Short Communication

ANALYZING SPATIAL DISTRIBUTIONS OF FMRI “BOLD” SIGNALS BY RQA VARIABLES.

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Introduction

Recurrence Quantification Analysis (RQA) is a model-free method sensitive to both linear and non-linear time-dependent processes. The assumption-free RQ estimation of brain activation patterns thus offers an extension and improvement of conventional General Linear Modeling (GLM) approaches. In the present work we check the conjecture that parameters obtained by RQA can be used as indicators of significant MR signal changes during activation in the human brain. We produced recurrence plots of experimental fMRI data acquired on a subject performing a motor task and, by means of RQA variables, we analyzed signals generated from different areas or volume elements of the brain. If brain activity can be reliably identified and imaged by such an approach, a spatial picture of the time dependent changes in the system may be developed and active/non active areas discriminated without too strict a priori assumptions.

BOLD fMRI signals and their analysis

One common form of functional MRI is known as blood oxygen level dependent imaging, or BOLD. The BOLD technique is based on measurements that are sensitive to changes of the effective transverse relaxation time of a magnetic resonance (MR) signal. These changes occur due to varying deoxy-hemoglobin concentrations following locally increased neuronal metabolic rates. To put it in different words, these physiological processes induce activation related signal variations in each volume element of a brain that can be detected with the BOLD technique.

With conventional analysis methods (4), activated brain areas can be revealed by comparing the temporal evolution of the MR signal in each voxel with an external reference model that represents the expected activation time-course. The overall results are transformed into a visual output, where active volume elements are rendered by false colors corresponding to the statistical significance of the difference of the dynamic features of the signal in that volume element, as compared to an external reference model. Unfortunately the choice of such a reference model remains arbitrary and subject to systematic and unforeseeable pitfalls, such as those induced by delays or differences in the shape between the MR signal variation and the adopted reference model. Thus, any conclusion drawn from conventional statistical regression
analysis of BOLD images will depend on the choice of reference model and therefore will be somewhat subjective.

One analytical technique that has proven successful for the quantitative analysis of dynamic systems is Recurrence Quantification Analysis (RQA). This method (1-3) identifies and quantifies recurrent patterns in dynamic systems without relying on assumptions and models. A number of dynamic systems have been studied using RQA techniques. In the present work RQA was applied to analyze the spatial distribution of RQA variables generated from time varying signals that have spatial contiguity, i.e. fMRI signals collected from a plurality of area or volume elements, of the human brain.

Analytical approach

For each collected MR voxel time-series, \( y_{\text{raw}} \), (see below) three preprocessing steps are performed previous to statistical analysis. Correction for involuntary motion during MR-scanning; then, in order to increase the MR signal-to-noise-ratio, a spatial smoothing filter is applied for each brain 3D-volume by convolution with an isotropic Gaussian kernel (FWHM = 6 mm for our data); afterwards, removal of low frequency noise (e.g. static magnetic field drift and other aliased effects) is achieved by temporal linear detrending of each time-series.

In conventional analysis, a reference model \( H \) is fitted to the data \( y \), pre-processed in this fashion. \( H \) is obtained after convolution of a train of stimulus events (delta functions centered on instants when the event occurred, \( T_{\delta(t-E)} \)) with an impulse hemodynamic response function (iHRF). The shape of the iHRF can be arbitrary chosen and usually is set as a linear combination of gamma functions, with a positive peak around 5 s, followed by an undershoot, with maximum ca 10 sec after the event. The output of conventional analysis applied on each voxel time-series consists of a \( \beta \)-value, which is proportional to the effect size (activation amplitude), and of a \( t \)-value, by which assesses quantitatively the statistical significance of the activation.

In RQ analysis, a recurrence 2D-plot is first worked out. Given the time-series \( y = (y(1) \ldots y(i) \ldots y(n)) \), an embedding procedure will produce a vector \( y_i = (y(i) y(i+L) \ldots y(i+(m-1)L)) \), where \( m \) is the embedding dimension and \( L \) the lag. Distances between vectors \( y_i, y_j \), if less than an established radius \( r \), will embody the element \( i,j \) of the auto-recurrence matrix visualized in the 2D-plot. Dissimilarly, when the two axes of the recurrence plot represent an external reference function (the stimulus train, \( T_{\delta(t-E)} \)) and the response signals \( y \), respectively, the matrix will be representative of cross-recurrences. In order to quantify important features of the recurrence plot, several strategies are developed, which lead to the generation of ten variables: recurrence, determinism, entropy, max-line, mean-line, laminarity, trap-time, max-vert, recurrence time1, recurrence time2\(^1\).

\(^1\) Recurrence (REC) provides a measure of the percentage of recurrence plots (RPs) filled with recurrent points. Determinism (DET) represents the percentage of recurrent points that form diagonal lines, with a minimum of two adjacent points. This is significant because recurrent points forming a diagonal line segment are considered as deterministic (as opposed to random). Entropy (ENT) is the Shannon information entropy of the line length distribution in a RP. The length of the longest line segment parallel to the diagonal is called max-line (MAXLIN), and, similarly, the mean length of such segments is called mean-line (MEALIN). Laminarity (LAM) represents the fraction of recurrence points forming continuous vertical alignments, and the average length of such vertical alignments is called trapping time (TRAPT). The maximum number of consecutive recurrence dots arranged in a vertical line is termed max-vert (MAXVERT). The time distance between a state of a system at time \( i \) and at its recurrence at time \( j \) (i.e.,
In Table 1, conventional (linear regression) and RQA steps described above are shown in synthesis.

