RESPONSE

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Combining Complex Signal Change in Functional MRI

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With the development of functional magnetic resonance imaging (fMRI) techniques, data analysis methods based on complex MR data have been proposed. However, the methods have not been popular for fMRI community, in part because the phase activation in conventional GRE fMRI has been suggested to originate from the large veins (1). Recently, novel fMRI methods such as transition-band SSFP fMRI and an alternating balanced SSFP method for neuronal current measurement (2) have been proposed. In these methods, the functional contrasts exist in the complex domain, providing significant and localized complex signal change. Hence, the usefulness of the complex-data analysis methods has become increasingly important for these applications by allowing them to reliably obtain complex activation.

As mentioned in his letter, Dr. Rowe has proposed a complex-data analysis method based on the generalized likelihood ratio test (3). Despite the usefulness of the method, the computational complexity of the method, which requires multiple iterations to estimate the parameters, hampers the routine use of the method. This is particularly true for high-resolution studies that we targeted in our study. To overcome this inefficiency, we have proposed a new method based on T^2 statistics combined with generalized linear model (4).

Dr. Rowe's letter expressed concerns about the relationship of our model to his model and some mathematical errors. Here we present our responses to his points:

Point 1

We agree with his comment on Appendix B. Although the test statistics in Appendix B are correctly derived, it started in Cartesian coordinates, whereas Dr. Rowe's method is in polar coordinates. Despite our oversight in Appendix B, the rest of the article remains correct.

Points 2 and 3

In his points 2 and 3, Dr. Rowe argued that our model is correct only when one constant and one bipolar regressor are used. He reached this conclusion based on his "simple inspection" that he can equate his model to our model. By doing so, he showed that our model results in an error for the noiseless observations that he used in his model (point 3).

He considered a case in which L = 2, n = 3, and the design matrix (X) has first column [1, 1, 1]' and second column = [0, 0.5, 1]'. With the same setup, let us assume the observation made was y_{R1} = [4, 5, 6]' and y_{I1} = [8, 7, 6]'. One can easily see that this is a noiseless observation in Cartesian coordinates because a contrast and a linear regressor are assumed ("x" marks in Fig. 1).

Upon inserting β_R = [4 2]' and β_I = [8 2]' into our model, one can see that

$$\begin{pmatrix} x_1'\beta_R \\ x_1'\beta_I \end{pmatrix} = \begin{pmatrix} 4 \\ 8 \end{pmatrix} = \begin{pmatrix} y_{R1} \\ y_{I1} \end{pmatrix}, \quad \begin{pmatrix} x_2'\beta_R \\ x_2'\beta_I \end{pmatrix} = \begin{pmatrix} 5 \\ 7 \end{pmatrix} = \begin{pmatrix} y_{R2} \\ y_{12} \end{pmatrix},$$

$$\begin{pmatrix} x_3'\beta_R \\ x_3'\beta_I \end{pmatrix} = \begin{pmatrix} 6 \\ 6 \end{pmatrix} = \begin{pmatrix} y_{R3} \\ y_{13} \end{pmatrix}$$

Hence, our model correctly produces a noiseless estimation.

Using the same observations, let us apply them to Dr. Rowe's model.

$$\begin{pmatrix} x_1'\beta\cos(u_1'\gamma) \\ x_1'\beta\sin(u_1'\gamma) \end{pmatrix} = \begin{pmatrix} \beta_1\cos\gamma_1 \\ \beta_1\sin\gamma_1 \end{pmatrix} = \begin{pmatrix} 4 \\ 8 \end{pmatrix},$$

$$\begin{pmatrix} x_2'\beta\cos(u_2'\gamma) \\ x_2'\beta\sin(u_2'\gamma) \end{pmatrix} = \begin{pmatrix} (\beta_1 + 0.5\beta_2)\cos(\gamma_1 + 0.5\gamma_2) \\ (\beta_1 + 0.5\beta_2)\sin(\gamma_1 + 0.5\gamma_2) \end{pmatrix} = \begin{pmatrix} 5 \\ 7 \end{pmatrix}$$

The solution for the first equation is β_1 = 8.94427 and γ_1 = 1.10715 (rad). From the second equation, one can obtain γ_1 = −0.68389 and β_2 = −0.31320. Following Dr. Rowe's step in his point 3, this solution should work for the last equation when we plug in the numbers

$$\begin{pmatrix} x_3'\beta\cos(u_3'\gamma) \\ x_3'\beta\sin(u_3'\gamma) \end{pmatrix} = \begin{pmatrix} (\beta_1 + \beta_2)\cos(\gamma_1 + \gamma_2) \\ (\beta_1 + \beta_2)\sin(\gamma_1 + \gamma_2) \end{pmatrix}$$

$$= \begin{pmatrix} 5.89071 \\ 5.79081 \end{pmatrix} \neq \begin{pmatrix} 6 \\ 6 \end{pmatrix}$$

Hence, his model does not estimate the parameters correctly.

