A Complex way to Compute fMRI Activations

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Outline

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Introduction

In MRI/fMRI, (non)Fourier "image reconstruction" results in complex valued proton spin densities that make up our voxel time course observations.

The complex part of the proton spin density is a result of phase imperfections due to magnetic field inhomogeneities.

Nearly all fMRI studies obtain a statistical measure of functional "activation" based on magnitude image time courses.

Introduction

However, it is the real and imaginary parts of the original signal that are measured with normally distributed error, and not the magnitude.

A more accurate model should use the correct distributional specification.

A model is presented that uses the original complex form of the data and not the magnitude.

The result is the correct distribution and twice as many quantities to estimate the model parameters which results in improved power for low SNR.

Focus on a single axial slice.

Complex Single Time Images



(a) real image

(b) imaginary image

Magnitude/Phase Single Time Images



(c) magnitude image

(d) phase image

Complex Time Course Images

In fMRI we observe a series of complex images over time.





Magnitude Time Course Images

And not a series of real magnitude images. Phase not used.



In a voxel, the complex valued quantity measured over time is

$$\rho_{mt} = (\rho_{Rt} + \eta_{Rt}) + i(\rho_{It} + \eta_{It}), \quad t = 1, ..., n$$

 $\rho_{mt} = \text{complex voxel measurement at time } t$ $\rho_{Rt} = \text{true real part of voxel measurement at time } t$ $\eta_{Rt} = \text{noise real part voxel measurement at time } t$ $\rho_{It} = \text{imaginary part voxel measurement at time } t$ $\eta_{It} = \text{noise imaginary part voxel measurement at time } t$

 $(\eta_{Rt},\eta_{It})' \sim \mathcal{N}(0,\Sigma), \ \Sigma = \sigma^2 I_2.$

The distributional specification is on the real and imaginary parts of the image and not on the magnitude.

Magnitude Time Course Model

The typical method to compute activations is to use the magnitude

$$\begin{aligned} |\rho_{mt}| &= \left[(\rho_{Rt} + n_{Rt})^2 + (\rho_{It} + n_{It})^2 \right]^{\frac{1}{2}}, \quad t = 1, ..., n \\ &= y_t \end{aligned}$$

that is Rician distributed and approximately normal for a large signal to noise ratio (relatively small error variance).

The phase which may contain information is not used.

$$\phi_t = \tan^{-1} \left[\frac{\rho_{It} + n_{It}}{\rho_{Rt} + n_{Rt}} \right]$$

Magnitude Time Course Model: Assumptions

The magnitude, does not have a normal distribution.



$$p(y_t) = \frac{y_t}{\sigma^2} e^{-\frac{(y_t^2 + \rho_t^2)}{2\sigma^2}} I_o\left(\frac{\rho_t \cdot y_t}{\sigma^2}\right) \qquad p(y_t) = \frac{y_t}{\sigma^2} e^{-\frac{y_t^2}{2\sigma^2}}$$

Magnitude Time Course Model: Assumptions

Data justification. Histogram of no signal, noise only outside voxels.



Outside histogram

Magnitude Sequence

Magnitude Time Course Model: Assumptions

Data justification. Histogram of no signal, noise only outside voxels.



Outside histogram

Rayleigh PDF's

A complex phase model was introduced that includes a phase imperfection θ in which at time t, the measured proton spin density is given by

$$\rho_{mt} = (\rho_t \cos \theta + \eta_{Rt}) + i(\rho_t \sin \theta + \eta_{It})$$

 $\rho_{Rt} = \rho_t \cos \theta$ $\rho_{It} = \rho_t \sin \theta$

$$(\eta_{Rt},\eta_{It})' \sim \mathcal{N}(0,\Sigma), \ \Sigma = \sigma^2 I_2.$$

This model which includes a phase error is an accurate representation of the true physical process that generates the data.

Complex Time Course Model: Assumptions

Data justification. Phase and correlation of no signal noise only outside voxels.



Constant Phase

R-I Uncorrelated

Complex Time Course Model: Assumptions

Data justification. Phase and correlation of no signal noise only outside voxels.



