



## Technical note

## Box-Jenkins intervention analysis of functional magnetic resonance imaging data

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**Abstract**

Data obtained in functional magnetic resonance imaging (fMRI) typically form a time series of MRI signal collected over a period of time at constant intervals. These data are potentially autocorrelated and may contain time trends. Therefore, any assessment of significant changes in the MRI signal over a certain period of time requires the use of specific statistical techniques. For that purpose we used the Box-Jenkins intervention time series analysis to determine brain activation during task performance. We found that for a substantial number of pixels there was significant autocorrelation and, occasionally, time trends. In these cases, use of the classical *t*-test would not be appropriate. In contrast, Box-Jenkins intervention analysis, by detrending the series and by explicitly taking into account the correlation structure, provides a more appropriate method to determine the presence of significant activation during the task period in fMRI data. © 1997 Elsevier Science Ireland Ltd.

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The analysis of fMRI data is a current issue of considerable discussion, development and debate. Typically, fMRI data comprise a time series of brain images taken at constant intervals, and experiments are commonly focused on a comparison between a baseline (control) and an active (task) state. Each image consists of a number of pixels, each with its individual time course. The purpose of the analysis is usually to identify those pixels that show a significant change during the active condition compared to the baseline state; for that purpose, the Student's *t*-test (Kim et al., 1993) and

cross-correlation analysis (Bandettini et al., 1993) have been widely used. However these statistical tests are applied in the analysis of fMRI data without consideration of possible autocorrelations which are indeed likely in the time series analyzed. In fact, such correlations are taken explicitly into account by the Box-Jenkins time-series analysis (Box and Jenkins, 1976) by which it can be determined whether a particular intervention has a statistically significant effect on the series. This is especially useful in the context of fMRI data analysis, in which the task can be considered as the intervention and the control period preceding it as the pre-intervention series. Therefore, an appropriate model can be generated for the time series and the effect of task intervention tested. We describe this approach in more detail in that what follows.

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The essence of Box-Jenkins time series analysis (Box and Jenkins, 1976) is the construction of a model for the ‘noise’ of the time series. This analysis assumes that the value of the series at each time lag can be described as a function of past lags plus a random impact. The general model is described as an Autoregressive-Integrated-Moving Average ARIMA process of order  $(p, d, q)$  and takes the following form:

$$Z_t = C + (\Phi_1 Z_{t-1} + \Phi_2 Z_{t-2} + \dots + \Phi_p Z_{t-p}) - (\Theta_1 \alpha_{t-1} + \Theta_2 \alpha_{t-2} + \dots + \Theta_q \alpha_{t-q}) + \alpha_t$$

In this equation,  $Z_t$  is the value of the series at time lag  $t$ .  $C$  is a constant level of the series. The first parenthesis represents the autoregressive (AR) polynomial of order  $p$  and describes the effect of the  $p$  past series values (lags); the second parenthesis represents the moving average (MA) polynomial of order  $q$  and describes the effect of the random impacts at  $q$  past lags;  $\alpha_t$  is the random impact at this time lag. If there is a trend in the series it is removed by differencing, as described by the term  $d$ . In the intervention analysis (Box and Tiao, 1975) the same method is used to model and test the effects of an exogenous influence (intervention) upon the level of the time series. In that case the intervention is introduced as a separate polynomial; different types of intervention (permanent or temporary, sudden or gradual) can be modeled. In this analysis, the level of the time series following the intervention is compared to the level of the series before the intervention (preintervention series) and the statistical significance of the effect of the intervention on the level of the series is assessed. The important point of this method is that the comparison above is performed after the characteristics of the series itself (e.g. trends) and of its noise (e.g. autocorrelation) have been taken explicitly into account and, therefore, the result of the comparison is most valid.

The classical intervention analysis is an interactive procedure which includes the following steps (Fig. 1): (i) *model identification* (i.e. estimation of the terms  $p, d, q$ ) which is achieved using the autocorrelation function (ACF) and the partial autocorrelation function (PACF) of the pre-intervention time series; (ii) *parameter estimation* (i.e. calculation of the coefficients  $\Phi_1 \dots \Phi_p$  and  $\Theta_1 \dots \Theta_q$ ); (iii) *diagnostic checking* of the model to ensure that all coefficients are significant and within the bounds of stationarity (for the AR coefficients) or invertibility (for the MA coefficients), and that the residuals do not differ from white noise; (iv) introduction of the *intervention* which can be sudden or gradual, permanent or temporary; and (v) estimation and diagnostic checking of the final model. A procedure for identifying functional activation using this intervention analysis is outlined in Fig. 2. Preliminary results have already been presented (Tagaris et al., 1995).

