An ARX model-based approach to trial by trial identification of fMRI-BOLD responses

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Introduction

Event-related or trial-based protocols are of great relevance for BOLD fMRI studies, since they allow for more flexible designs and can assess specific features of brain activity evoked by different kinds of brief stimuli or tasks (Josephs et al., 1997; Zarahn et al., 1997a; Rosen et al., 1998). Indeed, several studies have underlined the importance of fully characterizing the hemodynamic response (HR) to brief events by determining its onset, time to peak, peak amplitude and width, in order to obtain more comprehensive and quantitative measures of task-related brain activity (e.g., Menon et al., 1998; Bellgowan et al., 2003). Given the low contrast-to-noise ratio, in event-related paradigms one usually needs to take into account information deriving from several repetitions of the event to improve the sensitivity. Typical procedures consist in averaging the responses obtained from replications of the same task or in applying a General Linear Model approach to the identification of the HRs. This, however, implies loss of the unique information associated with each execution of the task, which is particularly crucial in cognitive tasks (Menon and Kim, 1999).

Being able to estimate the hemodynamic response following each single event allows to characterize its relationship to different aspects either of the stimulus or of the subject’s performance. In order to detect and characterize BOLD responses in single trials, we developed and validated a procedure based on an AutoRegressive model with eXogenous Input (ARX). The use of an individual exogenous input for each voxel makes the modeling sensitive enough to reveal differences across regions, avoiding any a priori assumption about the reference signal. The detection of variability across trials is ensured by a suitable choice, for each voxel, of the order of the moving average, which in our implementation determines the relative delay between the recorded and the reference signal. This is a quality useful in finding different time profiles of activation from high temporal resolution fMRI data. The results obtained from simulated fMRI data resulting from synthetic activations in actual noise indicate that such approach allows to evaluate important features of the response, such as the time to onset, and time to peak. Moreover, the results obtained from real high temporal resolution fMRI data acquired at 1.5 T during a motor task are consistent with previous knowledge about the responses of different cortical areas in motor programming and execution. The proposed procedure should also prove useful as a pre-processing step in different approaches to the analysis of fMRI data.

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subject’s head motion, scanner-related noise, cardiac and respiration cycles, and hemodynamic/metabolic factors. The spectrum of such “noise” has been reported having a 1/f form (e.g., Zarahn et al., 1997b), with additional peaks corresponding to periodic motions and to their possible aliased components (Weisskoff et al., 1993), and varying across brain areas (Friston et al., 2000).

In event-related protocols, temporal autocorrelation and random noise may be included in statistical analysis frameworks and/or noise reduction may be applied as a preprocessing step to further improve sensitivity, given the several constraints that exist on the number of trial repetitions. However, a complete modeling of the “no task-related” signal components is still lacking. This is one of the reasons of the many noise reduction strategies developed so far, including among others retrospective correction, pre-whitening, spectral subtraction, band-pass, Wiener and wavelets filters, ICA-based denoising (e.g., Jezzard, 2000; Glover et al., 2000; LaConte et al., 2000; Woolrich et al., 2001; Thomas et al., 2002; Pfeuffer et al., 2002; Bullmore et al., 2004; Kadah, 2004).

Currently, a few studies have monitored the time course of the BOLD response trial by trial. The majority used high magnetic fields (Richter et al., 1997a, 1997b; Kim et al., 1997; Duann et al., 2002) which improve signal sensitivity but also physiological noise sensitivity, therefore mitigating the expected contrast-to-noise ratio improvement (Krüger and Glover, 2001); to our knowledge, only two studies used a 1.5 T scanner (Formisano et al., 2002; Burke et al., 2004). One study (Windischberger et al., 1993) evaluated each single trial on whole-cortex data acquired at 1.5 T, while subjects were performing a finger-tapping motor task in an event-related design. This sort of task was chosen because it has been deeply investigated and therefore it is suitable for validation of new data analysis approaches.

Methodology of single-trial BOLD response identification

The fMRI signal model

For each single trial and each voxel, the fMRI measured signal is considered as the output $y(k)$ of a dynamic system like the one shown in Fig. 1, where it is represented as the additive superimposition of two terms: $s(k)$, the BOLD response and $n(k)$, a pseudo-stochastic signal denoted as “background noise”. An AutoRegressive with eXogenous input model (ARX) is chosen to describe signal–noise interactions: the “background noise” is described as an autoregressive process $H(z)$ driven by a white noise $e(k)$ (null mean and variance $\sigma^2$); the BOLD response is a filtered version, through the transfer function $G(z)$, of a reference signal $u(k)$ (the exogenous input).

The ARX model is described in its general form in the discrete time domain, by the equation (Astrom, 1970):

$$y(k) = -\sum_{i=1}^{n} a_i y(k-i) + \sum_{j=1}^{m+d-1} b_j u(k-j) + e(k)$$

where $n$ and $m$ are the orders of the autoregressive and moving average component respectively, $a_i$ and $b_j$ are the model coefficients, $u(k)$ is a reference signal and $e(k)$ is a white noise process. The relative delay between the input reference signal $u(k)$ and the output recorded noisy signal $y(k)$ is taken into account by the parameter $d$.