Constant Phase

R-I Uncorrelated

Complex Time Course Model: Assumptions

Data justification. Histogram of no signal noise only outside voxels.



Outside histogram

Complex Sequence

Magnitude Time Course Model

The magnitude model from the complex phase model

$$\begin{aligned} \rho_{mt} &| = \left[(\rho_t \cos \theta + n_{Rt})^2 + (\rho_t \sin \theta + n_{It})^2 \right]^{\frac{1}{2}} \\ y_t &= \left[\rho_t^2 + (n_{Rt}^2 + n_{It}^2) + 2\rho_t (n_{Rt} \cos \theta + n_{It} \sin \theta) \right]^{\frac{1}{2}} \\ &= \rho_t \left[1 + 2\frac{(n_{Rt} \cos \theta + n_{It} \sin \theta)}{\rho_t} + \frac{(n_{Rt}^2 + n_{It}^2)}{\rho_t^2} \right]^{\frac{1}{2}} \\ &\approx \rho_t + \epsilon_t, \quad t = 1, \dots, n \end{aligned}$$

 $\epsilon_t = n_{Rt} \cos \theta + n_{It} \sin \theta \sim N(0, \sigma^2).$ $\sqrt{1+u} \approx 1 + u/2, \ |u| \ll 1.$

Time Course Model

In fMRI, we take repeated measurements over time while a subject is performing a task.

We know the timing of the task, tap fingers for 16 seconds, rest for 16 seconds, and repeat several times.



In each voxel, compute a measure of association between observed time course and a preassigned reference function that characterizes the experimental paradigm (Bandettini et al., 1993; Cox et al., 1995).

Magnitude Time Course Model

Linear multiple regression model individually for each voxel

$$\rho_t = x'_t \beta = \beta_0 + \beta_1 x_{1t} + \dots + \beta_q x_{qt}.$$

$$y_t = x'_t \beta + \epsilon_t, \quad t = 1, ..., n$$

Also written as

$$y = X \qquad \beta + \epsilon$$

$$n \times 1 \qquad n \times (q+1) \ (q+1) \times 1 \qquad n \times 1$$

and $\epsilon \sim \mathcal{N}(0, \sigma^2 \Phi)$, Φ is the temporal correlation matrix usually $\Phi = I_n$.

Rowe, MCW



Magnitude Time Course Model

The magnitude activation likelihood is given by

$$p(y|\beta,\sigma^2,X) = (2\pi)^{-\frac{n}{2}}(\sigma^2)^{-\frac{n}{2}}e^{-\frac{(y-X\beta)'(y-X\beta)}{2\sigma^2}}$$

We want to see if the observed time course has a component related to the reference function.

 $H_0: \ C\beta = \gamma \text{ vs } H_1: \ C\beta \neq \gamma$ i.e. Is the coefficient for the reference function zero.

$$C = (0, ..., 0, 1), \ \beta' = (\beta_0, \beta_1, \cdots, \beta_q), \ \gamma = 0$$

Magnitude Time Course Model

By maximizing the likelihood under the unconstrained alternative

$$\hat{\beta} = (X'X)^{-1}X'y,$$
$$\hat{\sigma}^2 = \frac{1}{n} \left(y - X\hat{\beta} \right)' \left(y - X\hat{\beta} \right) \ .$$

By maximizing the likelihood under the constrained null hypotheses

$$\tilde{\beta} = \Psi \hat{\beta} + (X'X)^{-1}C'[C(X'X)^{-1}C']^{-1}\gamma,$$

$$\tilde{\sigma}^2 = \frac{1}{n} \left(y - X\tilde{\beta}\right)' \left(y - X\tilde{\beta}\right)$$

$$\Psi = I_{q+1} - (X'X)^{-1}C'[C(X'X)^{-1}C']^{-1}C .$$

Magnitude Model

By maximizing the likelihood under constrained null and unconstrained alternative hypotheses the GLR statistic is

$$\begin{split} \lambda &= \frac{p(y|\tilde{\beta}, \tilde{\sigma}^2, X, H_0)}{p(y|\hat{\beta}, \hat{\sigma}^2, X, H_1)} \\ &= \left(\tilde{\sigma}^2/\hat{\sigma}^2\right)^{-\frac{n}{2}} \\ \left(\frac{n-q-1}{r}\right)(\lambda^{-\frac{2}{n}}-1) &= \frac{(C\hat{\beta}-\gamma)'[C(X'X)^{-1}C']^{-1}(C\hat{\beta}-\gamma)}{rn\hat{\sigma}^2/(n-q-1)} \end{split}$$

This magnitude model uses n quantities to estimate the q + 2 parameters being the q + 1 regression coefficients, the 1 variance.