The first step is the elimination of trends, if present, by differencing. Then, on the stationary series, we follow a procedure of application and diagnostic evaluation of a group of simple ARIMA  $(p, d, q)$  models; specifically we examine nine models with all possible combinations of  $p$  and  $q$ , each ranging from zero to two. The evaluation of the models is based on the criteria defined by Box and Jenkins (Box and Jenkins, 1976; McDowall et al., 1980); a particular model is accepted if the ACF and the PACF of the residuals are within 95% confidence limits for the first two lags and if relevant coefficients are significant and within bounds of stationarity or invertibility. The most parsimonious model that passes the above criteria is accepted and applied to the whole series (control and task period), with the inclusion of an ‘intervention’ term. The final model is then re-evaluated and the sign and statistical significance of the intervention component is used for the labeling of the pixel as ‘positively activated’, ‘negatively activated’ or ‘non-activated’. If none of the models are acceptable, then the pixel is labeled ‘not modeled’. We performed this analysis in a Sun Spark 20 workstation and used the BMDP statistical software (BMDP Statistical Software, Los Angeles, CA) for the application and diagnostic evaluation of the nine models.

We applied the procedure described above to four data sets, obtained as part of a mental rotation fMRI study (Tagaris et al., 1996). Multislice images were

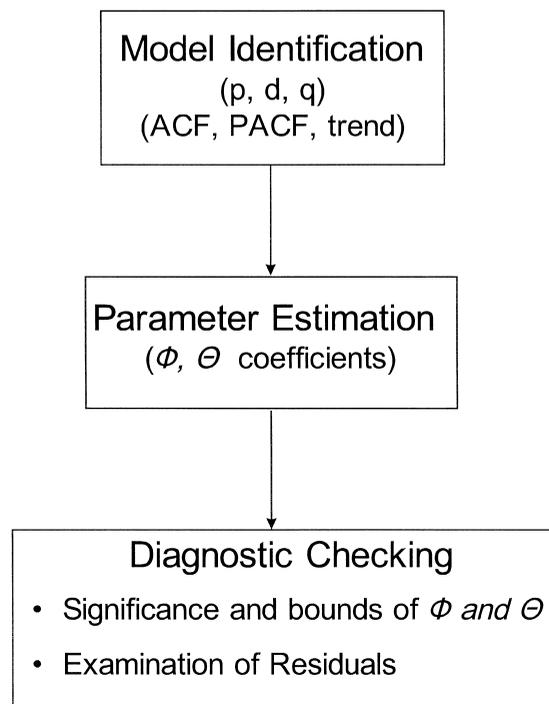


Fig. 1. Standard procedures for Box-Jenkins time series modeling and analysis. See text for abbreviations.