In the $z$-transform domain, Eq. (1) is transformed into:

$$A(z)Y(z) = B(z)U(z) + E(z)$$

where

$$A(z) = 1 + \sum_{i=1}^{n} a_i z^{-i}$$
$$B(z) = z^{-d} \sum_{j=0}^{m-1} b_j z^{-j}$$

and $Y(z)$, $U(z)$, $E(z)$ are the $z$-transform of $y(k)$, $u(k)$, $e(k)$.

The block diagram of Fig. 1 describes, in terms of the transfer functions $H(z)=1/A(z)$ and $G(z)=B(z)/A(z)$, the flow of information between the processes of Eq. (1).

Given the temporal series $y(k)$ and $u(k)$, one needs to identify the values of the coefficients $a_i$, $i=1, \ldots, n$, $b_j$, $j=d, \ldots, (m+d-1)$ which characterize the model of each voxel response. Because of the linear structure of the ARX model, the identification can be performed with a simple least squares (LS) approach with the aim of minimizing the function

$$J = \frac{1}{N} \sum_{k=1}^{N} [e(k)]^2$$

where $N$ is the number of samples of each of the three processes involved, $y(k)$, $u(k)$ and $e(k)$. In this sense, $e(k)$ represents the prediction error of the realization of the model of the process under analysis. The process $e(k)$ must result in a white noise in accordance with the hypothesized ARX model.

Fig. 1. The AutoRegressive model with eXogenous input (ARX): proposed signal–noise interactions.
The ARX modeling procedure

The exogenous input plays a central role in the present ARX procedure: a specific reference input for each voxel was chosen with no requirement for a priori hypothesis, resulting in a potential preservation of the characteristics of the hemodynamic responses for each event in different brain areas. The exogenous signal was selected as a filtered version of the average time course of the considered voxel across all the trials of the same kind. This should reinforce the repetitive frequency components of interest for that voxel, without limiting the detection of other less correlated components. Each average time course was low-pass-filtered (and compensated for the delay) by a 25th-order Chebychev windowed FIR filter (50 dB side lobe attenuation and cutoff frequency of 0.37 Hz). Its frequency response has been designed in order to have no effects up to about 0.22 Hz (to avoid spoiling the estimation of the responses), to exclude the components related to the cardiac cycle and, to limit those related to the respiration cycle (in fact, these latter components could still have a minor amplitude in a range of frequency shared with BOLD responses).

The identification algorithm could in principle be applied to each non-negative integer value of $n$ and $m$, and each integer value of $d$, independently. The selection of a specific value for each of them is required in order to have a number of coefficients $\eta = n + m$ large enough to take into account the necessary information about the correlation between the processes $y(k)$ and $u(k)$, while maximizing such information with a minimum of parameters. Our procedure implements an a posteriori evaluation of the optimal order for each acquired signal, using the Akaike’s Information Criterion (AIC) (Akaike, 1974) over defined ranges for $n$ and $m$. Moreover, the $m$ order was chosen to represent the extension of a symmetrical window centered in the sample $k$ under consideration and as a consequence the delay $d$ was strictly established (for instance, an order of $m = 11$ implied a choice of $d = -5$, so that the 11 $b$ parameters were centered in the sample $k$). Note that a value of $d > 0$ means an actual delay of the output with respect to the input, while a value $d < 0$ means a delay of the input with respect to the output. This type of non-causality in the time domain was considered, since we thought it could better cope with the difference in latency between the selected reference signal and the task-related fMRI-BOLD response in each voxel.

The $m$ value was allowed to vary in the range $[1:13]$, i.e. a symmetrical window with maximum values of ±6 points, corresponding to a little more than ±1 s, a range in accordance to the expected latency variability across repeated trials of real fMRI-BOLD responses (Kim et al., 1997; Kruggel and Von Cramon, 1999). The range for the $n$ parameter was chosen in accordance to the empirical results obtained with an AR modeling of “resting-state” trials (see “Background noise” modeling).

After model identification, the whiteness of the residuals was checked via the Anderson test (Box and Jenkins, 1976), with a confidence of 99%. A lack of significance of the whiteness test makes the identified values meaningless.

The entire procedure was implemented in the Matlab environment (MathWorks, Sherborn, MA).