Magnitude Model

For example with q = 2, $X = (e_n, c_n, r_n)$, $H_0 : \beta_2 = 0$ can be evaluated with C = (0, 0, 1), $\gamma = 0$, and any of the test statistics

$$t = \frac{\hat{\beta}_2}{[W_{33}n\hat{\sigma}^2/(n-2-1)]^{\frac{1}{2}}} \sim t_{n-2-1}$$

$$F = \frac{\hat{\beta}_2^2}{W_{33}n\hat{\sigma}^2/(n-2-1)} \sim F_{1,n-2-1}$$

$$\chi^2 = n\log(\tilde{\sigma}^2/\hat{\sigma}^2) \sim \chi_1^2$$

Where W_{33} is (3,3) element of $W = (X'X)^{-1}$.

The previous complex model

$$\rho_{mt} = (\rho_t \cos \theta + \eta_{Rt}) + i(\rho_t \sin \theta + \eta_{It})$$

can be written as

$$\begin{pmatrix} y_{Rt} \\ y_{It} \end{pmatrix} = \begin{pmatrix} \rho_t \cos \theta \\ \rho_t \sin \theta \end{pmatrix} + \begin{pmatrix} \eta_{Rt} \\ \eta_{It} \end{pmatrix}$$

where again $(\eta_{Rt}, \eta_{It})' \sim \mathcal{N}(0, \Sigma)$, $\Sigma = \sigma^2 I_2$.

A non-linear multiple regression model can be introduced in which

$$\rho_t = x'_t \beta = \beta_0 + \beta_1 x_{1t} + \dots + \beta_q x_{qt}$$

as in the magnitude model then written in terms of matrices as

$$y = \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \beta \cos \theta \\ \beta \sin \theta \end{pmatrix} + \eta$$
$$2n \times 1 \quad 2n \times 2(q+1) \ 2(q+1) \times 1 \quad 2n \times 1$$
where $y = (y'_R, y'_I)'$ and $\eta = (\eta'_{Rt}, \eta'_{It})' \sim \mathcal{N}(0, \Sigma \otimes \Phi)$

$$\Sigma = \sigma^2 I_2$$
, $\Phi = I_n$.

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1			і Г				l l		
	y_R	y_I		e_n	c_n	r_n		η_R	η_I
vec	y_{R1}	y_{I1}	$=I_2\otimes$	1	1	1	$*\frac{\mathbf{phase}}{\sin\theta}\otimes \begin{vmatrix} \beta \\ \beta \\ \beta \\ \beta \\ \beta \\ 1 \\ \beta \\ 2 \end{vmatrix} + \mathbf{vec}$	η_{R1}	η_{I1}
	:	:		÷	:	:		:	:
	y_{R8}	y_{I8}		1	8	1		η_{R8}	η_{I8}
	y_{R9}	y_{I9}		1	9	-1		η_{R9}	η_{I9}
	÷	:		:	:	:		÷	:
	y_{R16}	y_{I16}		1	16	-1		η_{R16}	η_{I16}
	:	:		÷	÷	:		÷	:
	:	:		÷	÷			E	:
	y_{R241}	y_{I241}		1	241	1		η_{R241}	η_{I241}
	:	:		:	÷	:		E	:
	y_{R248}	y_{I248}		1	248	1		η_{R248}	η_{I248}
	y_{R249}	y_{I249}		1	249	-1		η_{R249}	η_{I249}
	:	:		:	:	:		÷	:
	y_{R256}	y_{I256}		1	256	-1		η_{R256}	η_{I256}

The non-linear multiple regression model

$$y = \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \beta \cos \theta \\ \beta \sin \theta \end{pmatrix} + \eta$$
$$2n \times 1 \quad 2n \times 2(q+1) \quad 2(q+1) \times 1 \quad 2n \times 1$$

$$y = (y'_R, y'_I)'$$
, $\eta = (\eta'_{Rt}, \eta'_{It})' \sim \mathcal{N}(0, \Sigma \otimes \Phi)$, $\Sigma = \sigma^2 I_2$ and $\Phi = I_n$.

