [8], [9]. The above form of the Gamma Variate function is used for modelling purposes as the spread of parameters, the amplitude and the time delay relate to the shape of the modelled data.

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The Golish bolus function

The Golish bolus function [4] incorporates an asymptotic recirculation term

$$f_{Gol}(t) = f_{\max}\left(\frac{\exp(1)}{\alpha\beta}(t-t_0)\right)^{\alpha}\exp\left(\frac{-(t-t_0)}{\beta}\right) + f_0\left(1-\exp\left(-(\tau-t_0)/\tau\right)\right) \quad (4)$$

This function was designed for modelling the whole range of output data observed during the passage of a bolus of a contrast agent in MRI measurements, the first-pass and the recirculation (Figure 2).

In black-box modelling, the regression function parameters (such as α, β, t_0 and A in equations (3) and (4)) are termed the "macroparameters".

Grey-box model

A compartmental model of contrast agent distribution is shown in Figure **4**.

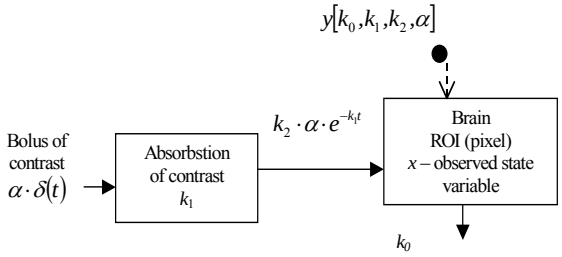

Figure 4: Compartmental model of contrast agent distribution; k_0, k_1 and k_2 are unknown microparameters of the parametric, grey-box model.

The model equations and their solution are:

$$\dot{x} = k_2\cdot\alpha\cdot e^{-k_1\cdot t} - x\cdot k_0,\ \ x(0)=0;\qquad y = x, \quad (5)$$

$$y = \frac{k_2\cdot\alpha}{k_0-k_1}\left(e^{-k_1\cdot t} - e^{-k_0\cdot t}\right) = p_1\cdot e^{-p_2\cdot t} + p_3\cdot e^{-p_4\cdot t} \quad (6)$$

From MRI measurements to macroscopic parameters

The ROI excitation, arterial input function AIF, is scanned in the middle cerebral artery. The fitting procedure gives sets of parameter estimates for chosen regression functions used for description of the input (AIF) and the output (ROI): f_{input} and f_{output}.

The functions are then used for calculating CBV, CBF and MTT. CBV is a measure of the relative blood volume of a ROI

$$CBV = \frac{\int_0^{\infty} f_{output}(t)\,dt}{\int_0^{\infty} f_{input}(t)\,dt} \quad (7)$$

Assuming the linearity of the process, the relationship between the input f_{input} and the output f_{output} can be described by means of the convolution integral

$$f_{regr\ ROI}(t) = \int_0^{\infty} f_{reg\ AIF}(t)\cdot R^*(t-\tau)\,d\tau \quad (8)$$

where $R^*(t) = CBF\cdot R(t)$ and $R(t)$ is the impulse response observed in the ROI.

With the identification of f_{output} and f_{input}, the $R^*(t)$ can be calculated via deconvolution. The CBF factor is the relative blood inflow to the ROI and $R^*(t=0) = CBF\cdot R(0) = CBF$.

Mean transit time MTT is defined as follows

$$MTT = \frac{1^{st}\ moment\ of\ h(t)}{0^{th}\ moment\ of\ h(t)} = \frac{\int_0^{\infty} t^1 h(t)\,dt}{\int_0^{\infty} t^0 h(t)\,dt} \quad (9)$$

where $h(t)$ is the impulse response at the ROI output and $R(t) = 1 - H(t)$ $h(t) = \frac{d}{dt}\left[H(t)\right]$.

It is possible to calculate MTT on the base of $R^*(t)$, previously obtained via deconvolution. It should be noted that the numerical deconvolution procedure used for assessing $R^*(t)$ and MTT could greatly amplify errors [8]. The errors made in each sequential estimate of $R^*(t)$ tend to accumulate. The result of deconvolution depends on the number and quality of the measurements.

Modelling the MRI data is a preparatory step necessary for achieving macroscopic parameters (such as CBF, CBV, MTT) and for mapping them for diagnostic purposes.

Parameter estimation

The five model functions shown in Table 1 were used for modelling the regression function in ROI, namely f_{output}.

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The parameter estimation means assigning numerical values to unknown model parameters.

