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FMRI Neurologic Synchrony Measures for Alzheimer's Patients With Monte Carlo Critical Values

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Abstract

It is well known that regions of the brain exhibit functional synchrony. A well established method is the average cross correlation termed the COSLOF index which has proved useful as a noninvasive quantitative marker of hippocampal synchrony for the preclinical stage of Alzheimer's disease. This paper presents the COMDET, an alternative index of functional synchrony, and compares it to the COSLOF with their statistical underpinnings. Logarithmic functions of these two statistics are presented with their asymptotic chi squared distributions. These two statistics are empirically compared under five correlation structures. It is found that the COMDET performs better than the COSLOF except under very specific cases. Critical values of the COMDET and COSLOF as well as their logarithmic functions are presented which are determined via Monte Carlo simulation.

1 [illegible]

The well-known phenomenon of functional synchrony [3, 6] in functional magnetic resonance imaging (FMRI) studies has been characterized b]qb[5mf-z[6-F1Gflbfl5¯]qbF5[illegible]

with the use of the generalized likelihood ratio test. The generalized likelihood ratio statistic is computed by maximizing the likelihood with respect to the unknown parameters under the null and alternative hypotheses. These estimated parameters are inserted into their respective likelihood functions and the ratio taken.

3

Often structure in a covariance matrix can aid in simplifying the spatial relationship between the voxels. One such spatial relationship is the intraclass correlation structure. The intraclass correlation structure is when the correlation matrix R has ones along the main diagonal and all other elements have the correlation parameter ρ.

The null hypothesis that

In the above, $G = (Y - XB)'(Y - XB)$ was defined and the property $tr(ABC) = tr(B'A'C')$ was used.

It can be shown that estimates of B, D, and ρ under the two hypotheses are

$$
\begin{aligned}
\tilde{B} &= (X'X)^{-} X'Y, & \tilde{D} &= \frac{}{-\rho_0}\; 1 - \frac{\rho_0}{+(p- \;)\rho_0} \;\; \mathrm{diag}\frac{G}{n}, & \tilde{\rho} &= \rho_0 \\
\hat{B} &= (X'X)^{-} X'Y, & \hat{D} &= \frac{}{-\rho}\; 1 - \frac{\rho}{+(p- \;)\rho} \;\; \mathrm{diag}\frac{G}{n}, & \hat{\rho} &= \bar{\rho}
\end{aligned}
$$

where $\tilde{G}$ and $\hat{G}$ which are equivalent are G above with $\tilde{B}$ or $\hat{B}$ substituted in for B and

$$\bar{\rho} = \frac{1}{p(p-1)} \left[\sum_{j}^{p} \sum_{j'}^{p} \frac{G_{jj'}}{\sqrt{G_{jj} G_{j'j'}}} - p \right].$$

The maximum likelihood estimate of the variances $\hat{D}$ is an approximate value. The maximum likelihood estimate of the correlation coe cient under the alternative hypothesis has been well approximated by its method of moments estimate because an explicit expression can not be found.

The generalized likelihood ratio statistic for the above hypothesis test is

$$
\begin{aligned}
\lambda &= \frac{p(Y|\tilde{B}, \tilde{D}, \tilde{\rho}, X)}{p(Y|\hat{B}, \hat{D}, \hat{\rho}, X)} \\
&= \frac{(2\pi)^{-\frac{np}{2}} |\tilde{\Sigma}|^{-\frac{n}{2}} e^{-\frac{1}{2} tr \Sigma^{-1} (Y-XB)(Y-XB)'}}{(2\pi)^{-\frac{np}{2}} |\hat{\Sigma}|^{-\frac{n}{2}} e^{-\frac{1}{2} tr \Sigma^{-1} (Y-XB)(Y-XB)'}} \\
&= \frac{\left| \frac{}{-\rho_0} \left(1 - \frac{\rho_0}{+(p- \;)\rho_0}\right) diag \frac{G}{n} \right|^{-n/} \;\; |R_0|^{-n/}}{\left| \frac{}{-\rho} \left(1 - \frac{\rho}{+(p- \;)\rho}\right) diag \frac{G}{n} \right|^{-n/} \;\; |\hat{R}|^{-n/}} \\
&= \\
\lambda &= \frac{(1-\rho_0)^{n/} \; [1 + (p-1)\hat{\rho}]^{n/} \; [1 - \frac{\rho}{+(p- \;)\rho}]^{np/}}{[1 + (p-1)\rho_0]^{n/} \; [1 - \frac{\rho_0}{+(p- \;)\rho_0}]^{np/} \; (1-\hat{\rho})^{n/}}
\end{aligned}
$$

It is readily seen that a test statistic for the hypothesis test should be a function of the COSLOF or average cross corelation coe cient. A natural choice for the test statistic is $\hat{\rho}$. It can be seen that $\hat{\rho}/[1 + (p-1)\hat{\rho}]$ is approximately zero then $\hat{\rho}$ can be explicitly solved for from the generalized likelihood ratio. The test statistic $-2 \ln \lambda$ can alternatively be used which has an asymptotic χ distribution with one degree of freedom.