The likelihood is

$$p(y|\beta, \theta, \sigma^2, X) = (2\pi)^{-\frac{2n}{2}} (\sigma^2)^{-\frac{2n}{2}} e^{-\frac{h}{2\sigma^2}}$$

where

$$h = \left[y - \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \beta \cos \theta \\ \beta \sin \theta \end{pmatrix} \right]' \left[y - \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \beta \cos \theta \\ \beta \sin \theta \end{pmatrix} \right]$$

Just as in the magnitude model, we want to see if the observed time course has a component related to the reference function.

 $H_0: \ C\beta = \gamma \text{ vs } H_1: \ C\beta \neq \gamma$

i.e. Is the coefficient for the reference function zero.

$$C = (0, ..., 0, 1), \ \beta' = (\beta_0, \beta_1, \cdots, \beta_q), \ \gamma = 0$$

By maximizing the likelihood under the unconstrained alternative

$$\hat{\theta} = \frac{1}{2} \tan^{-1} \left[\frac{2\hat{\beta}'_R(X'X)\hat{\beta}_I}{\hat{\beta}'_R(X'X)\hat{\beta}_R - \hat{\beta}'_I(X'X)\hat{\beta}_I} \right]$$
$$\hat{\beta} = \hat{\beta}_R \cos \hat{\theta} + \hat{\beta}_I \sin \hat{\theta},$$

$$\hat{\sigma}^2 = \frac{1}{2n} \left[y - \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \hat{\beta} \cos \hat{\theta} \\ \hat{\beta} \sin \hat{\theta} \end{pmatrix} \right]' \left[y - \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \hat{\beta} \cos \hat{\theta} \\ \hat{\beta} \sin \hat{\theta} \end{pmatrix} \right]$$
$$\hat{\beta}_R = (X'X)^{-1} X' y_R,$$
$$\hat{\beta}_I = (X'X)^{-1} X' y_I.$$

By maximizing the likelihood under the constrained null hypotheses

$$\begin{split} \tilde{\theta} &= \frac{1}{2} \tan^{-1} \left[\frac{2\hat{\beta}'_R \Psi(X'X)\hat{\beta}_I}{\hat{\beta}'_R \Psi(X'X)\hat{\beta}_R - \hat{\beta}'_I \Psi(X'X)\hat{\beta}_I} \right] \\ \tilde{\theta} &= \Psi[\hat{\beta}_R \cos \tilde{\theta} + \hat{\beta}_I \sin \tilde{\theta}] + (X'X)^{-1}C'[C(X'X)^{-1}C']^{-1}\gamma, \\ \tilde{\sigma}^2 &= \frac{1}{2n} \left[y - \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \tilde{\beta} \cos \tilde{\theta} \\ \tilde{\beta} \sin \tilde{\theta} \end{pmatrix} \right]' \left[y - \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \tilde{\beta} \cos \tilde{\theta} \\ \tilde{\beta} \sin \tilde{\theta} \end{pmatrix} \right] \\ \Psi &= I_{q+1} - (X'X)^{-1}C'[C(X'X)^{-1}C']^{-1}C \,. \end{split}$$

The way this is formulated, we have to worry about phase angles. An alternative formulation is to let $\alpha_1 = \cos \theta$ and $\alpha_2 = \sin \theta$

$$y = \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \quad \begin{pmatrix} \alpha_1 \beta \\ \alpha_2 \beta \end{pmatrix} + \eta, \qquad \alpha_1^2 + \alpha_2^2 = 1$$

$$y = (y'_R, y'_I)'$$
, $\eta = (\eta'_{Rt}, \eta'_{It})' \sim \mathcal{N}(0, \Sigma \otimes \Phi)$, $\Sigma = \sigma^2 I_2$ and $\Phi = I_n$.

