June 16th, 2004

Innovation approach to extracting connectivity information from fMRI time series

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1. Introduction

Data sets obtained by functional magnetic resonance imaging (fMRI) represent both spatial and temporal aspects of the hemodynamics of the human brain. Whereas usually in the analysis of fMRI data sets the focus lies on spatial aspects, the temporal dimension has been receiving less attention. In this contribution we show that by fitting spatiotemporal dynamical models to fMRI data sets information about the long-distance connectivity structure of the investigated brain can be obtained.

2. Methodology

Connectivity between two components $x_i(t)$ and $x_j(t)$, $t = 1, \ldots, N$ (each with mean zero) of multivariate time series $\boldsymbol{x}(t) = \big(x_1(t), \ldots, x_V(t)\big)$ may be quantified by measures of *linear correlation* such as

$$C(x_i, x_j) = \frac{\sum_t x_i(t) x_j(t)}{\sqrt{\sum_t x_i^2(t) \sum_t x_j^2(t)}} ,$$

or, alternatively, by *mutual information* [1 , 3]

$$I(x_i, x_j) = \sum_{k,l} p\big(x_i(k), x_j(l)\big) \log \frac{p\big(x_i(k), x_j(l)\big)}{p\big(x_i(k)\big) p\big(x_j(l)\big)} ,$$

where k, l label all possible values (states) of $x_i(t)$ and $x_j(t)$, and $p(.)$ denotes (marginal or joint) probability distributions. It is well known that estimating these distributions from time series data may be difficult, because:

- lack of data (fMRI time series are short!), making results from histogram estimators or kernel estimators unreliable;
- possibly complicated shape of the distributions (as a consequence of nonlinearities);
- temporal correlations among the $x_i(t)$ [3].

Instead of silently ignoring these temporal correlations, we propose to explicitly model them by spatiotemporal dynamical models which can be used to whiten the data, i.e. to estimate *innovations* (residuals) after predicting the deterministic part of the dynamics:

$$\boldsymbol{\epsilon}(t) = \boldsymbol{x}(t) - \mathcal{F}\big(\boldsymbol{x}(t-1), \boldsymbol{x}(t-2), \ldots\big) .$$

The linear approximation of $\mathcal{F}(.)$ is given by a multivariate linear autoregressive model of order q:

$$\boldsymbol{\epsilon}(t) = \boldsymbol{x}(t) - \sum_{t'=1}^{q} \mathsf{A}(t') \boldsymbol{x}(t - t') ,$$

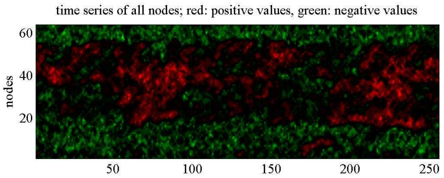
where the $\mathsf{A}(t')$ represent a set of q parameter matrices of size $V \times V$. By assuming that only neighbouring voxels will interact directly, most elements of the $\mathsf{A}(t')$ become zero, and the remaining elements can be estimated by a maximum-likelihood approach. Each component of $\boldsymbol{\epsilon}(t)$ will be temporally uncorrelated (*white*) and, according to the theory of Markov processes [2], will follow a Gaussian distribution. Furthermore, spatial whitening can be applied by multiplying the vector of all components $\boldsymbol{x}(t)$ with a Laplacian matrix, prior to model fitting; thereby components of $\boldsymbol{\epsilon}(t)$ become mutually uncorrelated.

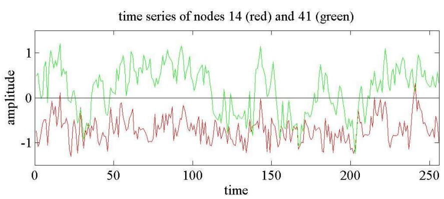
As a result, the data $\boldsymbol{x}(t) = \big(x_1(t), \ldots, x_V(t)\big)$ is replaced by the corresponding innovations, $\boldsymbol{\epsilon}(t) = \big(\epsilon_1(t), \ldots, \epsilon_V(t)\big)$. These innovations are more convenient for searching for long-distance connections than the raw data itself. For this purpose, pairs of voxels (i, j) are modelled, and the difference of (logarithmic) likelihood between uncoupled and coupled bivariate models (corresponding to absence and presence of direct connection) is calculated as an estimate of mutual information $I(x_i, x_j)$ [1], which is superior to previously employed estimators of $I(x_i, x_j)$.

3. Simulation study

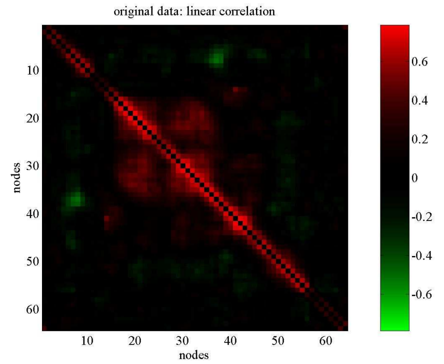
A stochastic dynamical system is generated by a (closed) chain of $V = 64$ nodes (voxels) with local linear second-order dynamics, sigmoid nonlinearity and neighbourhood coupling. The system represents a coupled-map lattice, with some properties of neural networks. The nodes are driven by Gaussian white noise processes, which are mutually independent for all pairs of nodes, except for nodes 14 and 41, which are driven by the same noise process.