Often it is believed that there is no structure in a covariance matrix or that the spatial relationship between the voxels is general and not independent. The general covariance (correlation) structure is when each element voxel has its own distinct variance and covariance with every other voxel.

The null hypothesis that the voxels are statistically independent versus the alternative hypothesis that the voxels have a general covariance is

$$H_0 : B \in \mathbb{R}$$

which is χ with $\gamma = p(p-1)/2$ degrees of freedom. Exact critical 5% and 1% values for v (which have been replicated in Tables 9 and 11) were presented [8] for $\nu = 3, \ldots, 20$, $p = 3, \ldots, 10$, $p \leq \nu$ where $\nu = n - q - 1$ along with the asymptotic critical values. Note that the statistic $-2n \ln |R|$ was not used. Monte Carlo investigations have found that the distribution and hence critical values of $-[\nu - (2p + 5)/6] \ln |R|$ was closer to the true sampling distribution than $-2 \ln |R|$.

The COSLOF, $\bar{\rho}$ and COMDET $|\hat{R}|$, which are derived from generalized likelihood ratio tests do not follow well known and easily integrable distribution functions. In order for the COMDET statistic to be computable $\hat{R}$ must be positive definite and is only so when $p \leq \nu$. The probability distribution function of was derived under the null hypothesis with exact 5% and 1% critical values along with the asymptotic χ distribution of v [8]. Both statistics $\hat{\rho}$ and ˆ are measures of functional synchrony. The distribution of the COSLOF ρ is not known or easily computable and critical values have not previously been presented. Monte Carlo generated critical values are presented in the appendix.

Given a set of data Y, the statistics $\hat{\rho}$ and ˆ (or $\hat{u}$ and $\hat{v}$) are computed. These test statistics are compared to critical values in the appendix. The null hypothesis is rejected at a level α if the test statistic $\hat{\rho}$ is larger than the tabulated α level critical value or ˆ is smaller than the tabulated value. Asymptotic hypothesis for population di erences can also be made as outlined in the appendix.

If functional synchrony were being measured in the presence of a presented stimulus or task, then a third column would be added to the design matrix X corresponding to a hemodynamic reference function.

The exact distributions of $\hat{\rho}$, u, ˆ, and v under the null hypothesis that the voxels are independent are extremely complicated as is the determination of exact critical values. Exact 5% and 1% critical values for v (and hence ˆ have only previously been given [8] for very specific combinations of ν and p. For from each set of vectors which resulted in $\hat{R}, \ldots, \hat{R}_L$ and $\hat{v}, \ldots, \hat{v}_L$. These v's were ranked then the $.90 * L^{th}$, $.95 * L^{th}$, $.975 * L^{th}$, $.99 * L^{th}$ and $.999 * L^{th}$

matrix while the COSLOF is simply the average cross-correlation. In the next section, the COSLOF and COMDET are compared for sensitivity and power to detect varying correlation structures.

For a power analysis of sensitivity to di erent correlation structures, data for $p = 25$, $q = 2$, and $n = 77, 102$, or 177 is generated with five di erent correlation structures. The correlation structures are intraclass (INT) with equal cross correlations, spatial distributed lag (SDL) one with a voxel having the same cross-correlation with its four-neighbors, what will be called spatial distributed lag one-minus (SDM) where the first thirteen voxels are SDL(1) while the last twelve are spatial SDL(1) with c replaced by $-c$, Markov (MKV) or temporal autoregressive one where the correlation between the numbered voxels is the correlation raised to the power of the di erence in their numbering, temporal distributed lag (TDL) one or tridiagonal where the correlation matrix has the correlation on the first super and sub diagonal. The last two may not be appropriate for the current application but are commonly used for others and are included for completeness. For each of the correlation structures, 10 data sets with the same model as above were generated with correlation parameter $c = 0.15$ or $c = 0.25$.

