Your Complex-Valued fMRI Data: What You Assume and Throw Away.

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Recall:



In MRI/fMRI, the Bloch differential equation provide a classical description of the time dependent behavior of the bulk magnetization in applied magnetic fields.

$$\frac{d\vec{M}(t)}{dt} = \gamma \vec{M}(t) \times \vec{B}(t) - \frac{M_{\perp}(t)}{T_2} + \frac{(M_z(t) - M_{z0})\hat{z}}{T_1}$$

where $M_{\perp} = M_x(t)\hat{x} + M_y(t)\hat{y}$ and $\gamma/2\pi = 42.6MHz/T$.

A receive coil is placed near the sample that induces a voltage in the coil by Faraday's law of induction. It is the voltage/signal in the wire s(t) that we measure over time

$$s(k_x, k_y) = \int \int \rho(x, y) e^{-i2\pi (k_x(t)x + k_y(t)y)} dx dy$$

 $\rho(x,y) = \mathsf{PSD}, \ k_x(t) = \frac{\gamma}{2\pi} \int_0^t G_x(t') dt' \text{ and } k_y(t) = \frac{\gamma}{2\pi} \int_0^t G_y(t') dt'$

The previous equation says that we measure a voltage over time or spatial frequencies and perform an IFT to get our PSD image.

But due to imperfections, the object is complex valued.

This occurs over time in fMRI and results in complex valued effective proton spin densities that make up our voxel time course observations.

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

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. More elaborate models and hypotheses possible.

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 and no distributional appproximation which results in improved power for low SNR.

Focus on a single axial slice.

Complex Single Time Images



(a) real image

(b) imaginary image

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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 thrown away.



Real/imaginary unfiltered vector observed over time. Block Design.



Rotate axis. Real/imaginary scatterplot.



Rotate axis. Real over time plot.



Rotate axis. Imaginary over time plot.



Rotate axis (Avg. Phase). Magnitude over time plot.



Phase over time plot.



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

$$y_t = (\rho_t \cos \theta_t + \eta_{Rt}) + i(\rho_t \sin \theta_t + \eta_{It}), \quad t = 1, ..., n$$

 $y_t = \text{complex voxel measurement at time } t$

- ρ_t = true magnitude of voxel measurement at time t
- θ_t = phase of voxel measurement at time t
- η_{Rt} = noise real part voxel measurement at time t η_{It} = 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

Transform to Magnitude-Phase from the Real-Imaginary

$$r_t = \left[(\rho_t \cos \theta_t + n_{Rt})^2 + (\rho_t \sin \theta_t + n_{It})^2 \right]^{\frac{1}{2}}$$

$$\phi_t = \operatorname{atan} \left[\frac{\rho_t \sin \theta_t + n_{It}}{\rho_t \cos \theta_t + n_{Rt}} \right], \quad t = 1, ..., n.$$

The magnitude is not a normal distribution. It's Ricean.

$$p(r_t) = \frac{r_t}{\sigma^2} e^{-\frac{(r_t^2 + \rho_t^2)}{2\sigma^2}} I_o\left(\frac{\rho_t \cdot r_t}{\sigma^2}\right), \quad t = 1, ..., n$$

$$I_o\left(\frac{\rho_t \cdot r_t}{\sigma^2}\right) = \int_{\phi_t = -\pi}^{\pi} \frac{1}{2\pi} \exp\left\{\frac{\rho_t r_t}{\sigma^2} \cos(\phi_t - \theta_t)\right\} d\phi_t$$

is the zeroth order modified Bessel function of the first kind The phase (half numbers) information is discarded.

Magnitude Time Course Model

Magnitude-only model (almost always) assumes

$$p(r_t) = \frac{r_t}{\sigma^2} e^{-\frac{(r_t^2 + \rho_t^2)}{2\sigma^2}} \int_{\phi_t = -\pi}^{\pi} \frac{1}{2\pi} \exp\left\{\frac{\rho_t r_t}{\sigma^2} \cos(\phi_t - \theta_t)\right\} d\phi_t$$
$$\approx \frac{1}{2\pi\sigma^2} \exp\left\{\frac{(r_t - \rho_t)^2}{2\sigma^2}\right\}$$

t = 1, ..., n.