A multivariate time series of length $N = 256$ points is sampled:

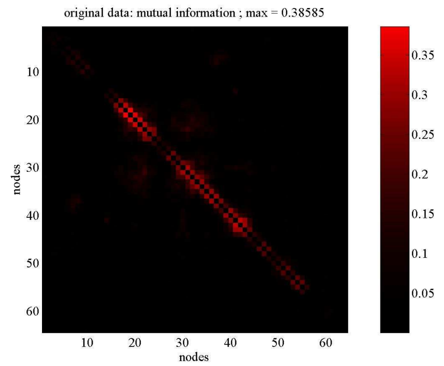




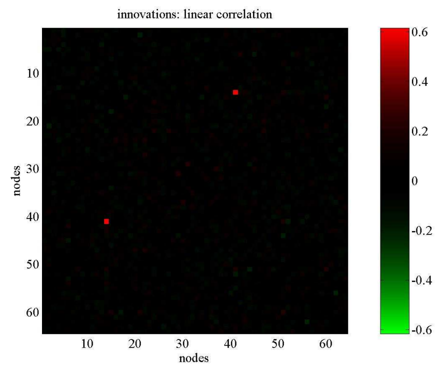
The linear correlation map of this data set shows a variety of structures:



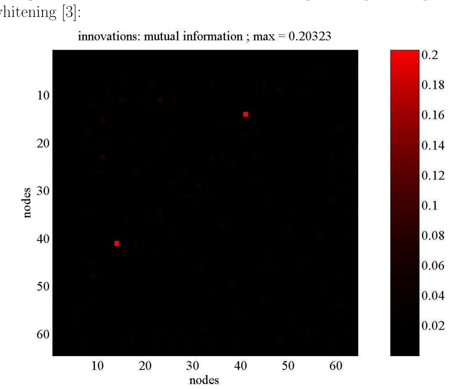
The same structures can be seen in a histogram estimate of the mutual information map of this data set [3]:



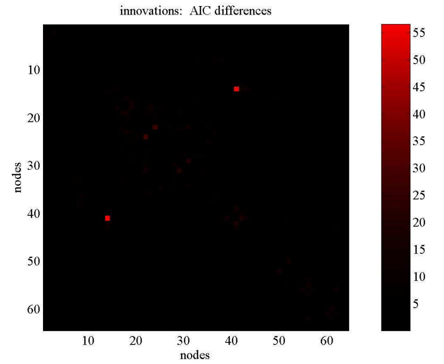
Now the linear correlation map is recomputed after spatiotemporal whitening; it can be seen that the strong correlation between nodes 14 and 41 is much more pronounced now:



Histogram estimate of mutual information map after spatiotemporal whitening [3]:



And finally the mutual information map is computed again, but now based on the differences of log-likelihood between uncoupled and coupled bivariate models (more precisely the difference of AIC is shown, where AIC represents the *Akaike Information Criterion*, a corrected estimator for $(-2)\times$ log-likelihood, introduced in order to avoid overfitting). It can be seen that, in contrast to the map obtained by a histogram estimator, this map clearly identifies the strong correlation between nodes 14 and 41, despite only a very short time series of 256 points being available.

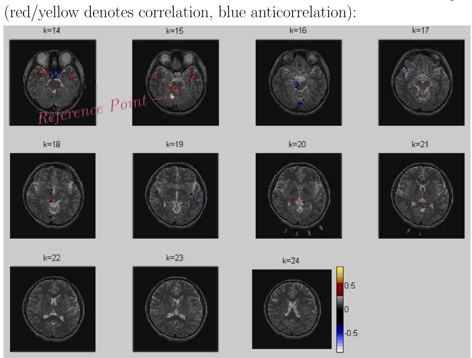


4. Example for analysis of real fMRI data

We apply the new approach to a fMRI data set from a visual-stimulation experiment (data courtesy of N.Sadato, National Institute of Physiological Sciences, Okazaki, Japan). Final results of the connectivity analysis for this data set are not yet available, but we can demonstrate the feasibility of the proposed methodology.

After applying the spatiotemporal whitening as described above, two voxels are arbitrarily chosen:

For this pair of voxels the uncoupled model yields an AIC of 1101.7768, and the coupled model yields AIC=1066.9254, indicating a clear improvement of the model by including an instantaneous correlation between these two voxels. In principle, the same analysis can be carried out for all pairs of voxels, and for many of them an improvement can be found. In this way for each chosen reference point a map of correlated or anti-correlated voxels can be found, as shown in the next example (red/yellow denotes correlation, blue anticorrelation):



5. Summary

We have presented a dynamical approach to extracting connectivity information from multivariate time series data, such as fMRI. Connectivity is defined in terms of correlation or mutual information between time series of innovations remaining after spatiotemporal whitening. Differences of log-likelihood for pairs of voxels directly serve as an improved estimator of mutual information.

We hope that this approach will contribute to resolving the current confusion on the proper definition of the concept of "functional connectivity", on efficient ways to explore it and on its relation to "anatomical connectivity".

The approach can easily be extended to time-delayed correlations, and thereby to quantitative measures of causality.

6. References

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