Table 2 contains the number of rejected null hypotheses for the two functional synchrony measures with each correlation structure at the $\alpha = .001$ level. The sensitivity power analysis indicates that for moderate to large sample

Table 2: Correlation structure power analysis. $p = 25$

		c .					c .				
$n = 75$		[illegible]			[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	
		[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
$n = 100$		[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	
		[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
$n = 175$		[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]
		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

sizes or moderate to large spatial correlations, always use the COMDET; but for low sample sizes and low spatial correlations, use the COSLOF. Further, when there are both positive and negative correlations use the COMDET and not the COSLOF. The COSLOF and COMDET performed similarly with no correlation with about ten rejected hypotheses. In neuroscience, voxels are most often positively correlated. In other applications, there may be both positive and negative correlations which could sum to zero and result in a COSLOF which is not significant but a COMDET which is very significant.

The COMDET, a new measure of functional synchrony was presented and compared with the previous measure, the COSLOF. For a simulated data set, both measures of functional synchrony were computed and found the correlation between the voxels to be significant, but the COMDET declared it to be significant at a much higher level. A power analysis of sensitivity to different correlation structures was performed with the aid of Monte Carlo generated critical values for significance. It was found that for moderate to large sample sizes or moderate to large correlations, the COMDET should be used, but for low sample sizes and low correlations the COSLOF may be prefered. It was also found that when there are both positive and negative correlations, the COMDET should be used.

Suppose we now wish to test hypotheses regarding the COSLOF and COMDET for a population or the di erence in populations. Let $s = 1, \ldots, S$ denote the subjects in a population. Denote the estimated COSLOF and COMDET for subject s by $\hat{\rho}_s$ and $\hat{\ }_s$. For a single population, there are two functional synchrony hypotheses which can be evaluated. Associated with the COSLOF, is the hypothesis

$$
\begin{array}{rrcl}
H_0 : & B_s & \in & \mathbb{R}^{(q+\ )\times p_s} \\
 & \mathrm{diag}(D_s) & = & \mathbb{R}^{p_s +} \\
 & \rho_s & = & \rho_{s'}
\end{array}
\quad vs \quad
\begin{array}{rrcl}
H : & B_s & \in & \mathbb{R}^{(q+\ )\times p_s} \\
 & \mathrm{diag}(D_s) & = & \mathbb{R}^{p_s +} \\
 & \rho_s & \neq & \rho_{s'}
\end{array}
$$

that the average cross-correlation for the subjects in the population is the same with test statistic

$$\hat{u} = \sum_{s}^{S} \hat{u}_s.$$

Asymptotically, $\hat{u} \sim \chi\ (S)$ where S is the number of subjects. The large degrees of freedom approximation $\hat{u} \sim N($

Table 3: Critical 10% COSLOF values from sampling.

ν, p	[illegible]																							
	[illegible]																							
	[illegible]	[illegible]																						
	[illegible]	[illegible]	[illegible]																					
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Table 4: Critical 5% COSLOF values from sampling.

ν, p	[illegible]
	[illegible]

Table 5: Critical 2.5% COSLOF values from sampling.

ν, p	[illegible]
	[illegible]
	[illegible]
	[illegible]
	[illegible]
	[illegible]
	[illegible]
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	[illegible]
[illegible]	[illegible]
	[illegible]
[illegible]	[illegible]

Table 6: Critical 1% COSLOF values from sampling.

ν, p	
[illegible]	[illegible]

Table 7: Critical .1% COSLOF values from sampling.

ν, p

Table 8: Critical 10% ν values from sampling.

ν, p	[illegible]
[illegible]	[illegible]
∞	[illegible]

Table 9: Critical 5% v values from sampling.

ν, p	[illegible]
[illegible]	[illegible]

Table 10: Critical 2.5% ν values from sampling.

ν, p	
[illegible]	[illegible]

Table 11: Critical 1% v values from sampling.

ν, p	[illegible]				
[illegible]	[illegible]				
[illegible]	[illegible]	[illegible]			
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 12: Critical .1% v values from sampling.

v, p

[1] L.J. Bain and M. Engelhardt. *Introduction to Probability and Mathematical Statistics*. PWS-Kent Publishing Company, Boston, Massachusetts, USA, second edition, 1992.

[2] P. Bandettini, A. Jesmanowicz, Eric Wong, and James Hyde. Processing strategies for time-course data sets in functional MRI of the human brain.