Validation tests

First of all, the hypothesis of modeling the “background noise” as an autoregressive process driven by white noise was validated. Then, two sets of synthetic data, both resulting from synthetic activations in actual noise, were generated to test the range of

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Fig. 2. Signal frequency components in “resting-state” trials: average power spectrum computed over all the brain voxels (left, top) and in a few single voxels (right) in a representative subject. “Background noise” modeling (left, bottom): AIC-based “best AR” order distribution computed over 16,136 voxels resulting from randomly selected “resting-state” trials acquired from several subjects.
validity of the ARX modeling technique. The first set, simulating a collection of single trials varying in amplitude and shape of the BOLD response, was mainly aimed at testing the sensitivity in response identification; the second set, simulating a whole event-related fMRI experimental session, was aimed at taking into account inter-trials variability and at testing the suitability of the methodology adopted in computing the reference functions for real data analysis. Finally, the ARX modeling was tested on real data acquired while subjects were performing a finger-tapping motor task. This was done to provide a control of the validity of our identification procedure on BOLD responses in a deeply investigated task.

“Background noise” modeling

Methods

The hypothesis of modeling the “background noise” as an autoregressive process driven by white noise was validated using “resting-state” data acquired from an axial brain section during real fMRI experiments (see Real fMRI data section). Here, therefore, the considered model was:

\[ y(k) = -\sum_{i=1}^{n} a_i y(k-i) + e(k) \]

Such investigation was conducted over 20 randomly selected trials (trial duration=20 s; TR=200 ms) obtained from 7 subjects resulting in a total of 16,136 examined voxels. The maximum allowed order for the AR process was set to 25, corresponding to a quarter of each time series points. For each voxel, optimal AR orders were chosen \( a \) posteriori using the AIC and the whiteness of the residuals were tested by the Anderson test with a confidence of 99%. The number of voxels successfully modeled and the distribution of the optimal AR orders were computed. From these results, a suitable range in which let the AR order vary in the ARX modeling, was selected. Power spectral density in single voxels was also estimated and the spatial variability of the noise frequency profile was evaluated.

Results

The mean value of signal fluctuation over the 20 “resting-state” trials was about 2% (range 1.7–2.8%). Fig. 2 (left, top) displays the average power spectrum computed over all the brain voxels during one “resting-state” trial in a representative subject: it exhibits a “1/f" form, with additional peaks due to respiratory and cardiac effects. Across-voxels variability was detected particularly in the low frequency range (up to about 0.1 Hz), where task frequency of typical “slow” event-related designs falls. Fig. 2 (right) shows representative examples of power spectrum estimations in single gray matter voxels, where the deviation from the “1/f" characteristic and the variability in respiratory and cardiac effects are evident.

Regarding the AR modeling, Fig. 2 (left, bottom) shows the distribution of the order selected by the AIC criterion when the imposed range was [1:25]. Gradually decreasing the upper bound of the interval, it was found that the great majority of voxels could still be modeled reaching, at a value of AR=5, a percentage of voxels equal to 0.6% where the Anderson test was not verified (for comparison, at an upper bound equal to 3 the percentage increased to 3%). Therefore a suitable range for the AR order, to be applied in the ARX modeling, was considered to be [1:5]. With an upper bound of 5, the mean value of the AR order over the 16,136 voxels was 2.3±1.56.

Synthetic single trials

Methods

A collection of single trials was simulated. In order to model task-related BOLD responses, gamma–variate functions or a combination of them were used (Cohen, 1997). The time courses of BOLD signals acquired from one subject during a single randomly chosen “resting-state” trial (see Real fMRI data section) were used as “background noise”. An example of the construction of a simulated time course in one voxel is shown in Fig. 3 (left, top).

![Fig. 3. Synthetic single trials construction (top, left): an example of background activity \( n(t) \) (top), simulated activation signal \( S_{\text{A}}(t) \) (middle) and the final simulated signal \( S(t)=S_{\text{A}}(t)+n(t) \) (bottom) are shown for one voxel.](image-url)

Plots of the simulated activations signals used to construct the 5 tests reported in Table 1 (top, right).

Schematic drawing of the measured parameters on the identified responses (bottom). Peaks were defined as maxima (A) of the response time course; L indicates time to peak; point F was identified on the left side of the response at its peak half maximum, and the intercept of the line tangent to the response in F with the baseline was taken to be the onset point (O=time to onset). These parameters were automatically computed.
To reproduce variations of the functional responses, several functional images composed of 736 voxels each were constructed modulating the amplitude and peak time delay of the gamma–variate functions (see Table 1 for details and Fig. 3, right, top).

The identification of the ARX model was carried out with the same approach described in The ARX modeling procedure subsection, but for each trial, the reference signal \( u(k) \) coincided with the specific gamma–variate functions simulating the task-related activity.

The effectiveness of the ARX identification procedure on synthetic single trials was evaluated by computing the following parameters:

- the errors in detecting the onset, time to peaks, and peaks amplitude of each modeled voxel’s time course with respect to the expected signal; at this regard, Fig. 3 (bottom) illustrates how the shape parameters of the modeled time courses were obtained (see legend of the figure for the details);
- the Pearson’s cross-correlation coefficient between each modeled voxel’s time course and the corresponding expected signal;
- contrast-to-noise ratios (CNR). For the activation signals and for the signals before modeling, CNR was defined as the maximum peak variation of the gamma–variate function divided by the standard deviation of the signals itself. For the ARX-modeled signals CNR was defined as the maximum peak variation of the signal divided by the standard deviation of the signal (see also Table 3).