With this formulation, it can be seen that this is a reduced rank regression model (Reinsel, 1998).

By maximizing the likelihood under the unconstrained alternative

$$\begin{aligned} \hat{\alpha}_{1} &= \hat{\beta}'(X'X)\hat{\beta}_{R}/[(\hat{\beta}'(X'X)\hat{\beta}_{R})^{2} + (\hat{\beta}'(X'X)\hat{\beta}_{I})^{2}]^{1/2} \\ \hat{\alpha}_{2} &= \hat{\beta}'(X'X)\hat{\beta}_{I}/[(\hat{\beta}'(X'X)\hat{\beta}_{R})^{2} + (\hat{\beta}'(X'X)\hat{\beta}_{I})^{2}]^{1/2} \\ \hat{\beta} &= \hat{\alpha}_{1}\hat{\beta}_{R} + \hat{\alpha}_{2}\hat{\beta}_{I}, \\ \hat{\sigma}^{2} &= \frac{1}{2n} \left[y - \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \hat{\alpha}_{1}\hat{\beta} \\ \hat{\alpha}_{2}\hat{\beta} \end{pmatrix} \right]' \left[y - \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \hat{\alpha}_{1}\hat{\beta} \\ \hat{\alpha}_{2}\hat{\beta} \end{pmatrix} \right] \\ \hat{\beta}_{R} &= (X'X)^{-1}X'y_{R}, \\ \hat{\beta}_{I} &= (X'X)^{-1}X'y_{I}. \end{aligned}$$

By maximizing the likelihood under the constrained null hypotheses

$$\begin{split} \tilde{\alpha}_1 &= \tilde{\beta}'(X'X)\hat{\beta}_R / [(\tilde{\beta}'(X'X)\hat{\beta}_R)^2 + (\tilde{\beta}'(X'X)\hat{\beta}_I)^2]^{1/2} \\ \tilde{\alpha}_2 &= \tilde{\beta}'(X'X)\hat{\beta}_I / [(\tilde{\beta}'(X'X)\hat{\beta}_R)^2 + (\tilde{\beta}'(X'X)\hat{\beta}_I)^2]^{1/2} \\ \tilde{\beta} &= \Psi(\tilde{\alpha}_1\hat{\beta}_R + \tilde{\alpha}_2\hat{\beta}_I) + (X'X)^{-1}C'[C(X'X)^{-1}C']^{-1}\gamma, \\ \tilde{\sigma}^2 &= \frac{1}{2n} \left[y - \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \tilde{\alpha}_1\tilde{\beta} \\ \tilde{\alpha}_2\tilde{\beta} \end{pmatrix} \right]' \left[y - \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \tilde{\alpha}_1\tilde{\beta} \\ \tilde{\alpha}_2\tilde{\beta} \end{pmatrix} \right] \\ \Psi &= I_{q+1} - (X'X)^{-1}C'[C(X'X)^{-1}C']^{-1}C \,. \end{split}$$

GLR statistic is

$$\lambda = \frac{p(y|\tilde{\beta}, \tilde{\sigma}^2, X, H_0)}{p(y|\hat{\beta}, \hat{\sigma}^2, X, H_1)}$$
$$= \left(\tilde{\sigma}^2/\hat{\sigma}^2\right)^{-n}$$

or

$$-2\log\lambda = 2n\log\left(\tilde{\sigma}^2/\hat{\sigma}^2\right)$$
.

This complex model uses all the 2n observations to estimate the q + 3 parameters being the q + 1 regression coefficients, the 1 variance, and the 1 phase error or trigonometric coefficient.