The maximum-likelihood (ML) approach was used for parameter estimation. This is in the form of least squares (LS) for a measurement error assumed to be Gaussian.

Let us consider regression functions $f(\mathbf{p},t)$ and output measurements $y(t_i)$ at time points $t_i, i = 1,2,..,N$. The vector $\mathbf{p} = [p_1, p_2, .., p_{n_p}] = [\alpha, \beta, ...]$ represents conveniently ordered unknown n_p model parameters (micro or macroparameters). The LS estimate $\mathbf{p}$ of $\mathbf{p}$ is:

$$\mathbf{p} = arg\ \min_p OF(y,\mathbf{p}) \qquad (10)$$

Vector $\mathbf{p}$ is estimated in the time domain by minimising the weighted residual sum of squares (WRSS) with the objective function *OF*

$$OF(\mathbf{y},\mathbf{p}) = WRSS(\mathbf{y},\mathbf{p}) = \sum_{i=1}^{N} \frac{1}{R}\left[y(t_i) - f(t_i,\mathbf{p})\right]^2 \qquad (11)$$

where $\mathbf{y} = [y(t_1),..,y(t_N)]^T$ is the column vector of measurements. The measurement noise variance R is assumed to be known as a scale factor estimated from the final *WRSS* [8].

The precision of the parameter estimates was evaluated from the inverse of the Fisher information matrix $\mathbf{M}$ by

$$\mathrm{cov}(\hat{\mathbf{p}}) = R \cdot \mathbf{M}^{-1} \qquad (12)$$

where

$$R = \frac{WRSS(\hat{\mathbf{p}})}{\text{degrees of freedom}} \qquad (13)$$

and the degree of freedom equals the difference between the number of measurements N and the number of model parameters n_p and $\hat{\mathbf{p}}$ is the value of the parameter vector, which satisfies $OF(\mathbf{y},\mathbf{p})\big|_{\mathbf{p}=\hat{\mathbf{p}}} = \min$.

Selection of model

When alternative models have been considered, it is necessary to select one model among a number of competing ones. The first criterion is the ability of the model to fit the data. Where the fit is satisfactory and comparable (small WRSS and unbiased residuals) for a number of competing models, additional criteria have to be considered. In the literature, a number of methods are presented [10] for the selection of the best model. Some of these have referred to information criteria [11], [12]. When parameter estimation is performed in LS, the common strategy is to select a model based on the Akaike criterion. According to the criterion, the model of choice is the one that gives the minimum of the index

$$AIC = 2 \cdot n_p + WRSS(\mathbf{p}) \qquad (14)$$

where n_p is the number of model parameters and $WRSS(\mathbf{p})$ is the value of the objective function at its minimum. The *AIC* index penalised the higher number of model parameters and rewarded the smaller $WRSS(\mathbf{p})$, linked to the goodness of fit.

Results

The parametric and non-parametric models of first-pass MRI data, shown in Table 1, were examined in detail.

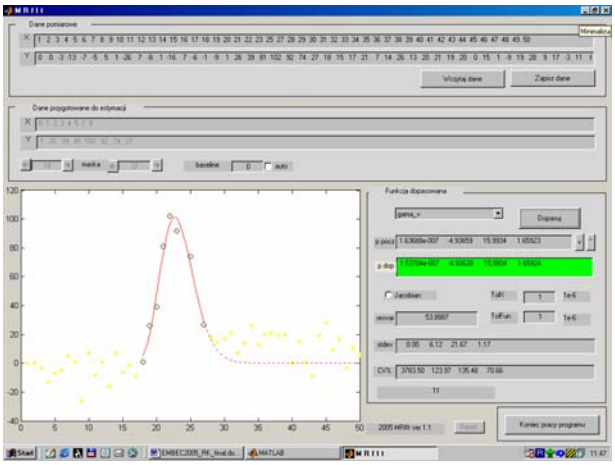

Figure 5: Specially designed software (MATLAB) was used for identification. The figure shows the intermediate results obtained for a set of measurements and the Gamma Variate chosen as the tested regression function. All the measurements (the baseline, the first-pass data and the recirculation data) are shown as circles. The measurements chosen for the first-pass fit are marked dark. The solid line shows the model function fitted to the measurements chosen as the first-pass data.

Table 1: The first-pass MRI data models under consideration.