This result leads to exactly the opposite conclusion from Dr. Rowe's letter. The discrepancy can be understood by looking at the two examples in a two-dimensional plane (Fig. 1).

Because our model is in Cartesian coordinates, the regressors exist in Cartesian coordinates. Hence, when the observation is in Cartesian coordinates, it produces a correct estimation. This is also true for Dr. Rowe's model

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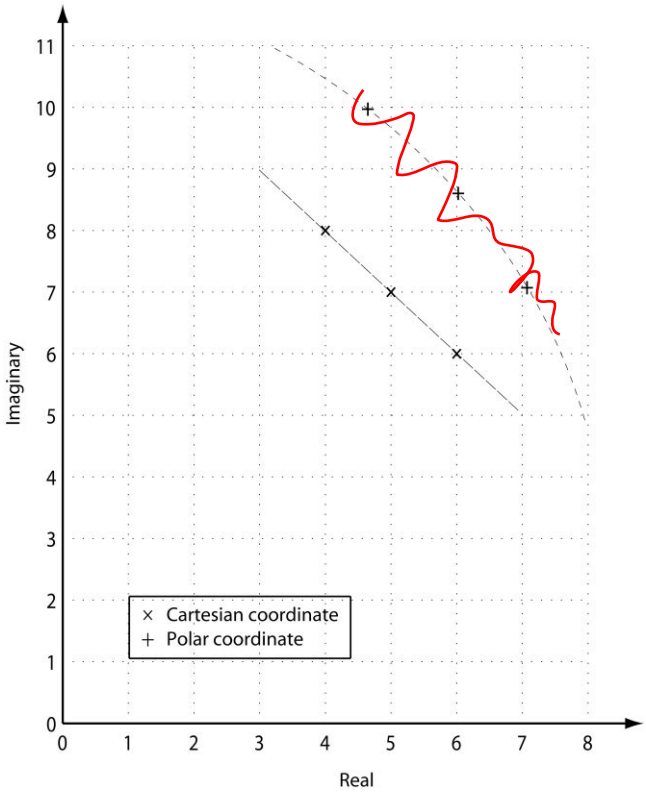

FIG. 1. The observation points with the "x" marks are the example given above, whereas the "+" marks are the example from point 3 in Dr. Rowe's letter.

when the observation is in polar coordinates. The two models are different because their regressors exist in different coordinates. As a result, the two models cannot be equated as Dr. Rowe did in his point 2 and point 3. This misled him to conclude our model is limited in the number of regressors and the shape of the regressors.

One implication of this result is that our model fits better when the observation exists in Cartesian coordinates, whereas Dr. Rowe's model fits better for polar coordinates. For functional contrast, true coordinates are not known (for example, Cartesian coordinates are also used to represent the functional contrast in SSFP fMRI (5) and GRE fMRI (6)). Nonetheless, if the contrast is relatively small, both Cartesian and polar coordinate models can estimate the observation closely because the first-order approximation of one coordinate will accurately represent the other coordinate. This is illustrated in Fig. 2. When the phase contrast is 0.05 rad (= 2.8°), the time course of the hemodynamic response in phase (blue line) is closely approximated by the Cartesian regressors leaving a small amount of residual errors (red and green lines). The estimated error, calculated by the mean absolute values of the real and imaginary axes residuals divided by the mean absolute values of the phase, is only 0.6%. The estimation error is still only 3.3%, even for a relatively large phase contrast of 0.3 radian (= 17.2°). Considering the variability of the hemodynamic response function (7) and the noise of fMRI measurement, these error levels are negligibly small. Therefore, for the applications that the complex-data analysis has been used in fMRI so far and for other methods