That is, when we use the magnitude-only model, we assume that the Ricean distribution is actually the Normal distribution.

The magnitude-only operation is non-unique. Not one-to-one.

Magnitude Ricean Distribution



SNR= ρ_t/σ . Looks normal for decent SNR. Tails?

Magnitude Ricean Distribution



Does it still look normal?

Magnitude & Complex Time Course Model

Linear multiple regression model individually for each voxel

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

Magnitude

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

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

Complex

$$y = \begin{pmatrix} A_1 & 0 \\ 0 & A_2 \end{pmatrix} \begin{pmatrix} X & 0 \\ 0 & X \end{pmatrix} \begin{pmatrix} \beta \\ \beta \end{pmatrix} + \eta$$
$$2n \times 1 \qquad 2n \times 2n \qquad 2n \times 2(q+1) \qquad 2(q+1) \times 1 \qquad 2n \times 1$$
where $r = (r_1, \dots, r_n)'$, $\epsilon \sim \mathcal{N}(0, \sigma^2 I_n)$,

 $y = (y'_R, y'_I)'$, $\overline{A_1} = \operatorname{diag}(\cos \theta_t)$, $A_2 = \operatorname{diag}(\sin \theta_t)$, and

 $\eta = (\eta'_{Rt}, \eta'_{It})' \sim \mathcal{N}(0, \sigma^2 I_{2n}).$

Complex Time Course Model, $\theta_t = \theta$

The phase in a voxel is related to the magnetic field in that voxel.

Since the magnetic field in voxels is relatively constant, the phase in voxels as we previously saw is relatively constant.

So consider $\theta_t = \theta \ \forall t. \rightarrow$ Rowe and Logan, 2004a, NeuroImage (In Press).

$$\begin{pmatrix} y_{Rt} \\ y_{It} \end{pmatrix} = \begin{pmatrix} x'_t \beta \cos \theta \\ x'_t \beta \sin \theta \end{pmatrix} + \begin{pmatrix} \eta_{Rt} \\ \eta_{It} \end{pmatrix} , \quad t = 1, \dots, n .$$

Activation Statistics

We like to test linear contrast hypotheses on β . C is $r_c \times (q+1)$ full row rank matrix

 $H_0: \ C\beta = 0, \theta_t = \theta \text{ vs } H_1: \ C\beta \neq 0, \theta_t = \theta$

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

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

MLE's from both under null and alternative hypotheses.

Form GLR test statistic, λ .

By maximizing the likelihood under the unconstrained alternative

$$\hat{\theta} = \frac{1}{2} \operatorname{atan} \left[\frac{\hat{\beta}'_R(X'X)\hat{\beta}_I}{(\hat{\beta}'_R(X'X)\hat{\beta}_R - \hat{\beta}'_I(X'X)\hat{\beta}_I)/2} \right]$$
$$\hat{\beta} = \hat{\beta}_R \cos \hat{\theta} + \hat{\beta}_I \sin \hat{\theta}, \quad \lt Note$$

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

$$\hat{\beta}_I = (X'X)^{-1}X'y_I.$$

By maximizing the likelihood under the constrained null hypotheses

$$\tilde{\theta} = \frac{1}{2} \operatorname{atan} \left[\frac{\hat{\beta}'_R \Psi(X'X) \hat{\beta}_I}{(\hat{\beta}'_R \Psi(X'X) \hat{\beta}_R - \hat{\beta}'_I \Psi(X'X) \hat{\beta}_I)/2} \right]$$
$$\tilde{\beta} = \Psi[\hat{\beta}_R \cos \tilde{\theta} + \hat{\beta}_I \sin \tilde{\theta}],$$

$$\tilde{\sigma}^2 = \frac{1}{2n} \left[y - \begin{pmatrix} X\tilde{\beta}\cos\tilde{\theta} \\ X\tilde{\beta}\sin\tilde{\theta} \end{pmatrix} \right]' \left[y - \begin{pmatrix} X\tilde{\beta}\cos\tilde{\theta} \\ X\tilde{\beta}\sin\tilde{\theta} \end{pmatrix} \right]$$
$$\Psi = I_{q+1} - (X'X)^{-1}C' [C(X'X)^{-1}C']^{-1}C .$$

 \cup

Same Ψ as magnitude-only model.

