Modelling the haemodynamic response function
Chapter 4

Extracting the haemodynamic response function using Fourier-wavelet regularised deconvolution

Abstract

We present a method to extract the haemodynamic response function (HRF) from a functional magnetic resonance imaging (fMRI) time series. The method is based on Fourier-wavelet regularised deconvolution (ForWaRD). The extraction algorithm is very general: it relies only on the assumptions of the general linear model (GLM) and the fact that signal and noise can be distinguished in the frequency and wavelet domain, respectively. Before extracting the HRF, low-frequency trends are removed from the time signals by a standard wavelet-based method. The combined routine of detrending and extraction is tested extensively, using noise from an fMRI data set and simulated event-related activation. The output of the extraction program is a time series of image volumes, containing the HRF at each voxel location. Such a time series may be used in many fMRI-related problems, like defining region-specific HRFs (by combining the HRFs found in a specific region), finding a set of basis functions to efficiently describe the HRF (by decomposing the extracted HRF into a more general set of functions), or comparing subject-specific HRFs. A new HRF model is introduced, and it is used in combination with the extraction method to describe fMRI responses. The use of these modelled responses is demonstrated in the analysis of an event-related fMRI experiment. Test results show that using subject-specific, regional HRFs dramatically improves the detection of active regions in fMRI.
4.1 Introduction

Functional magnetic resonance imaging (fMRI) is one of the most versatile methods for functional neuroimaging. Regional brain activation is accompanied by temporal changes in blood oxygenation, generating a blood oxygenation level dependent (BOLD) contrast in MR images (Ogawa et al. 1990). Many of the current analysis methods for fMRI time series are based on hypothesis testing. Given a model for the response to a stimulus pattern, a statistic can be computed in every voxel of the correspondence between the predicted signal and the measured signal. The most widely-used technique based on hypothesis tests is statistical parametric mapping (Friston et al. 1995c). Given a noise distribution, this technique uses the estimated parameters of the noise in every voxel to determine a threshold for the computed statistic. The general linear model (GLM) treats the response to a stimulus pattern as the output of a linear, time invariant (LTI) system (Boynton et al. 1996). Two consequences of the GLM are that (i) the response to stimuli of one type can be modelled by convolving the time pattern of those stimuli with the corresponding response function, and (ii) the total response is the sum of responses to all stimulus types (see Fig. 4.1a). The stimulus pattern is known from the experimental setup, and the haemodynamic response function (HRF), the temporal change in blood oxygenation that generates the BOLD contrast, is unknown. The HRF is the BOLD response to an impulse. It is usually modelled as a smooth curve, starting about 2 seconds after the impulse, peaking about 6 seconds after the impulse, and returning to baseline in about 30 seconds.

The focus of this chapter is on extracting the HRF from fMRI data. The method proposed in this chapter is based on Fourier-wavelet regularised deconvolution, ForWaRD for short, which was developed recently (Neelamani et al. 2004). ForWaRD combines deconvolution in the frequency domain with regularisation in the frequency domain and in the wavelet domain. The advantage of deconvolution in the frequency domain is the ability to deal with overlapping responses. Its main weakness is noise amplification. Noise can be reduced in the frequency domain by shrinking frequency coefficients, but noise and signal may be difficult to separate. ForWaRD solves this by using wavelet domain Wiener shrinkage. ForWaRD is related to a number of recent wavelet-based techniques for noise suppression during deconvolution (Sanchez-Avila 2002, Kalifa et al. 2003). An advantage of ForWaRD is that signal and response can be interchanged without violating the assumptions of the algorithm.

The novelty of our application of deconvolution is that the underlying signal (the stimulus pattern) is known and that the response function is reconstructed. The only prerequisites are an fMRI data set, the stimulus time pattern, and the GLM. The current method extracts one HRF per experiment, in the future this may be extended to multiple HRFs (e.g., for different stimulus types) and multiple time series (e.g., extracting a mean HRF in a group study). The output of our method is a post-stimulus time series of image volumes, containing the HRF at each voxel location. An example application of such a time series is the extraction of subject-specific, group-specific, and region-specific HRFs, which is easily implemented by averaging time signals from the corresponding
Extracting an HRF from fMRI data is difficult, and most current methods require strong assumptions about the data. The simplest way to acquire the HRF is selective averaging: use a long interstimulus interval (ISI) and assume that responses do not overlap (Bandettini and Cox 2000, Buckner et al. 1996, Aguirre et al. 1998). Selective averaging works, but because of the long ISI that is required, it is very time-consuming. Another method is averaging trials with overlapping responses, ignoring the fact that overlapping responses introduce errors (Boynton et al. 1996, Zarahn et al. 1997, Burock et al. 1998, Dale 1999). More advanced techniques use a function to describe the HRF, and determine the parameters of that function via curve-fitting (Glover 1999, Miezin et al. 2000, Hinrichs et al. 2000, Ollinger et al. 2001b). Another approach, based on the GLM, is the expansion of the HRF into a set of basis functions (Friston et al. 1995a, Josephs et al. 1997, Friston et al. 1998a).