In the ARX modeling of real fMRI data, a shift in time of the exogenous input in comparison to the BOLD response might occur. In fact the \( u(k) \) signal is constructed, in that case, as a filtered version of the average time course of the considered voxel across all the trials of the same kind. The effects of these potential shifts have been evaluated on the synthetic single trials, imposing a shift in time between the reference signal and the simulated activation signal.

### Results

Fig. 4 shows the results of the ARX modeling in a representative voxel for the five tests, which convey different challenges to the identification procedure. Table 2 reports mean optimal orders and accuracy of the ARX modeling from 736 voxels for each test. The Pearson’s coefficients values, which assess the similarity between the estimated and simulated responses, show a progressive improvement of the estimate, going

<table>
<thead>
<tr>
<th>Test</th>
<th>Time to onset (s)</th>
<th>Time to peak a (s)</th>
<th>Peak height a</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2.4</td>
<td>7.4</td>
<td>1.01 (1%)</td>
</tr>
<tr>
<td>B</td>
<td>2.4</td>
<td>7.4</td>
<td>1.02 (2%)</td>
</tr>
<tr>
<td>C</td>
<td>2.4</td>
<td>7.4</td>
<td>1.05 (5%)</td>
</tr>
<tr>
<td>D</td>
<td>2.4</td>
<td>7.4–12.6</td>
<td>1.02–1.05</td>
</tr>
<tr>
<td>E</td>
<td>2.4</td>
<td>7.4–10.6</td>
<td>1.05–1.05</td>
</tr>
</tbody>
</table>

\[g(t)=K \times (t-d)^r \times e^{-(t-d)/e}\n\]

\[g(t)=0 \text{ for } t<d;\]
\[e=0.57; \quad r=8.6; \quad t \text{ in seconds}\]

\(S_A\) = simulated activation signal; \(\Delta t=0.2 \text{ s; } (\%)\) = simulated % change.

\(a\) For test D and E, values for the two function peaks are reported.

Fig. 4. Synthetic single trials. Signal time courses of a representative voxel for the 5 tests constructed with the activation signals of Table 1. On top the simulated signals and on bottom the modeled signal (thick line), compared with the simulated activation signals (thin line).
from Test A to Test E, as expected. For the “time to onset” parameter, the errors decreased going from Test A to C; for Test D we obtained a similar error as in Test B, according to the resemblance of the first part of its composite gamma–variate to the gamma–variate of Test B. An analogous comment holds for the error of Test E relative to Test C. For the “time to peak” parameter, errors are somehow similar among the five tests, with a more evident decrease for Test C (and for the second peak of E) as expected, because in these tests the amplitudes of the gamma–variate were the greatest. The errors in the amplitude detection were stable over the five tests, except for the second peak of Test D, probably due to the significant asymmetry in the shape of the simulated activation.

Mean CNR values for the simulated and modeled signals compared with the activation signals are reported in Table 3. Starting from a CNR of about 3, adding noise to the simulated activations lowers the mean CNR by a factor of about 6, 3, 1.5 for Tests A, B, C, respectively. After modeling, mean CNR was 2.61, 2.91, and 3.01 for Tests A, B, and C, respectively. Thus a good recover of the CNR was obtained, albeit partial for Test A in which the simulated percentage change of the BOLD response was 1%.

Fig. 5 shows mean error in time to peak detection as a function of the shift in time of the reference input in comparison to the activation signal. To take into account separately only the effects of the imposed shift and not those derived from the noise, we chose the 193 voxels for which the optimal delay of the ARX model turned out to be zero and the latency was correctly evaluated, when no shift was imposed.

**Synthetic experimental session**

**Methods**

A second set of synthetic data was composed of 12 different trials simulating an experimental session. Each trial was formed of

| Table 2
<p>| Synthetic single trials: mean optimal orders and accuracy of the ARX modeling |</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>Model orders</th>
<th>Identification errors</th>
<th>Pearson’s coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AR</td>
<td>MA</td>
<td>Peak amplitude (% change)</td>
</tr>
<tr>
<td>A</td>
<td>2.73 (1.64)</td>
<td>4.10 (4.17)</td>
<td>0.44 (0.43)</td>
</tr>
<tr>
<td>B</td>
<td>2.71 (1.63)</td>
<td>4.07 (4.15)</td>
<td>0.44 (0.43)</td>
</tr>
<tr>
<td>C</td>
<td>2.72 (1.64)</td>
<td>4.14 (4.15)</td>
<td>0.45 (0.48)</td>
</tr>
<tr>
<td>D</td>
<td>2.56 (1.64)</td>
<td>5.81 (4.50)</td>
<td>0.33 (0.40)</td>
</tr>
<tr>
<td>E</td>
<td>2.64 (1.66)</td>
<td>4.43 (4.12)</td>
<td>0.46 (0.63)</td>
</tr>
</tbody>
</table>

Mean values and standard deviation in parentheses over 736 voxels for each test.