Real fMRI Experiment

```
Imaging Parameters:

1.5T GE Signa

5 axial slices of 128x128

96 acq.-2.0833mm<sup>2</sup>

128 recon.-1.5625mm<sup>2</sup>

FOV =20cm

TR=1000ms

TE=47ms

FA=90°
```

Task: Bilateral finger tapping Block design 16 off $+ 8 \times (16 \text{ on} + 16 \text{ off});$

Time Course Models

Compare the two models for testing $H_0: \beta_2 = 0$. (q = 2, $X = (e_n, c_n, r_n)$, C = (0, 0, 1), $\gamma = 0$)

$$\begin{split} \chi_M^2 &= n \log \left(\tilde{\sigma}_M^2 / \hat{\sigma}_M^2 \right) \stackrel{\cdot}{\sim} \chi_1^2 \\ \chi_C^2 &= 2n \log \left(\tilde{\sigma}_C^2 / \hat{\sigma}_C^2 \right) \stackrel{\cdot}{\sim} \chi_1^2 \end{split}$$

Both χ_1^2 distributed for large samples!

Real fMRI-Magnitude H1 Estimated



Real fMRI-Magnitude H0 Estimated



Real fMRI-Complex H1 Estimated



Real fMRI-Complex H1 Estimated



Real fMRI-Complex H0 Estimated



Real fMRI-Magnitude/Complex H1 Estimated $\hat{\beta}_2$



These coefficients are not visually that different.

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Real fMRI-Magnitude/Complex $-2\log(\lambda)$ **Maps**



These voxel statistics are $\stackrel{.}{\sim} \chi_1^2!$

Real fMRI-Magnitude/Complex $-2\log(\lambda)$ **Maps**



5% Unadjusted Threshold

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Real fMRI-Magnitude/Complex $-2\log(\lambda)$ **Maps**



5% Bonferroni Threshold

Real fMRI-Magnitude/Complex $-2\log(\lambda)$ **Maps**



5% FDR Threshold

Simulation

In each voxel, simulate complex valued time courses like real data.

$$y_t = [(\beta_0 + \beta_1 x_{1t} + \beta_2 x_{2t})\alpha_1 + n_{Rt}] + i[(\beta_0 + \beta_1 x_{1t} + \beta_2 x_{2t})\alpha_1 + n_{It}]$$

From a real dataset, fitted complex model, took $\hat{\beta}_C$ and $\hat{\sigma}_C^2$ from a "highly activated" voxel. $\hat{\alpha}_1$'s and $\hat{\alpha}_2$'s from whole image.

Created complex data where the coefficients in each voxel were the first two elements of $\hat{\beta}_C$. Effect to noise ratio $ENR = \beta_2/\hat{\sigma}_C$.

Created four 7×7 square ROI's, ENR = 1, 1/2, 1/4, 1/8, $\beta_2 = 0$ outside ROI's.

Added normal noise $\mathcal{N}(0, \hat{\sigma}_C^2)$. Varied $SNR = \beta_0/\sigma$.

Activation: 5% Unadjusted



Activation: 5% Bonferroni





M: SNR = 5



Activation: 5% FDR



Simulation

Repeated simulation 1000 times.

For each thresholding method, the power in, or relative frequency over the 1000 simulated images with which each voxel was detected as active, was recorded.



5% Unadjusted, 5% FDR, and 5% Bonferroni thresholds.

Power: 5% Unadjusted



Power: 5% Bonferroni

C: SNR = 1



16 32 C: SNR = 2.5C: SNR = 5

Power: 5% FDR



C: SNR = 1C: SNR = 2.5C: SNR = 5

Power Differences: 5% Unadjusted



Power Differences: 5% Bonferroni

112

16

SNR = 10

32

112

128

16 32 48

SNR = 7.5

64

80

96 112 128



48 64 80 96 112 128

16 32 48 64

 $\overline{\mathsf{SNR}} = 30$

80

96 112

128

-10

Power Differences: 5% FDR



Power versus SNR: Complex (blue) and magnitude (red)



Discussion

A complex data fMRI activation model was presented .

Complex and magnitude models activation compared on real data.

Complex and magnitude models power compared on simulated data.

For a given ENR the complex model power constant irrespective of SNR while the magnitude model power decreases.

For smaller SNR's, the complex activation model demonstrated better power

The complex model more useful as SNR decreases with voxel size.