Ciuciu et al. (2003) use a Bayesian method to extract the HRF. They assume a causal, smooth HRF that starts and ends at baseline, for each stimulus type. A Gaussian temporal autocorrelation is imposed on the HRF. The method is capable of extracting multiple HRFs from multiple experiments in one run.

We present a new model for the HRF, based on general notions in dynamical systems theory. The model is used in combination with the HRFs extracted from a first fMRI experiment, to predict the responses in a second fMRI experiment. Results indicate that a modelled HRF based on a region-specific extracted HRF yields a more precise estimator than a standard HRF.

A difference between our HRF model and other models in use today is that it was
4.2 Modelling fMRI Time Signals

derived from systems theory. Many HRF models lack a theoretical description of fMRI responses. Many groups use a Poisson function (Boynton et al. 1996, Miezin et al. 2000) or extensions thereof (Friston et al. 1998a, Gössl et al. 2001). These functions are popular because they seem to fit the data very well, but they are not based on a model of the BOLD response. Studies have shown that the BOLD response is not linear if the durations or the amplitudes of the stimuli vary (Vazquez and Noll 1998, Friston et al. 2000a). This chapter treats only fMRI experiments with very short stimuli, and the GLM is assumed to be valid.

The remainder of this chapter is organised as follows. Section 4.2 describes how fMRI time signals are modelled. Section 4.3 treats the problem of regularisation, and presents the regularisation methods used in this article. A method for extracting the HRF is given in section 4.3.3. The method is tested on simulated activation in section 4.4. A model for the BOLD HRF based on dynamical systems is presented, and noise from an fMRI time series is superimposed on the modelled activation. The model is used with the extracted HRFs in section 4.5. The test data are from an event-related fMRI experiment of a motor task, consisting of two runs. The first run uses a fixed interstimulus interval, the second run uses random interstimulus times. The HRF model and the coefficients extracted from one experiment are used to predict the responses in the other experiment. Results show that using the modelled HRF leads to an improvement in the localisation of activation, and increased statistical significance, compared to the standard method. Section 4.6 contains some general conclusions.

4.2 Modelling fMRI Time Signals

The common method for hypothesis testing in fMRI is statistical parametric mapping (SPM). SPM assumes independent, identically distributed (i.i.d) Gaussian temporal noise. After parameterising the noise, SPM consists of:

1: computing a statistic at every voxel location;
2: choosing a threshold based on the parameters of the noise and the correction for multiple testing;
3: thresholding the map of statistic values.

4.2.1 The General Linear Model

The GLM describes the response in an fMRI experiment as a weighted sum of explanatory signals. An explanatory signal models the response to stimuli of one type. Let the matrix \( Y_{[T \times N]} \) denote the data of an fMRI experiment, where each element \( y_{ij} \) is the measurement at time \( i = 1, \ldots, T \) and voxel location \( j = 1, \ldots, N \). According to the GLM,

\[
Y = X\beta + e. \tag{4.1}
\]
$X_{(T \times M)}$ is the design matrix, whose column vectors are the explanatory signals. These are multiplied by the weights in matrix $\beta_{(M \times N)}$. The matrix $e_{(T \times N)}$ contains the residual signal at each voxel location in each scan. A least-squares estimate $b$ for $\beta$ is given by $(X^T X)^{-1} X^T Y$. Given a Gaussian temporal distribution of the residuals, which follows from the GLM if $Y$ contains Gaussian temporal noise, the significance of the elements of $b$ can be computed in each voxel via standard hypothesis tests. For stationary noise, the threshold need only be determined once and can be applied to the entire map of statistic values.