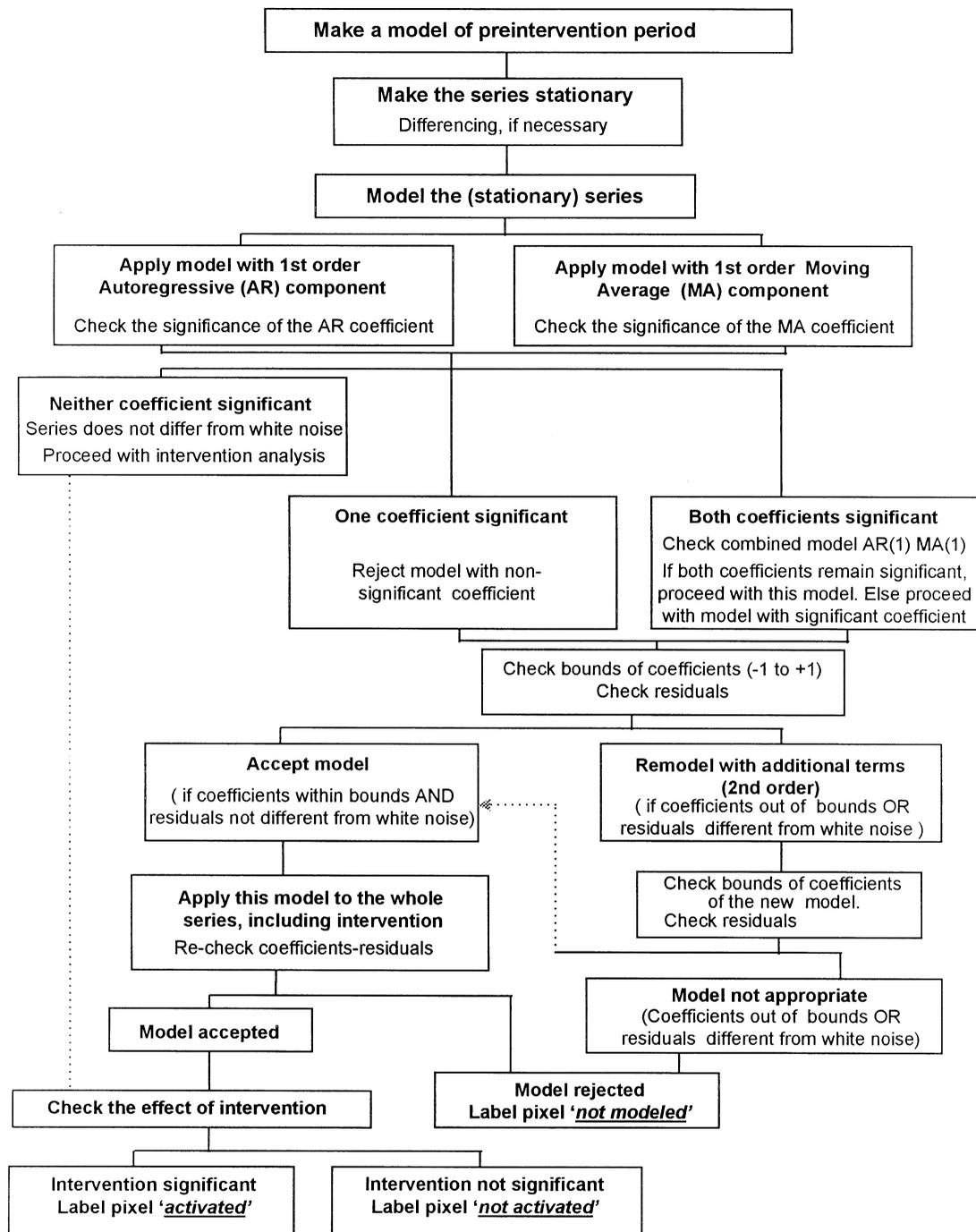


Fig. 2. Suggested algorithm for the application of Box-Jenkins intervention analysis to fMRI data.

acquired in a 4 Tesla magnet using a Turbo-FLASH sequence (TE = 28 ms, TR = 6 ms, flip angle  $11^\circ$ , spatial resolution  $3.1 \times 3.1 \times 10$  mm and a temporal resolution of 12 s (Hu and Kim, 1993)). In this study there was a 'task' period preceded and followed by two 'control' periods (Fig. 3). For the purposes of intervention analysis, the first control period was treated as the pre-intervention period and the task period as the inter-

vention period. The time series analyzed comprised these two periods and consisted of forty images: twenty five for the first control period and fifteen for the task period. The task was treated as a sudden and permanent intervention.

The results of the intervention analysis, as well as those of a usual *t*-test comparison between the same two periods, are summarized in Table 1. The signifi-

Table 1  
Results of the intervention analysis and Student's *t*-test in each of the four subjects