Model	Regression functions f_{output}	n_p
1	$f_{comp} = p_1 exp[-p_2 t] + p_3 exp[-p_4 t]$	4
2	$f_{gamvar} = p_{1v} \cdot (t - p_{2v})^{p_{3v}} \cdot exp[-p_{4v}(t - p_{2v})]$	4
3	$f_{gamvar0} = p_{1v0} \cdot t^{p_{3v0}} \cdot exp[-p_{4v0} \cdot t]$	3
4	$f_{gamvarb} = p_{1b} e^{-t} t^{p_{2b}} (t p_{3b} - 1)$	3
5	$f_{gamvara} = p_{1a} e^{-t} t^{p_{2a}}$	2

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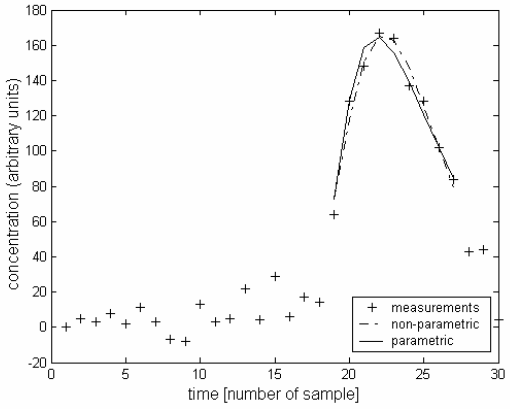

Figure 6: An exemplary result of modelling. Functions numbered 1 and 2 were chosen as regression functions (as parametric and non-parametric model functions respectively) from Table 1. The solid and the dashed lines indicate the model functions fitted to the measurements chosen as the first-pass data. Samples were taken at $t_r = r \cdot \Delta t$, $r = 1 \div 30$, $\Delta t = 1.43$ sec.

Figure 6 shows all the measurements (ROI in grey matter) and the measurements chosen for the first-pass fit (sample numbers 18 to 27).

Table 2: Model parameter estimates p_i for 5 considered models.

Model	p_1	p_2	p_3	p_4
1	10.4050	0.8060	-10.6314	1.3834
2	0.9226	-1.7497	21.7448	7.6708
3	19.6701	-	2.1421	2.1802
4	0.0614	0.1433	91.7607	-
5	5.5685	1.1603	-	-

Table 3: Standard deviations *std dev* and $CV_i[\%] = \frac{std\ dev_i}{p_i} * 100\%$ of the model parameter estimates p_i.

Model	$std\ dev_1$ $CV_1[\%]$	$std\ dev_2$ $CV_2[\%]$	$std\ dev_3$ $CV_3[\%]$	$std\ dev_4$ $CV_4[\%]$
1	13.3680 128.4 [%]	0.3305 41.0 [%]	13.3550 125.6[%]	0.4551 32.8 [%]
2	2.9791 332.9[%]	0.3812 21.7[%]	6.2093 28.5[%]	1.1474 14.9[%]
3	1.1470 5.8[%]	-	0.0521 2.4[%]	0.0540 2.4[%]
4	0.1082 176.2[%]	0.0319 22.3[%]	159 174.0[%]	-
5	0.290 5.2[%]	0.114 9.8[%]	-	-

The first function from Table 1 is the regression function of the compartmental model shown in Figure 4. Functions 2 to 5 are based on the general form of the Gamma Variate function (3), and are the propositions of simplifications of the general form with the purpose of reducing the number of parameters.

Model parameter estimates were obtained for measurements taken on grey matter ROI.

Table 4: *WRSS*, n_p and the *AIC* index for the considered models.

Model	*WRSS*	n_p	*AIC*
1	0.1075	4	8.1075
2	0.0814	4	8.0814
3	0.0842	3	6.0842
4	0.0851	3	6.0851
5	0.0769	2	4.0769

Conclusions

For all the considered model functions the quality of fit, measured as the WRSS, was similar. All the models show a similar ability to mimic the phenomena tested. The results presented show that the parameter estimate accuracy, the quality of model used for the description of the phenomenon, depends on the complexity of the model. As anticipated, better results are obtainable for a less complex model, if only the quality of fit is comparable. The final choice of model and parameters for mapping important macroscopic parameters (such as CBF, CBV, MTT, which are calculated on the bases of modelling results) requires detailed medical analysis and is left to the decision of the physician.

The accuracy of the parameter estimates presented in Table 3 may be assessed as poor where engineering systems are concerned. For biomedical systems, however, with all the constraints imposed by limited measurements and medical considerations, some degree of inaccuracy in the parameter estimates is often unavoidable and may be acceptable.

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