### 4.2.2 Determining the HRF

In the GLM, the explanatory signal $g_{f,h}$ representing responses with shape $h$ to a stimulus pattern $f$, can be written as a convolution:

$$g_{f,h}(n) = (h * f)(n), \quad n = 1 \ldots N,$$

(4.2)

with ‘*’ denoting discrete circular convolution. A convolution in the time domain is a pointwise multiplication in the frequency domain, and a deconvolution is a pointwise division:

$$G_{f,h}(k) = H(k) F(k),$$

and

$$H(k) = G_{f,h}(k) / F(k), \quad k = 1 \ldots N,$$

(4.3)

where $F(k)$, $G_{f,h}(k)$ and $H(k)$ denote the Fourier transforms of $f(n)$, $g_{f,h}(n)$ and $h(n)$, respectively. If the signal contains unmodelled components, represented in (4.1) by $e$, these are also present in the extracted response (see Fig. 4.1b). At frequencies $k$ where $F(k)$ is small, noise is amplified. If $F(k) = 0$, the deconvolution problem is singular.

To cope with these situations, regularisation is required. The ForWaRD regularisation scheme, used in this chapter, is described in section 4.3.

### 4.2.3 Modelling the HRF

The temporal resolution of fMRI data may be too coarse to accurately describe the HRF. A description at a finer scale is often obtained by using a model for the HRF.

We present an HRF model based on a linear system showing damped oscillations. The (canonical) differential equation that describes such a system, represented by state variable $O(t)$, is:

$$O''(t) + O'(t) + O(t) = 1,$$

where

$$O(0) = 0, \quad O'(0) = 0.$$

(4.4)

The primes denote derivatives with respect to the time variable $t$. $O(t)$ represents the regional blood oxygenation level, with value 0 before $t=0$, and value 1 as the new level after a transition period. Equation (4.4) has a unique solution:

$$O(t) = 1 - \left( \frac{\sqrt{3}}{3} \sin \left( \frac{\sqrt{3}t}{2} \right) + \cos \left( \frac{\sqrt{3}t}{2} \right) \right) e^{-t/2}$$

(4.5)
and \( O'(t) \) can be derived:

\[
O'(t) = \frac{2}{3} \sqrt{3} \sin \left( \frac{\sqrt{3} t}{2} \right) e^{-t/2},
\]

(4.6)

see Fig. 4.2. The first-order Taylor expansion of \( O(t) \) states that \( O(t + dt) = O(t) + O'(t)dt \), so that the response to a longer stimulus can be modelled by convolving the stimulus with \( O'(t) \). We define a function \( \text{HRF}_{\text{par}} \) based on \( O'(t) \) with parameters \( H(\text{eight}), D(\text{ilation}), P(\text{eriod}) \) and \( L(\text{ag}) \):

\[
\text{HRF}_{\text{par}}^{H,D,P,L}(t) = \begin{cases} 
H \sin \left( \frac{t-L}{P} \right) e^{-t/L}, & \text{if } t > L \\
0, & \text{otherwise}
\end{cases}
\]

(4.7)

In our tests we used \( H = 4, D = 6, P = 3, \) and \( L = 2, i.e., \)

\[
\text{HRF}_{\text{do}}(t) = \text{HRF}_{\text{par}}^{4,6,3,2}(t),
\]

(4.8)

to resemble other HRFs in use today (see Fig. 4.4). The subscript ‘do’ refers to ‘damped oscillator’.

![Figure 4.2](image_url)

**Figure 4.2.** The change in the blood oxygenation (solid line) and its time derivative (dashed line) modelled by Eq. (4.5) and (4.6), respectively.

The other HRF model used in this chapter is the canonical HRF from the SPM program (Friston et al. 1995c), denoted by \( \text{HRF}_{\text{spm}}(t) \), which is the sum of two Poisson functions. Poisson functions are often used, without motivation, to describe the HRF. A Poisson function \( p_{m,l}(t) \) with shape parameter \( m \) and dilation parameter \( l \) has the form:

\[
p_{m,l}(t) = \frac{t^{m-1} e^{-lt}}{\Gamma(m)} , \quad \text{where}
\]

\[
\Gamma(m) = \int_0^\infty t^{m-1} e^{-t} dt.
\]

(4.9)
The standard HRF in the SPM program has the form

\[ \text{HRF}_{\text{spm}}(t) = p_{6,1}(t) - \frac{1}{6} p_{16,1}(t). \] (4.10)

It is often used in combination with (i) its temporal derivative and (ii) its derivative with respect to dilation, to capture small response variabilities within an experiment (Friston et al. 1998a, Henson et al. 2002). In this chapter, \( \text{HRF}_{\text{spm}} \) is used as a reference for evaluating our model.