Iq+1

 Ψ

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

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

$$-2\log\lambda \stackrel{.}{\sim} \chi^2_{r_c}!$$

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 imperfection.

Complex Time Course Model, $\theta_t \neq \theta_{t'}$

What if for who knows what uniformed reason we don't want to assume anything about the magnetic field in voxels and hence the phase in voxels.

So consider $\theta_t \neq \theta_{t'} \forall t, t'$. \rightarrow Rowe and Logan, 2004b, NeuroImage (In Press).

$$\begin{pmatrix} y_{Rt} \\ y_{It} \end{pmatrix} = \begin{pmatrix} x'_t \beta \cos \theta_t \\ x'_t \beta \sin \theta_t \end{pmatrix} + \begin{pmatrix} \eta_{Rt} \\ \eta_{It} \end{pmatrix} , \quad t = 1, \dots, n .$$

Unique phase at each time point.

Activation Statistics

We want to test linear contrast hypotheses on β . C is $r \times (q+1)$ full row rank matrix

 $H_0: \ C\beta = 0, \theta_t \neq \theta_{t'} \text{ vs } H_1: \ C\beta \neq 0, \theta_t \neq \theta_{t'}$

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

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

MLE's from both under null and alternative hypotheses.

Form GLR test statistic, λ .

Complex Unconstrained Phase Model

By maximizing the likelihood under the unconstrained alternative

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

By maximizing the likelihood under the constrained null hypotheses

$$\tilde{\beta} = \Psi \hat{\beta},$$

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

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

Same Ψ as complex model.

Magnitude Model

The GLR statistic for the complex unrestricted phase AKA magnitude-only model is

$$\lambda = \frac{p(r|\hat{\beta}, \hat{\sigma}^2, X, H_0)}{p(r|\hat{\beta}, \hat{\sigma}^2, X, H_1)}$$
$$= \left(\tilde{\sigma}^2 / \hat{\sigma}^2\right)^{-\frac{n}{2}}$$
$$-2\log\lambda \stackrel{\sim}{\sim} \chi^2_{r_c}!$$

$$\left(\frac{n-q-1}{r_c}\right)(\lambda^{-\frac{2}{n}}-1) = \frac{(C\beta-0)'[C(X'X)^{-1}C']^{-1}(C\beta-0)}{r_c n\hat{\sigma}^2/(n-q-1)}$$

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

Related Work

Cramer-Rao Lower bounds for parameters (submitted). -CRLB for SE of variance 1/2 in complex model

$$CRLB_{M} = \begin{array}{c} \beta & \sigma^{2} \\ \sigma^{2} & \left[\begin{array}{c} \sigma^{2} (X'X)^{-1} & 0 \\ 0 & 2\sigma^{4}/n \end{array} \right] \\ CRLB_{C} = \begin{array}{c} \beta \\ \sigma^{2} \\ \theta \end{array} \begin{bmatrix} \sigma^{2} (X'X)^{-1} & 0 & 0 \\ 0 & \sigma^{4}/n & 0 \\ 0 & 0 & \sigma^{2}/\beta'(X'X)\beta \end{bmatrix}$$

Real fMRI Experiment

Imaging Parameters: 1.5T GE Signa 5 axial slices of 128×128 96 acq.-2.0833mm² 128 recon.-1.5625mm² FOV =20cm TR=1000ms TE=47ms FA=90°

Task: Bilateral sequential finger tapping Block design 16 off $+ 8 \times (160n + 160ff);$

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))

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

Both χ_1^2 distributed for large samples!