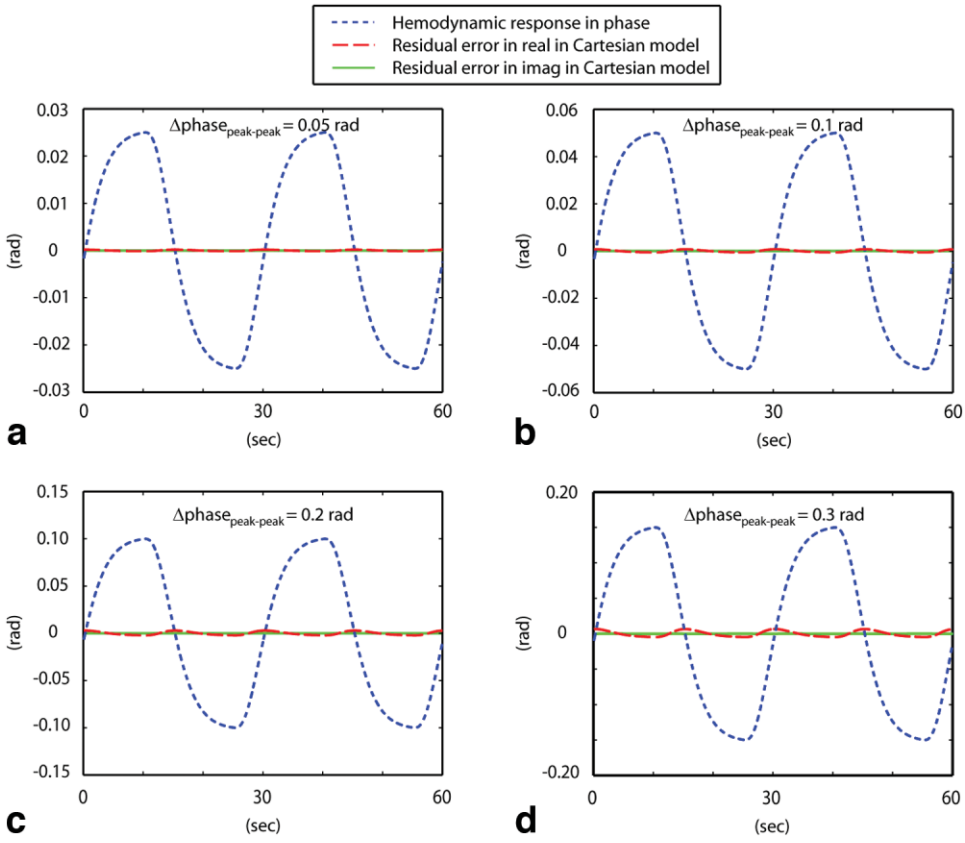

FIG. 2. Functional contrast in phase (blue line) and the residual errors in real (red) and in imaginary (green) axes when the phase contrast is modeled in Cartesian coordinates. The magnitude was set to 1 (i.e., 1*exp(–i*p(t)), where p(t) is the phase contrast change over time) to put the residuals in the same scale as the phase. In the Cartesian model, the same regressor, p(t), was used for the real and imaginary regressors.

that have a relatively small contrast, both Dr. Rowe's and our models would properly represent the contrast.

Point 4

The degrees of freedom and the scaling factor (the value in front of the F-distribution) in Eq. 5 are correctly written in our article. A detailed derivation of theses parameters can be found in (8). Dr. Rowe's conclusion in his point 4 originates from the assumption in his article that the residual errors are independent. In our article, this was not assumed in the theory section. Only in Appendix B (page 916), where we mentioned "[a]ssuming the case in which noise in the real and imaginary axes is independent, as assumed in Ref. 9 [which is Dr. Rowe's article]." Hence, the degrees of freedom should be m, n–m, as is written in Eq. 5 of our article. In general, the residual errors could be correlated because of physiologic noise, because of hardware imperfection, and when phased-array coils are used. When the independence of the residual errors is assumed, the correct scaling factor is $2(n-1)/(2n-4)$, which is still different from what Dr. Rowe has suggested in his comment.

In conclusion, we thank Prof. Rowe for his interest in our article. With this letter, we believe most of his concerns have been addressed. The models differ in the coordinate systems used, Dr. Rowe using polar coordinates, whereas our method is in Cartesian coordinates. Despite the different coordinate systems used, our method serves to detect the complex activation and is not limited to the number of regressors or the shape of the regressors. In practical fMRI applications in which the signal changes are small, both our method and Dr. Rowe's method should successfully detect complex functional contrast.

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