Subject	Box-Jenkins Time Series Model				Intervention analysis				<i>t</i> -test analysis					
	<i>p</i> = 0, <i>q</i> = 0	<i>p</i> = 1, <i>q</i> = 0	<i>p</i> = 0, <i>q</i> = 1	Other model	Not modeled	Total	Significant positive	Significant negative	Not signifi- cant	Total	Significant positive	Significant negative	Not signifi- cant	Total
1	76.98	12.70	5.62	0.29	4.44	100	12.89	6.91	80.20	100	13.87	8.28	77.83	100
2	77.47	7.59	9.01	0.39	5.44	100	3.81	2.59	93.60	100	6.69	4.93	88.38	100
3	75.36	9.33	9.72	0.81	4.84	100	4.83	3.34	91.83	100	3.30	5.98	90.72	100
4	75.98	10.84	8.84	0.49	3.88	100	4.91	3.59	91.50	100	6.71	5.25	88.04	100
Average	76.47	10.10	8.27	0.49	4.70	100	6.61	4.11	89.28	100	7.64	6.11	86.24	100

The numbers shown are percentages. The total number of pixels in each subject was 4096. Pixels are labeled 'significantly positive' or 'significantly negative' with respect to the sign of the intervention (in intervention analysis) or the sign of the *t*-value (in the *t*-test). In addition, the results of Box-Jenkins time series modeling, regardless of the significance of the intervention, are shown: *p* = 1, *q* = 0 refers to a first-order autoregressive model [1, d, 0]; *p* = 0, *q* = 1 refers to a first-order moving average model [0, d, 1]; 'other model' refers to pixels modeled by a second-order model or by a model with both autoregressive and moving average components (models (2, d, 0), (0, d, 2), (1, d, 1)); *p* = 0, *q* = 0 is a zero-order model statistically equivalent to white noise; the percent of pixels not modeled by any of the models tried is also given.

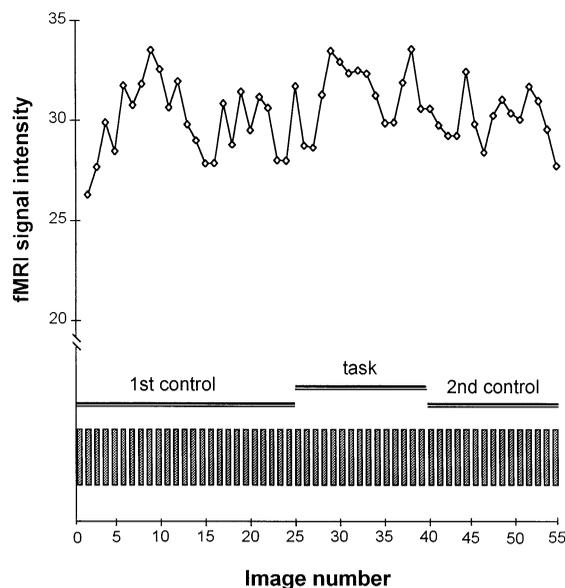


Fig. 3. (a) Time course of the fMRI signal intensity (in arbitrary units) of a single pixel. Student's  $t$ -test showed a significant change during the task period (images 25–39) compared to the first control period (images 1–24,  $P < 0.02$ ). However, Box-Jenkins intervention analysis showed that the task effect was not statistically significant ( $P > 0.2$ ). The series was successfully modeled as a first-order (1, 0, 0) process. (b) Schematic representation of data acquisition during the experiment (Tagaris et al., 1996). Images were acquired continuously. Data from the second control period were not used in the present analysis.

cance level was set at  $P < 0.05$  for both methods. Differencing was required in subject 3, since there was a significant baseline drift. For the majority of pixels (76.5% on average) modeling was deemed not to be necessary; this means that the null hypothesis, that the noise of the series was 'white noise', was not rejected. However, in 18.9% of the time courses modeling was required (usually, either first order AR or first order MA model). Finally, 4.7% of the pixels could not be modeled with a first or second-order model.

In terms of functional activation, both methods yielded comparable results (Table 2). In general, intervention analysis was more conservative, identifying a

Table 2  
Cross tabulation of the results (percentages of pixels activated positively [+], negatively [–] or not activated [0]) of intervention analysis and  $t$ -test

		Intervention analysis				Total
		+	0	–	NM	
$t$ -test	+	5.81	1.97	0.00	0.43	8.21
	0	1.03	79.55	0.22	3.83	84.64
	–	0.07	2.87	3.85	0.35	7.15
	Total	6.92	84.39	4.07	4.62	100

NM, not modeled.

smaller number of pixels as activated. A notable exception was subject 3; in this subject the number of positively activated pixels, as well as the ratio of positively to negatively activated pixels was higher with intervention analysis, compared to  $t$ -test.