### 4.3 Regularisation

#### 4.3.1 Shrinkage I: the Frequency Domain

Deconvolution problems are generally ill-posed, i.e., a solution does not exist, or it is not unique, or it is not stable, and regularisation is required. For one stimulus signal, one response function and additive noise, Eq. (4.2) becomes:

\[ g(n) = (h \ast f)(n) + e(n). \] (4.11)

An estimate \( H_{\text{est}} \) of the Fourier transform of \( h \) is given by (4.3):

\[
H_{\text{est}}(k) = \frac{G(k)}{F(k)} = \begin{cases}
H(k) + E(k) \frac{F(k)}{F(k)}, & \text{if } |F(k)| > 0 \\
0, & \text{otherwise}
\end{cases}
\] (4.12)

where \( E(k) \) is the Fourier transform of \( e(n) \). Regularisation is performed by shrinking the estimate at frequencies where \( F(k) \) is small. Given a regularisation parameter \( \tau \) and an estimate \( \bar{\sigma}_e \) for the noise strength, a Wiener filter multiplies each frequency coefficient \( H_{\text{est}}(k) \) with a factor \( \lambda \):

\[
H_{\lambda}(k) = H_{\text{est}}(k) \lambda(k),
\]

where

\[
\lambda(k) = \frac{|F(k)|^2}{|F(k)|^2 + \tau \frac{\bar{\sigma}_e^2}{|H(k)|^2}}. \] (4.13)

The HRF estimate \( h_{\lambda}(n) \) is the inverse Fourier transform of \( H_{\lambda}(k) \). This regularisation method is known as Wiener shrinkage. Wiener shrinkage minimises \(|h_{\lambda} - h|^2\). Where \( F(k) \) is large, \( \lambda(k) \approx 1 \) and where \( F(k) \) is small, \( \lambda(k) \approx 0 \). Wiener shrinkage is the optimal method to remove noise from regular (smooth) signals, but signals with irregularities (such as steep edges) are handled less well. Irregularities contain high frequencies, so either noise is not suppressed, or artifacts (such as ringing) occur (Neelamani et al. 2004). Wiener shrinkage requires the power spectrum \(|H(k)|^2\) of \( h \), e.g., by estimating it iteratively (Hillery and Chin 1991). Tikhonov shrinkage, which computes \( \lambda(k) \) as

\[
\lambda(k) = \frac{|F(k)|^2}{|F(k)|^2 + \tau^2},
\] (4.14)
does not require \( h \)'s power spectrum. Optimal values for the regularisation parameter \( \tau \) in (4.13) and (4.14) are derived from the strength of the signal and of the noise. Given a signal \( g \) of length \( N \) and mean \( \mu_g \) and a noise strength estimate \( \tilde{\sigma}_e \), optimal values for \( \tau \) are in the range \([0.01, 10]N\tilde{\sigma}_e^2/|g - \mu_g|^2\) (Neelamani et al. 2004).

### 4.3.2 Shrinkage II: Wavelets and ForWaRD

If the impulse response \( h(n) \) belongs to a smoothness class (i.e., if it is regular according to some regularity measure (Donoho and Johnstone 1995, Cai 2003)), and if \( F(k) \) does not contain zeros, the irregularity in the system is caused by the noise \( e \). This turns the regularisation problem into a denoising problem. ForWaRD (see Algorithm 4.1) regularises the deconvolution with frequency domain shrinkage and additional wavelet domain Wiener shrinkage (Ghael et al. 1997). Wavelet domain Wiener shrinkage is a very powerful regularisation method for signals containing irregularities. It requires an estimate of the (regular part of the) signal. ForWaRD uses the wavelet transform to obtain this estimate.