Real fMRI-Complex CP H1 Estimated Reference Coefficients



Real fMRI-UP/MO & CP H1 Estimated $\hat{\beta}_2$



These coefficients are not visually that different but numerically different.

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Real fMRI-UP/MO & CP $-2\log(\lambda)$ Maps



5% Bonferroni Threshold

Real fMRI-UP/MO & CP Bonferroni Overlap Maps



Yellow = UP/MO&CP; Red = UP/MO; Orange = CP;

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. $\hat{\theta}$'s from whole image.

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

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

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

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 versus CNR: Complex (blue) and magnitude (red)



 $\mathsf{SNR} = 1$

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



SNR = 2.5

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



SNR = 5



Recent work has suggested that certain voxel phase time courses may also exhibit task related phase changes (Borduka et al.,1999; Menon,2002).

Both Magnitude and Phase change linearly over time.

$$y_t = [\rho_t \cos \theta_t + \eta_{Rt}] + i[\rho_t \sin \theta_t + \eta_{It}]$$

$$\rho_t = x'_t \beta = \beta_0 + \beta_1 x_{1t} + \dots + \beta_{q_1} x_{q_1t}$$

$$\theta_t = u'_t \gamma = \gamma_0 + \gamma_1 u_{1t} + \dots + \gamma_{q_2} u_{q_2t}, \qquad t = 1, \dots, n$$

 x'_t is the t^{th} row of a design matrix X for the magnitude and u'_t is the t^{th} row of a design matrix U for the phase.

Last Col of X and U are task related reference functions.

Phase changes with task in this voxel!





Magnitude-only change

Magnitude & Phase change

We want to see if there is anything in either the magnitude or phase of the observed complex valued time course has a component related to the reference function.

i.e.

$$C = (0, ..., 0, 1), \ \beta = (\beta_0, \beta_1, \cdots, \beta_{q_1})'$$

 $D = (0, ..., 0, 1), \ \gamma = (\gamma_0, \gamma_1, \cdots, \gamma_{q_2})'$

MLE's from both under null and alternative hypotheses.

Form GLR test statistic, λ .

Four readily visible hypotheses for testing.

 $H_a: C\beta \neq 0, D\gamma \neq 0$ $H_b: C\beta = 0, D\gamma \neq 0$ $H_c: C\beta \neq 0, D\gamma = 0$ $H_d: C\beta = 0, D\gamma = 0$

We can combine these four hypotheses in different ways to form specific hypothesis pairs.

Can write down the likelihood and Log likelihood.

Can maximize the log likelihood under each hypothesis using various Lagrange constraints.

$$LL = -n \log(2\pi) - \sum_{t=1}^{n} \log r_t - n \log \sigma^2$$

- $\frac{1}{2\sigma^2} \sum_{t=1}^{n} \left[r_t^2 + (x_t'\beta)^2 - 2(x_t'\beta) \underbrace{r_t \cos(\phi_t - u_t'\gamma)}_{r_{*t}} \right]$
= $-n \log(2\pi) - \sum_{t=1}^{n} \log r_t - n \log \sigma^2$
- $\frac{1}{2\sigma^2} \left[(r - X\beta)'(r - X\beta) + 2(r - r_*)'X\beta \right]$

Focus on

 $H_d: C\beta=0, \ D\gamma=0 \text{ vs } H_a: C\beta\neq 0, \ D\gamma\neq 0$

Unrestricted MLEs

$$\hat{\beta} = (X'X)^{-1}X'\hat{r}_{*},
\hat{\gamma} = (\hat{Z}'\hat{Z})^{-1}\hat{Z}'\hat{\phi}_{*},
\hat{\sigma}^{2} = \frac{1}{2n} \left[(r - X\hat{\beta})'(r - X\hat{\beta}) + 2(r - \hat{r}_{*})'X\hat{\beta} \right] ,$$

 \hat{r}_* is an $n \times 1$ vector with t^{th} element $r_t \cos(\phi_t - u'_t \hat{\gamma})$, \hat{Z} is an $n \times (q_2 + 1)$ matrix with t^{th} row $\hat{z}'_t = u'_t \sqrt{r_t x'_t \hat{\beta}}$, $\hat{\phi}_*$ is an $n \times 1$ vector with t^{th} element $\phi_t \sqrt{r_t x'_t \hat{\beta}}$. An iterative maximization algorithm is used.