\* Referred to the second peak.

\( \Delta = \text{max peak variation.} \)

\( \text{CNR}_1 = \Delta S_1 / \text{sd}(S_1) \)

\( \text{CNR}_2 = \Delta S_2 / \text{sd}(S_2) \)

\( \text{CNR}_3 = \Delta M / \text{sd}(M) \)

Baseline normalized signals; \( S_1 = \text{simulated activation signal}; S_2 = \text{simulated signal}; M = \text{modeled signal}; \text{sd} = \text{standard deviation}. \)

Table 3

<table>
<thead>
<tr>
<th>Test</th>
<th>( \text{CNR}_1 )</th>
<th>( \text{CNR}_2 )</th>
<th>( \text{CNR}_3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3.00</td>
<td>0.60 (0.18)</td>
<td>2.61 (0.98)</td>
</tr>
<tr>
<td>B</td>
<td>3.03</td>
<td>1.17 (0.33)</td>
<td>2.91 (0.60)</td>
</tr>
<tr>
<td>C</td>
<td>3.04</td>
<td>2.24 (0.47)</td>
<td>3.01 (0.37)</td>
</tr>
</tbody>
</table>

signals from one “resting-state” trial among those acquired from a randomly selected subject (see Real fMRI data section), to which an identical composite gamma–variate function was added in 50 “brain” voxels chosen randomly. Such function was one among 6 chosen to model the inter-trial variability of the response to the same task (see Fig. 6). Therefore, the background noise was always different among trials (12 different “resting state” trials were used) and voxels, whereas couples of trials shared the same simulated response to test the robustness of its identification. The inter-trial variability range of the peaks amplitude and latency of the simulated responses was set to 0.25–1.56 (in % change over baseline) and 0.2–1.2 s, respectively. The ARX modeling was carried out with the same approach described in The ARX modeling procedure subsection.

The quality of the modeling on the synthetic experimental session was evaluated through the Pearson’s cross-correlation coefficient between each modeled voxel’s time course and the corresponding expected signal. Moreover, to test the robustness of the model identification, a paired t-test for the “time to onset” parameter was computed between couple of trials that shared the same simulated response but different background noise.

**Results**

The spectral analysis reported in Fig. 7 shows an example of the effect of the FIR filter on one exogenous input in comparison to the spectrum of one gamma–variate function which simulated activation.

The mean (±SD) of the optimal order values of the model over all voxels and trials was 2.6±1.4 (AR) and 6.7±5.2 (MA), respectively.

Fig. 8 plots the time courses of a representative voxel in each trial making up the session. Note that the recovery of the time to

![Fig. 5. Synthetic single trials. Mean (±SD) errors in the detection of the time to peak as a function of the imposed shift in time between the reference signal and the simulated activation signal for Test B. See text for details.](image)
peak of the simulated activation is well marked in the 5th $S_A$, in spite of the same exogenous input shared among trials. However, a certain degree of variability in the estimation of the peak amplitude of the responses is manifest. Such variability does not have an evident relationship with the peak amplitude of the simulated activations.

A summary of the results obtained over all the simulated voxels is shown in Fig. 9 and data on the quality of the modeling are reported in Table 4.

The “time to onset” values of couple of trials sharing the same simulated response but with different background noise, were not significant different, indicating a certain robustness of their identification.

Real fMRI data

Methods

For the purpose of the present work, we used a few data from a larger fMRI study on cortical motor-related activity, where different acquisition protocols and brain coverage were used. The study was approved by the local Committee on Ethics. Eight healthy, right-handed subjects were instructed to perform a simple motor task, i.e. a single self-paced finger-to-thumb opposition sequence (2-3-4-5) lasting on average 1.5 s. An event-related paradigm was used, consisting in a pseudo-random sequence of “right hand” and “left hand” finger movements. The timing of each trial is shown in Fig. 10 (see legend for details). The direction of a visually presented arrow indicated which hand had to be moved. One-half of the subjects were instructed to begin the finger tapping immediately after the appearance of the arrow, the other half immediately after its disappearance. While at rest, subjects held each hand on a device which could measure the onset of hand movement through a pressure sensor. “Resting-state” trials were also randomly intermingled, during which the subject lay at rest for the whole duration of the trial. The experimental session included 36 trials balanced among “right hand” and “left hand” events and “resting-state” trials.