A wavelet transform describes a signal \( c^0 \) as a sum of localised basis functions. The regular and irregular part \( c^1 \) and \( d^1 \) are written as weighted sums of shifted and dilated versions of a scaling function \( \phi \) and an accompanying wavelet \( \psi \), respectively. Analysis at multiple levels is done by dividing subsequent \( c^j \) into \( c^{j+1} \) and \( d^{j+1} \). The corresponding inverse wavelet transform uses \( c^j \) and \( d^j \) to reconstruct \( c^{j-1} \). The wavelet transform of a signal is efficiently computed via the fast wavelet transform, FWT (Mallat 1989). The FWT transforms a signal of length \( N \) in \( O(N) \) computations into a transform of length \( N \). Efficiency is obtained by downsampling at each level. The FWT is not translation-invariant, making it less useful for deconvolution. A wavelet transform using polyphase decomposition (subsample for all possible shifts) is translation-invariant. The size of a level \( J \) transform is \((J + 1) \times N\), its complexity is \( O(N \log_2(N)) \) (Mallat 1991). This transform is denoted by SI-DWT (shift-invariant discrete wavelet transform), its inverse by SI-IDWT.

ForWaRD applies the wavelet domain Wiener shrinkage to the estimate \( h_\lambda \), see (4.13) and (4.14). For smooth signals, most energy is stored in the approximation \( c^J \), and the coefficients of \( d^j \) are small (Donoho and Johnstone 1995). Large coefficients of \( d^j \) appear at irregularities in the underlying signal. The regular and irregular parts of the signal are separated: \( c^J \) and large coefficients of \( d^j \) are regarded as signal, the rest is noise. Two different wavelet transforms of \( h_\lambda \), represented by the basis functions \((\phi_1, \psi_1)\) and \((\phi_2, \psi_2)\), respectively, are similar. ForWaRD uses this similarity as follows. A first estimate of is obtained by computing the SI-DWT of \( h_\lambda \), using \((\phi_1, \psi_1)\), and thresholding the detail coefficients \( \{d^j_1(n)\}_{j=1}^J \) to remove noise. The threshold is \( \theta \tilde{\sigma}_e \) with \( \theta \in \{1, 2, 3, 4\} \). The noise standard deviation \( \tilde{\sigma}_e \) is estimated using the median absolute value (MAD) of the first-level detail coefficients (Donoho and Johnstone 1995). This estimate of the (wavelet) spectrum of the underlying signal is used for the second step, wavelet domain Wiener shrinkage. After computing a second SI-DWT using \((\phi_2, \psi_2)\), its
Given: signal $g$, stimulus pattern $f$, wavelet basis functions $(\phi_1, \psi_1)$ and $(\phi_2, \psi_2)$

1: $g \xrightarrow{\text{SI-DWT}}$ estimate $\tilde{\sigma}_e$ using the MAD (see section 4.3.2)
2: compute $\tau$ using $\tilde{\sigma}_e$, $g$ (see section 4.3.1)
3: $g \xrightarrow{\text{FFT}} G$, $f \xrightarrow{\text{FFT}} F$
4: first estimate: $H_{\text{est}} := G/F$
5: if {Wiener shrinkage} then
6: approximate $|H|^2$ using $F$, $G$ (see (Hillery and Chin 1991))
7: compute $\lambda$ using $\tau$, $\tilde{\sigma}_e$, $F$, $|H|^2$ (see Eq. (4.13))
8: else {Tikhonov shrinkage}
9: compute $\lambda$ using $\tau$, $F$ (see Eq. (4.14))
10: end if
11: shrink: $H_{\text{Shrink}} := H_{\text{est}} \lambda$
12: $H_{\lambda} \xrightarrow{\text{IFFT}} h_{\lambda}$
13: $h_{\lambda}, (\phi_1, \psi_1) \xrightarrow{\text{SI-DWT}} c_1^j, \{d_1^j\}^J_{j=1}$
14: $h_{\lambda}, (\phi_2, \psi_2) \xrightarrow{\text{SI-DWT}} c_2^j, \{d_2^j\}^J_{j=1}$
15: using $\theta$, $\tilde{\sigma}_e$, $d_1^j$ threshold, $\{\tilde{d}_1^j\}^J_{j=1}$ (see section 4.3.2)
16: compute $\kappa^j$ using $\tilde{d}_1^j$, $\tilde{\sigma}_e$ (see Eq. (4.15))
17: shrink: $d_{\kappa,2}^j := d_2^j \kappa^j$
18: final estimate: $(c_2^J, \{d_{\kappa,2}^j\}^J_{j=1}, (\phi_2, \psi_2) \xrightarrow{\text{SI-IDWT}} h_{\kappa}$

**Algorithm 4.1: ForWaRD in pseudo-code**

Detail coefficients are shrunk: $d_{\kappa,2}^j(n) = d_2^j(n) \kappa^j(n)$, where

$$\kappa^j(n) = \frac{|\tilde{d}_1^j(n)|^2}{|d_1^j(n)|^2 + \tilde{\sigma}_e^2}. \quad (4.15)$$

Here, $\tilde{d}_1^j(n)$ denotes $d_1^j(n)$ after thresholding. The final estimate $h_{\kappa}$ is the SI-IDWT of $c_2^J$ and $\{d_{\kappa,2}^j\}^J_{j=1}$.

