Evaluation of the Simplified Method for Mapping Cerebral Metabolic Rate of Oxygen Based on ^{17}O NMR Approach

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Introduction

We have developed a simplified model for mapping cerebral metabolic rate of oxygen ($CMRO_2$) based on the non-invasive ^{17}O NMR approach and validated this model on rats anesthetized with α-chloralose. This simplified model fits the curve of the accumulated metabolic water ($H_2{}^{17}O$) in the brain tissue during the inhalation of $^{17}O_2$ (C_b) with a polynomial function and the coefficient of the linear term is used to calculate $CMRO_2$[1]. In theory, fitting the C_b curve with a polynomial of higher order gives more accurate $CMRO_2$ results as the fitting model better approximates the true model. However, noise in the measured data tends to induce larger fitting variance for the higher order polynomials as the statistical power of fitting decreases, and thus, the fitted results will be less reliable. It is therefore interesting and very important to find an optimal fitting function that can lead to both accurate and reliable $CMRO_2$ results for each particular experimental condition. It is also important to examine the validity of the simplified models for larger ranges of physiologic and pathologic parameters and for different species.

Theory

The details of the simplified model for mapping $CMRO_2$ based on the non-invasive ^{17}O NMR approach are described in ref 1. Practically, only linear and quadratic fittings have been used for the experimental data. In principle, quadratic fitting should give more accurate but less reliable results whereas linear fitting should give less accurate but more reliable regression results. The evaluation between the linear fitting model vs. quadratic fitting model depends on the experimental factors such as SNR, $^{17}O_2$ inhalation duration (or the number of fitting points) and ^{17}O enrichment of the inhalated $^{17}O_2$ (α), and physiologic parameters like CBF, arterial input function (A value[1]) and $CMRO_2$ values. The assessment for the two models is quantified using the method introduced in ref. 2. The rationale of this method is briefly described as the following:

When a mathematical model is fitted to an experimental data set by regression analysis, a residual sum of square (RSS_c) is calculated with v_c degrees of freedom. If the same data set is fitted by a reduced model, which is a subset of the first one, a new and greater value of residual sum of square, RSS_r, with a larger number of degrees of freedom, v_r, will be calculated. If the increase in the sum of squares associated with the reduced model is purely ascribed to statistical fluctuation, reduced model can be used to replace the original model because the original model overfits the data; if the increase in the sum of squares associated with the reduced model is due to lack of fitting (underfitting), the reduced model has to be rejected. Comparison between the variance due to lack of fit (σ_{lf}^2) in the reduced model and the variance due to pure error (σ_{pe}^2), which is assumed to be approximated by the variance of the fit by the original model, tells the relative fitting performances between the two models. The value of F score is calculated from the ratio of these variances:

$$\sigma_{lf}^2 = \frac{(RSS_r - RSS_c)}{(v_r - v_c)} \qquad \sigma_{pe}^2 = \frac{RSS_c}{v_c} \qquad F = \frac{\sigma_{lf}^2}{\sigma_{pe}^2}$$

If the calculated value of F is larger than that for probability p with ($v_r - v_c$, v_c) degrees of freedom, there is less than p chance that the increased sum of squares is solely due to random fluctuations and in the case that p is smaller than the statistic threshold, the reduced model should be discarded.

Method

The default values of the physiologic and experimental parameters[3] were predefined as $CMRO_2$ = 2.19 μmol/g/min, CBF = 0.53 ml/g/min, A value = 1.68, α = 0.72, SNR = 40 and fitting number = 11. SNR was calculated as 2.5 × *signal intensity / maximal peak to peak noise intensity*, where *signal intensity* is the ^{17}O natural abundance in the tissue water (20.35 μmole per gram brain water); noise was randomly generated with the peak to peak amplitude calculated from the corresponding SNR value and signal intensity. A noise free $C_{b0}(t)$ curve was calculated based on the complete model[1] using the predefined parameter values and constants $m = 0.84$, $n = 0.67$. The simulated $C_b(t)$ is, on a point-to-point base, the sum of the noise free $C_{b0}(t)$ and the noise generated. $CMRO_2$ values were fitted to the simulated $C_b(t)$ curve using the simplified models and then compared to the predefined $CMRO_2$ value(s) to evaluate the models and fitting performance. Each parameter was varied at one time in a relatively large range to examine the impact of this parameter on the models. Every simulation was repeated for 100 times. The fitting accuracy and reliability (i.e. variation) were expressed as the mean and standard deviation of the 100 trials, respectively. The fitting performance of the linear model versus the quadratic model was quantitatively assessed by calculating the F score and the corresponding p value for each condition simulated.

Results

Fig. 1a shows the influence of variation in $CMRO_2$ in a relatively large range on fitting accuracy and reliability for the linear and quadratic models. The dependence of $CMRO_2$ change on F score shown in Fig. 1b indicates that the fitting performance of the linear model is statistically indistinguishable from that of the quadratic model in the simulated range of $CMRO_2$. The influences of variations in such experimental parameters as SNR, enrichment and number of fitting points and physiologic parameters as CBF and arterial input function were independently simulated (data not shown due to the limited space) by the same means. The dependences of these parameters changes on F scores and p values were obtained similarly.

Discussion and Conclusion

Various factors that may have impacts on the simplified $^{17}O_2$ approach for $CMRO_2$ measurement are extensively studied. The simulation results validate the simplified method in measuring $CMRO_2$ in relative large ranges of physiologic/pathologic conditions as well as different experimental environments. Comparisons between the linear and quadratic fitting models confirm the notion that quadratic fitting gives more accurate but less reliable results whereas linear fitting gives less accurate but more reliable results (see Fig. 1a). However, there is no statistic significance to distinguish the linear fitting model from the quadratic model (see Fig. 1b). Considering its relatively simple form, the linear fitting model is generally preferred for $CMRO_2$ calculation. More important, by calculating the tangential slope of the C_b curve at any time, the linear fitting model enables the measurement of dynamic $CMRO_2$ change during certain physiologic conditions such as ischemia in addition to $CMRO_2$ values at steady state. The verified validity of the linear fitting model in large ranges of physiologic and experimental conditions supports this concept. The simulation results would also have impact on the measurement of relative $CMRO_2$ changes at different brain conditions such as brain activation vs. resting condition. In those situations, for a small fractional change between two different conditions, fitting reliability is critical to precisely obtain relative change, especially when the change is subtle.

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References

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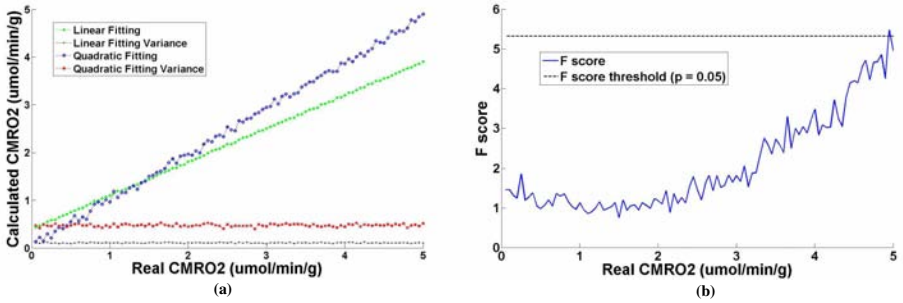

Fig. 1 (a) Influence of $CMRO_2$ on accuracy and reliability of linear and quadratic fittings. (b) Dependence of $CMRO_2$ on F score and the corresponding p value in evaluation between linear and quadratic fitting models.