Functional images were acquired with a GE Horizon Lx-Echospeed 1.5 T MRI system equipped with quadrature RF head coils, using a gradient-echo T2*-weighted echo-planar sequence. This work we analyzed data acquired at high temporal resolution (TR = 200 ms) from a single axial section of the brain (3.75 × 3.75 × 6 mm) approximately parallel to the AC–PC plane, centered on the putative hand representation area of the sensorimotor cortex. The axial section was identified using anatomical landmarks from structural T1-weighted brain images (see Yousry et al., 1997; Porro et al., 2000). The following regions of interest (ROIs) were manually defined on the anatomical image: the putative lateral premotor (lp), primary motor (m1), and primary somatosensory (s1) cortex of each hemisphere, and the putative supplementary motor area (sma) from the two sides of the brain.

The free software AFNI (http://afni.nimh.nih.gov/afni)( Cox, 1996) was used for fMRI data pre-processing and ROI selection. Specifically, data were pre-processed in order to reduce motion effects, linear trends and outliers and for the extraction of brain voxels. The time courses of each voxel were then normalized to their baseline. The ARX modeling was carried out with the same approach described in The ARX modeling procedure subsection and applied to data from one subject performing the “appearance” motor task (Subject A) and from another subject performing the “disappearance” motor task (Subject B). For each trial, the mean time to peak and amplitude of the main peak of the modeled response were computed in each ROI. These variables were compared across ROIs by ANOVA and t-tests.

Results

For Subject A, the mean (±SD) of the optimal order values of the model over the 256 voxels inside the ROIs and all trials was 2.6±1.5 (AR) and 7.4±4.9 (MA), respectively; over the 443 voxels outside the ROIs it was 2.6±1.5 (AR) and 7.9±4.8 (MA). Corresponding values for subject B were 2.6±1.6 and 6±4.8 over the 344 voxels inside the ROIs, and 2.9±1.7 and 5.8±4.9 over the 386 voxels outside the ROIs.

Fig. 11 (left) reports “BOLD-image” plots (Duann et al., 2002) of the modeled time courses of the 12 single trials related to “right hand” events for subject B. For each trial, the values are mean values of the estimated responses over the indicated ROI. This kind of visualization highlights a certain degree of variability across trials.

To roughly control for spatial localization of task-related responses, activation maps were obtained using the correlation method (Bandettini et al., 1993). Fig. 11 (right), reports two
representative activation maps relative to one “right hand” and one “left hand” event for Subject B.

After the ARX procedure, responses within ROI could be characterized in each single trial in Subject B and in 22 out of 24 trials in Subject A. The average time courses of the modeled responses in one representative “right hand” trial are shown for both subjects in Fig. 12. Mean values of the time to peak and amplitude of the main identified peaks, over the twelve “right hand” trials, are reported in Table 5. Considering values from the two subjects, a significant difference in peak amplitudes among regions was found (ANOVA, $F=49.23$, $p<0.001$); peak amplitudes were significantly higher in m1 than in all other regions (paired $t$, $p<0.001$ for each comparison). Moreover, a significant difference in peak latencies was found among regions ($F=66.28$, $p<0.001$). Time to main peak was shorter for lp relative to sma (paired $t=−8.901$, $p<0.001$), for sma relative to m1 ($t=−3.701$, $p<0.001$) and for m1 relative to s1 ($t=−1.897$, $p<0.05$, 1-tailed).

Note also the shorter latencies to peak activation in motor-related areas following the “go” signal in the disappearance task, namely after a 2-s preparatory period. For both subjects, the amplitude of peak signal increases was higher in ROIs of the
contralateral than in those of the ipsilateral hemisphere (Subject A: $F=59.99$, $P<0.001$; Subject B: $F=237.76$, $P<0.001$).

The resulting responses, after the ARX modeling, of several voxels chosen from one “resting-state” trial, are shown for a comparison with the original time courses in Fig. 13.

**Discussion**

We developed and tested a procedure based on an AutoRegressive model with eXogenous Input (ARX), aimed at identifying BOLD responses on a trial by trial basis.

The results obtained from modeling synthetic and real fMRI single trials indicate that the developed approach is an effective general filtering procedure, which allows to evaluate important features of the responses, such as time to onset, time to peak, and amplitude. This parametric approach is more powerful than simple linear filtering since it requires a model for both the noise and the searched signal.

Two aspects have been addressed in developing the ARX algorithm to follow the inter-trial variability of the fMRI signals: the validation of background activity as an autoregressive process and an appropriate choice of the reference signal.

The spatial average power spectrum of the measured signals in the “resting state” condition did show what is considered to be a typical form for fMRI noise data. However, a non negligible variability across voxels was found, supporting the necessity of specific voxel by voxel model identification. Our finding confirmed a successful modeling of the background noise as an AR process.