### 4.3.3 Using ForWaRD to extract the HRF

Given a stimulus pattern $f$ and an fMRI time series, ForWaRD (see Algorithm 4.1) was used to extract an HRF in each voxel. The BOLD response is the time signal relative to the baseline, which is usually the time series mean. Low-frequency trends that are not synchronous to the stimulus pattern are a possible source of artifacts. These were removed as much as possible beforehand by a wavelet technique known from the literature (Meyer 2003). Transform each time signal (with length $N$) to the wavelet domain, using an FWT of $\log_2(N) - 3$ levels; remove the detail coefficients, and subtract the low-scale signal from the time series. The total extraction routine for each voxel is:
1: load the time series $g$ and the stimulus pattern $f$;  
2: subtract the time series mean;  
3: remove low-frequency trends;  
4: apply ForWaRD to $g$, estimate the HRF $h_\kappa$ to the stimuli with pattern $f$.

Time signals at different voxel locations can be processed independently, which enables partitioning the images during extraction to reduce the computation load. Given a maximum block size $B$, the time signals are read, processed, and written $B$ at a time. The output of the algorithm is a time series of volumes which, inside activated brain areas, contain the HRF. These routines were implemented in MatLab (The Mathworks, USA). The next section describes a series of tests, using simulated time series with activations of known shape and strength. Section 4.5 presents test results on an event-related fMRI data set.

### 4.4 Simulation Tests

#### 4.4.1 Test Setup

The routine presented in section 4.3.3 was tested on signals with varying properties (SNR, temporal resolution, low-frequency trends), while the parameters of the routine (decomposition level, wavelet filters, etc.) were also varied. Figure 4.5 shows the test setup: (i) create an activation signal with noise and a low-pass trend (Fig. 4.5a-b), (ii) recover the HRF from this noisy signal (Fig. 4.5c), (iii) reconstruct the activation signal (Fig. 4.5d), and (iv) measure the mean square error (MSE) between the original activation signal and the reconstruction.

#### Using noise from a real time series of MR images

A sequence of 128 scans of a subject in rest (no activation) was acquired on a 3T Intera system (Philips Medical Systems, the Netherlands), with a repetition time (TR) of 3 s and images of $64 \times 64 \times 46$ voxels, with a voxel size of $3.5 \times 3.5 \times 3.5$ mm$^3$. A sample of 512 time signals was collected from these images by selecting a region of $8 \times 8 \times 8$ voxels from this data set (see Fig. 4.3).

#### Adding simulated activation

A randomised stimulus signal was created by thresholding a vector containing random values. A time signal $s(n), n=1,\ldots,N$ was made by convolving the stimulus signal with an HRF. We used two different HRFs in our tests (see Fig. 4.4): HRF$_{do}$, see Eq. (4.8) and HRF$_{spm}$, see Eq. (4.10).
Figure 4.3. The area that was sampled to obtain MR noise time signals: (a) transverse, (b) sagittal view, (c) coronal view.

Figure 4.4. (a) The HRFs used for simulating activations: (i) HRF_{do} and (ii) HRF_{spm}. (b) The modelled low-frequency behaviour: (i) no trend, (ii) linear trend, (iii) sinusoidal trend, (iv) quadratic trend.

Adding low-frequency trends

Four types of low-frequency trends were tested: no trend, and a linear, sinusoidal and quadratic trend (see Fig. 4.4b). Given the standard deviations $\sigma_s$ of the signal, $\sigma_e$ of the noise and $\sigma_t$ of the trend, the noise was amplified by a factor $m_n$ so that

$$\text{SNR} = 10 \log_{10} \frac{\sigma_s}{m_n \sigma_e}. \quad (4.16)$$

had the desired value, and the trend was scaled by a factor $m_t$ so that $m_t \sigma_t = m_n \sigma_e$. The activation, the trend and the noise (see 4.5a) were added together at each voxel location, resulting in a noisy time signal (see Fig. 4.5b).
Reconstructing the activation signal