One issue of concern is related to those pixels that are not modeled satisfactorily by the models tried. The noise of the preintervention series for these pixels differs significantly from white noise and, therefore, methods like the  $t$ -test would also be inappropriate for them. Although some of them might be modeled by higher order ARIMA models, it seems likely that those pixels either have been subjected to the influence of other factors (e.g. motion) or simply represent statistical extremes. In the present study those pixels represented only 4.7% of the total (Table 1); they did not show any particular distribution and were excluded from further analysis.

The results of this study, using the modified intervention analysis described above, leads to the following conclusions. First, Box-Jenkins intervention analysis can be successfully used to analyze fMRI data. Second, a small number of relatively simple models is sufficient for the modeling of the majority of time series of individual pixels. Third, although the results of Student's  $t$ -test are generally congruent, there was a significant number of pixels (18.9% on average) in which the time series did not resemble white noise, due to a significant autoregressive or moving average component. For these pixels the results of a classical  $t$ -test would not be easily interpretable because of the obvious violation of the assumption of independence of the errors and, therefore, time-series intervention analysis is appropriate. Fourth, intervention analysis can accommodate common nuisance situations such as baseline drifts. As a matter of fact, in intervention analysis such drifts can be easily removed by differencing (see subject 3, Table 1). Finally, intervention analysis can model different types of intervention. In this study, we investigated only one of them, namely the 'abrupt permanent impact' due to the design and the low temporal resolution (12 s) of our experiment. In studies with faster image acquisition a 'gradual' type of intervention might be preferable in order to simulate the physiological response. Also, depending on the design of the experiment, non-permanent impacts or multiple intervention models might be investigated. Moreover, in studies with higher temporal resolution, other periodical components that comprise the 'physiological noise' (e.g. pulse rate, respiration etc.) could be modeled as 'seasonal' components and eventually removed.

In summary, from a theoretical viewpoint, intervention analysis is most appropriate for analyzing fMRI data, due to their nature as sampled time series. However, it should be noted that, compared to time series in other fields where this analysis has been successfully

used, e.g. social sciences and economics (McDowall et al., 1980), fMRI time series are relatively short. On the other hand, in the analysis of fMRI data the requirements are not as high as in the other fields mentioned above. Indeed, in fMRI one is not looking for a detailed model of the time series that will be used, for example, for purposes of forecasting future values of the series. Instead, one needs a model that would account for most of the variability and correlation structure of the fMRI signal in order to assess the true effect of the task intervention, uncontaminated by autocorrelations and/or time trends of the series.

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### References

- Bandettini, P.A., Jesmanowicz, A., Wong, E.C. and Hyde, J.S. (1993) Processing strategies for time-course data sets in the human brain. *Magn. Res. Med.*, 30 (2): 161–173.
- Box, G.E.P. and Tiao, G.C. (1975) Intervention analysis with applications to economic and environmental problems. *J. Am. Stat. Assoc.*, 70: 70–92.
- Box, G.E.P. and Jenkins, G.M. (1976) *Time series analysis forecasting and control* (revised edition). Holden Day, Oakland.
- Hu, X. and Kim, S.G. (1993) A new T2\*-weighting technique for magnetic resonance imaging. *Magn. Res. Med.*, 30: 512–517.
- Kim, S.G., Ashe, J., Hendrich, K., Ellermann, J.M., Merkle, H., Ugurbil, K. and Georgopoulos, A.P. (1993) Functional magnetic resonance imaging of motor cortex: asymmetry and handedness. *Science*, 261 (5121): 615–617.
- McDowall, D., McCleary, R., Meidinger, E.E. and Hay, R.A. (1980) *Interrupted time series analysis*, Sage Publications, Newbury Park, CA.
- Tagaris, G.A., Kim, S.G., Ugurbil, K. and Georgopoulos, A.P. (1995) Box-Jenkins intervention analysis of functional MRI data. *Proc. SMR*, Vol. 2, p. 814.
- Tagaris, G.A., Kim, S.G., Strupp, J., Andersen, P., Ugurbil, K. and Georgopoulos, A.P. (1996) Quantitative relations of performance in mental rotation and superior parietal activation. *NeuroReport*, 7: 773–776.