In a preliminary implementation of the ARX model, tested on real fMRI data (Maieron et al., 2002), we used an unique reference signal in events of the same kind for all the investigated voxels: it was obtained averaging the time courses of a few voxels belonging

---

**Table 4**

<table>
<thead>
<tr>
<th>Trials</th>
<th>Time to onset (s)</th>
<th>Pearson’s cross-correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$S_A$</td>
<td>$M_b^h$</td>
</tr>
<tr>
<td>1st pair</td>
<td>3.73 (0.72)</td>
<td>3.33 (0.72)</td>
</tr>
<tr>
<td>2nd pair</td>
<td>3.07 (0.74)</td>
<td>3.12 (0.74)</td>
</tr>
<tr>
<td>3rd pair</td>
<td>3.27 (0.68)</td>
<td>3.42 (0.68)</td>
</tr>
<tr>
<td>4th pair</td>
<td>2.63 (0.70)</td>
<td>2.91 (0.70)</td>
</tr>
<tr>
<td>5th pair</td>
<td>4.14 (1.68)</td>
<td>3.99 (1.68)</td>
</tr>
<tr>
<td>6th pair</td>
<td>3.73 (0.72)</td>
<td>3.62 (0.72)</td>
</tr>
</tbody>
</table>

$S_A =$ simulated activation; $M_b =$ modeled signal.

$^a$ Each pair of trials share the same $S_A$ with different background noise.

$^b$ Mean values over 50 voxels; standard deviation in parentheses.
to a region were the task-related response was expected. A similar approach has been recently proposed by Burke and colleagues (Burke et al., 2004), with the aim of obtaining maps of activation relative to each single trial. Following this approach, two disadvantages are evident: first, it requires an *a priori* knowledge about the brain region from which suitable task-related time courses can be obtained; secondly, it decreases the consistency of the shape characterization of the responses among brain areas, since choosing an unique reference signal tends to enhance its frequencies content over the all data set. Therefore, such approach does not seem well suited for both the identification and spatial localization of task-related responses.

We used here a specific exogenous input for each voxel, derived from the average time courses of the voxel itself across repeated trials; this allowed to reinforce the repetitive components of interest for that voxel, without limiting the detection of other components less correlated. Moreover, proper filtering of each average time course allowed to limit physiological components not

![Fig. 11. Real fMRI data: “BOLD-image” plots of the modeled time courses of 12 single trials related to “right hand” events for Subject B (left). For each trial the pictured values correspond to the mean value of the estimated responses over the indicated ROI (y-axis: number of each single trial; x-axis: seconds). A differentiation of the responses, particularly in terms of the time to peak, is evident and physiologically consistent among regions going from top to bottom. Contra=Contralateral to the moving hand. Activation maps (right) relative to one “right hand” and one “left hand” event are shown in radiological convention over the corresponding anatomical image. Maps were obtained using the AFNI software package, by applying the correlation method to match a gamma–variate function convolved with the motor task timing to the intensity signal in each voxel. Given the outstanding temporal autocorrelation of ARX modeled signals, maps were thresholded at a value of \( r=0.82 \), experimentally defined on ARX modeled rest events (considered as the null distribution).](image1)

![Fig. 12. Real fMRI data: hemodynamic responses identified in one representative trial relative to a “right hand” event for subject A (left) and subject B (right). Averaged responses in three regions of interest (lp, m1, s1) of the contralateral hemisphere and in the sma region of both hemispheres. The timing of the task for the two subjects is shown under each panel.](image2)
related to BOLD responses. The only drawback is the need of a reasonable number of trial repetitions. We used 12 trials in our simulations, with meaningful results, but we did not examine in detail how the results would change as a function of the number of trials. However, having a limited number of good quality trials should determine a major dependence of the exogenous input on the response coherence across the trials. On the other hand, would a voxel respond only to a few of a reasonable number of trials, the estimation of the frequencies content of the BOLD response by the computed exogenous input will of course be biased, but the modeling of the voxel response would not be completely compromised.

This approach, coupled to a proper choice of the order of the moving average component and consequently, for our implementation, of the negative delay value, ensures the detection of the response variability across trials and regions, a quality specifically useful for high temporal resolution fMRI data or complex experimental paradigms. The range in which let the MA order vary has to be nearly tuned to the expected latency variability of real fMRI-BOLD responses across events. Instead, the order of the AR component did not appear to be critical: its overestimation did not significantly enhance the quality of the modeled signals, whereas a limitation of its range reduces the complexity of the model and increases computation speed.

The results obtained on synthetic data underline how the ARX modeling is a powerful technique for the identification of responses even when overlapping HRs in a trial were simulated. As expected, the efficacy decreased with the decreasing of CNR ratio, but simulated activations were almost completely recovered even when the starting CNR was of the order of 0.5. The error in the detection of time to peak of the response was always less than 2 time points, i.e. 400 ms in our data, also when a composite activation signal was simulated. An imposed temporal shift of the reference signal relative to the simulated activation showed a good recovery of this parameter, at least over shift of the reference signal relative to the simulated activation.

Subject B.

Using “rest” event as background noise and linearly superimposed activation signals to simulate realistic fMRI images could somehow be inaccurate, due to the presence of the activity of resting-state networks (e.g., Biswal et al., 1995; De Luca et al., 2006). Despite that, since such activity would add up to the simulated activation signals, our computed errors could be mainly overestimated in some voxels, but conceivably not underestimated. Therefore, our main results should not be invalidated.