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**Application to fMRI BOLD data**

A 24 year-old male volunteered to participate in this study, approved by the local ethics committee. A total of 270 BOLD sensitive image volumes were acquired with a Siemens Vision Magnetom MR system (Siemens Medical Systems, Erlangen, Germany) operating at 1.5 T and equipped for echo-planar imaging. Each volume was subdivided in 11 planes, starting from the vertex and stretching caudally (radio-frequency pulse: 60°; TR: 1000 ms; TE: 60 ms; in-plane resolution: 3x3 mm, slice thickness = 4 mm and gap between slices = 0.4 mm). The 14 initial BOLD images were discarded from further analysis to remove any possible T1 saturation effects. Visual stimuli indicating onset of the events (finger tapping) were projected via

“RECUTIME1”) may be measured by vertical distances of the line segments in a RP. Discarding the states at time \( j-i \) (sojourn times) leads to recurrence times of a second type (i.e., “RECUTIME2”).

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mirroring to a front projection screen using a LCD video projector (Model VPL-351QM, Sony Corp., Tokyo) located inside the MR room and connected to a PC located outside the MR room.

The subject had to fixate the front projection screen on which the visual stimuli were presented. In response to the occurrence of a green dot on the monitor (with a 16 MR scans ON/OFF cycle), the volunteer had to push a button of a response box.

Figure 1: MR signals (Siemens Vision 1.5 Tesla, GE-EPI, 256 scans, TR = 1 s, TE = 60 ms, voxel dim = 3x3x4.8 mm) related to 5 contiguous voxels pertaining to two different brain areas (a),(b)).

Figure 1 shows the magnetic resonance signals obtained from five contiguous voxels in an active region of the brain (left) and the magnetic resonance signals obtained from five contiguous voxels in a non-active region of the brain (right). Notice that in the present context, activity is determined by means of the conventional approach (statistical threshold p < 0.001, uncorrected for multiple comparisons, and t > 3.01). Statistical t-values ranged from 7.8 to 10.8 and from −0.4 to −1 for time series “a” and “b”, respectively.

Figure 2: a), b) Auto-recurrence plot relative to time-series 3a and 3b of Figure 1, respectively.
The two classes of time-series, “a” and “b”, could also be discriminated by RQA variables. Auto- and cross-recurrence plots were generated for each time-series and examples relative to time-series 3a and 3b of Figure 1 are shown in Figure 2. A repetitive pattern is clearly evident in Figure 2a (for example, on the diagonal 8 mini-blocks, about 16 points long, as the design ON periods, can be distinguished); for time-series 3b (Figure 2b) recurrences are less pronounced, although the presence of some structure indicates the somewhat colored feature of the noise. Quantification of recurrences leads to a variable REC that was twice as high for time-series 2a, than for 2b.

The same analytical strategies (conventional and RQA) were applied to the entire 3D brain-volume collected by fMRI. Ten RQA variables were calculated for each of the volume elements in the volume element array and an image showing the spatial distribution of the RQA variables of each brain slice was generated for each of the ten variables (calculated both for auto- and cross-recurrence plots, see Table 1, right). Figure 3 (upper panels) shows the resulting images for two of the ten RQA variables relative to one slice, namely cross-REC and cross-MAXLIN.

**Figure 3.** Upper panels: Cross-recurrence (left) and cross-maxline (right) computed on the experimental data-set. The working parameters of RQA were adjusted to the following values and kept the same in all cases: embedding dimension = 8; shift length (lag between subsequent windows) = 1; distance = Euclidean; radius = 1.7 standard deviation (SD) units in the distribution of distances; deterministic line = 2). Bottom panels: Results of conventional analysis: (left) estimated β-values; (right) t-values.
The bottom panels in Figure 3 contain the results (\(\beta\) and \(t\)-values) over the same brain regions obtained by conventional linear regression analysis (see Table 1, left). Notice that the graphical representation of Figure 3a,b is based on a false color scale.

Four RQA descriptors (auto-recurrence, auto-laminarity, cross-recurrence and cross-max-line) were able to detect regions common to conventional analysis activation maps. In the former maps the activated regions appear somewhat more blurred; their location, however, could be characterized by a completely iHRF-assumption-free approach.

Conclusions

Preliminary results obtained by RQA on fMRI data of a volunteer performing a motor task showed clear activation clusters corresponding to the outcome of linear analysis. Although the exact relationship and statistical significance of the RQA parameters need to be established, this method seems a promising tool for the analysis of functional MR images of the human brain. With respect to conventional GLM techniques, in fact, RQA has the exclusive feature of being model-free and of detecting potentially both linear and non-linear dynamic processes, without requiring stationarity of the signal under investigation.

References