In MLE for $\hat{\gamma}$, $\cos(\alpha) = 1 - \alpha^2/2$. $\alpha = \pi/12$ radians or 15 degrees, $\cos(\alpha) = 0.9659$ while $1 - \alpha^2/2 = 0.9657$

Similarly, constrained MLEs ($H_0: C\beta = 0, D\gamma = 0$)

$$\tilde{\beta} = \Psi(X'X)^{-1}X'\tilde{r}_{*},
\tilde{\gamma} = \Omega(\tilde{Z}'\tilde{Z})^{-1}\tilde{Z}'\tilde{\phi}_{*},
\tilde{\sigma}^{2} = \frac{1}{2n} \left[(r - X\tilde{\beta})'(r - X\tilde{\beta}) + 2(r - \tilde{r}_{*})'X\tilde{\beta} \right]
\Psi = I_{q_{1}+1} - (X'X)^{-1}C'[C(X'X)^{-1}C']^{-1}C
\Omega = I_{q_{2}+1} - (\tilde{Z}'\tilde{Z})^{-1}D'[D(\tilde{Z}'\tilde{Z})^{-1}D']^{-1}D$$

 \tilde{r}_* is an $n \times 1$ vector with t^{th} element $\tilde{r}_t \cos(\phi_t - u'_t \tilde{\gamma})$, \tilde{Z} is an $n \times (q_2 + 1)$ matrix with t^{th} row $\tilde{z}'_t = u'_t \sqrt{r_t x'_t \tilde{\beta}}$, $\tilde{\phi}_*$ is an $n \times 1$ vector with t^{th} element $\phi_t \sqrt{r_t x'_t \tilde{\beta}}$. An iterative maximization algorithm is used.

Other models are special cases.

 $H_b: C\beta = 0, D\gamma \neq 0$ vs $H_a: C\beta \neq 0, D\gamma \neq 0$ with $U = I_n$ and $D = I_n$ is complex unrestricted phase (R-L 04b) AKA magnitude-only model

 $H_b: C\beta = 0, D\gamma \neq 0 \text{ vs } H_a: C\beta \neq 0, D\gamma \neq 0 \text{ with}$ U = (1, ..., 1)' is complex constant phase (R-L 04a)model

 $H_c: C\beta \neq 0, D\gamma = 0$ vs $H_a: C\beta \neq 0, D\gamma \neq 0$ with $X = I_n$ and $C = I_n$ is complex unrestricted magnitude model AKA phase-only model (Meller 2004 Thesis)

etc.

Real $-2\log(\lambda)$ Maps



5% Bonferroni Threshold

Current Work: Bonferroni Threshold



Yellow =UP/MO&CP&LP; Red =UP/MO; Magenta=UP/MO&CP Orange=CP; Blue=LP; Green CP&CL

Current Work: Bonferroni Threshold Average magnitude time course of



Red+Magenta=208Yellow=230

Current Work: Bonferroni Threshold

Average phase time course of



(a) red,magenta voxels

(b) yellow voxels

Current Work: Bonferroni Threshold Histogram of correlations: magnitude tc vs ref funct.



$$\label{eq:meanRedMagenta} \begin{split} meanRedMagenta &= 0.3189 \\ meanYellow &= 0.5213 \end{split}$$

Current Work: Bonferroni Threshold Histogram of correlations: phase tc vs ref funct.



(a) red, magenta voxels

(b) yellow voxels

meanRedMagenta = -0.1960meanYellow = -0.1452

Current Work: Bonferroni Threshold

The red, magenta voxels appear to have magnitude time course that

are less related to the reference function than the yellow ones and

phase time courses that are more related to the reference function

than the yellow ones.

Simulations are under way (as I speak) to characterize this.

Conclusion

To be continued ...

Further research is needed.

Thanks