Following the ARX procedure, we were able to discriminate the response of different cortical motor-related regions, in terms of time to main peak and amplitude of the HR. The obtained results are mainly consistent with available information on the functional properties of the brain regions involved in the motor task (Richter et al., 1997b; Kim et al., 1997; Weilke et al., 2001; Cunnington et al., 2002). Specifically, in the hemisphere contralateral to the moving hand, activity was greater than in the ipsilateral one. Moreover, the latency of activation increased in the order lp-sma-m1-s1, namely from areas involved in visuo-motor programming (lp), motor sequence organizing (sma), motor commands to spinal motoneurons targeting finger muscles (m1) and sensory feedback (s1) (Rizzolatti and Luppino, 2001; Tanji and Mushiake, 1996). Finally, differences in time to peak could be clearly pointed out in the two kinds of motor paradigms.

Fig. 13. Real fMRI data: original (top) and modeled (bottom) time courses of nine representative voxels relative to one “rest” trial. The specific exogenous input for each voxel was obtained as the FIR-filtered version of the average time course of the same voxel among 12 “resting-state” trials. Data from Subject B.

### Table 5
Real fMRI data: characterization of the responses in regions of interest

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Main peak amplitude (% change)</td>
<td>Time to main peak (in s from time to go)</td>
</tr>
<tr>
<td>lp</td>
<td>1.07 (0.11)</td>
<td>5.80 (0.43)</td>
</tr>
<tr>
<td>m1</td>
<td>1.76 (0.38)</td>
<td>6.88 (1.03)</td>
</tr>
<tr>
<td>s1</td>
<td>1.10 (0.30)</td>
<td>7.02 (0.36)</td>
</tr>
<tr>
<td>sma</td>
<td>1.10 (0.24)</td>
<td>6.38 (0.55)</td>
</tr>
</tbody>
</table>

All data are mean (SD) over 12 “right-hand” events. Data from lp, m1 and s1 refer to the hemisphere contralateral to the moving hand.

* In both tasks “time to peak” in the lp region is computed from the appearance of the arrow.
On the basis of the good characterization of responses in the motor task, we believe it is worthwhile to test in-depth the ARX filtering procedure on cognitive tasks and more complex protocols. Indeed, when time-dependent modulation occurs, averaging over trials looses the unique information associated with each individual execution of the task. The identification of each single-trial response will be particularly useful in perceptual-related fMRI based on single-trial protocols (Porro et al., 2004), to investigate the neural basis of variability of the perceptual responses over trials. Moreover, our approach can be used to investigate neural processes characterized by rapid changes over time, such as learning, habituation and sensitization, in specific brain circuits. Potential fields of application include for instance the study of the brain correlates of repetition suppression (Ishai et al., 2004), habituation to novel events (Yamaguchi et al., 2004), or of the placebo analgesic mechanisms (Wager et al., 2004), namely conditions where brain activity is expected to change over the course of a few trials. Due to limitations displayed by our method on simulated data in the detection of BOLD signal variation less than 1%, it is likely that, in order to detect subtle activation signals as those expected in many cognitive tasks, data acquisition should be still performed at high magnetic fields.

By using event-related time-resolved fMRI, the brain regions involved in processing different neural components of a task can be determined, allowing to separate intrinsic hemodynamic differences from neural activity differences. This can be done by recording fMRI time courses under conditions where behavioral parameters can vary (e.g. reaction times differing according to cognitive processing of various length) and correlating it to a BOLD response parameter (e.g. onset time or width) (see Menon and Kim, 1999 for a review on this approach). In this contest, having the opportunity to identify “true” single-trial responses, lightens the charge of classical “averaging” approaches, where one have to collect a large amount of trials and strictly align them accordingly to the behavioral correlates.

If our methodology is used to determine the HR relationship to different aspects either of the stimulus, or of the subject’s performance, a slow event-related design is recommended, since it allows to follow the whole response, including its recovery. Moreover, a high sampling rate improve the responses estimation, allows to follow the whole response, including its recovery. For performance, a slow event-related design is recommended, since it allows to follow the whole response, including its recovery.

We hypothesize that our ARX filtering procedure should prove useful as a pre-processing step in data driven approaches to the analysis of fMRI data, e.g. for clustering techniques aim at having the opportunity to identify “true” single-trial responses, lightens the charge of classical “averaging” approaches, where one have to collect a large amount of trials and strictly align them accordingly to the behavioral correlates.

If our methodology is used to determine the HR relationship to different aspects either of the stimulus, or of the subject’s performance, a slow event-related design is recommended, since it allows to follow the whole response, including its recovery. Moreover, a high sampling rate improve the responses estimation, allows to follow the whole response, including its recovery. For performance, a slow event-related design is recommended, since it allows to follow the whole response, including its recovery.

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References


Medical radiology.