Each noisy time signal was processed by the ForWaRD-based extraction routine of section 4.3.3, the HRF was extracted from each time signal, and the signal was reconstructed using the mean HRF. The performance of the HRF extraction routine was measured via the MSE between $s$ and its reconstruction $r$. The following properties of the signal were varied in the tests: (a) input SNR, (b) low-frequency trends, (c) repetition time (TR), and (d) response onset. All tests were done with both $\text{HRF}_{do}(t)$ and $\text{HRF}_{spm}(t)$. Parameters of the routine that were varied: (a) type of frequency domain shrinkage, (b) levels of the wavelet transform, (c) threshold level in the wavelet domain, and (d) the wavelet filters for $4.15$. The default test setup was as follows: $\text{SNR} = 0$ dB, $\text{HRF} = \text{HRF}_{spm}$, no trend, $\text{TR} = 2$ s, onset delay = $0$ s, Tikhonov shrinkage, $\tau = 0.1$, decomposition level = 3, $\theta = 3$, $\phi_1$: Daubechies-4, $\phi_2$: Daubechies-3 (Daubechies 1988). Each test varied one of these parameters.
4.4.2 Test Results

Output MSE as a function of input SNR

Figure 4.6 shows the outcome of a test run with various input SNR values. It shows that the MSE decreases for input SNRs up to 5 dB, above 5 dB the MSE increases.

![Figure 4.6](image)

\[ \text{Figure 4.6. } \log_{10}(\text{MSE}) \text{ of the noisy (×) and reconstructed (ο) signals.} \]

Wiener shrinkage vs. Tikhonov shrinkage, choosing \( \tau \)

The number of iterations of the algorithm (Hillery and Chin 1991) to estimate \(|H|^2\) before applying Wiener shrinkage (see line 6 of Algorithm 4.1) was limited to ten. Figure 4.7 shows the MSE with both types of frequency domain shrinkage, for varying SNR and regularisation parameter \( \tau \). These graphs show that with heavy regularisation (\( \tau \geq 1 \)), and for a low SNR, Tikhonov regularisation performs as well as Wiener shrinkage. For the higher SNRs and with mild regularisation, Wiener shrinkage performs better (i.e., smaller MSE).

The best setting of \( \tau \) depends on the shrinkage type, the SNR and the TR. Figure 4.7 shows that for short TR, mild regularisation (\( \tau \leq 0.1 \)) yields the best results. A long TR requires heavy shrinkage, and Wiener shrinkage outperforms Tikhonov shrinkage.

Different response delays

For most fMRI analysis techniques such as analysis of variance (ANOVA) and analysis of covariance (ANCOVA), temporal alignment is very important. To correct for small synchronisation errors in the response onset, a temporal derivative of the HRF is sometimes included in the model (Friston et al. 1998a). Figure 4.8 shows that HRFs with different onset delays can equally well be extracted with ForWaRD, which does not use such derivatives. The MSE hardly changes with different delays, indicating that the
shape of the response is preserved. This is an attractive alternative to other delay correction methods. The increased MSE for negative shifts is caused by the fact that the HRF was only sampled in the post-stimulus interval.

**Extractability of HRFs**

We compared the extraction of HRF_{do}(t) vs. HRF_{spm}(t). Figure 4.9 shows that with a TR of 0.5 s, HRF_{do} is better reconstructible, and with a TR of 3 s, HRF_{spm} is better reconstructible. The graphs indicate that the reconstructibility of the HRF is depends heavily on the temporal resolution.

**Different wavelet filters**

We tested 15 different wavelet filters for (\phi_1,\psi_1), as well as for (\phi_2,\psi_2): Daubechies wavelets 1 . . . 5 (the filter number indicates the number of vanishing moments), Daubechies’
Figure 4.8. Output MSEs with varying response onset delays, for Tikhonov (a) and Wiener (b) shrinkage. SNR = -2 dB (×), 0 dB (○), 2 dB (□), 4 dB (∗), and 6 dB (+).

Figure 4.9. Output MSE for different SNRs and different HRFs, (a) TR = 0.5 s, (b) TR = 3 s. ×: HRF_{do}, ○: HRF_{spm}.

symmetric wavelets 2...6 (Daubechies 1993) (filter 1 corresponds to the Daubechies-1 filter), and Coiflets 1...5 (Daubechies 1993). Different filters did not yield large differences in performance.

Decomposition level and noise threshold

The wavelet-domain threshold level $\theta$ also influences the output MSE. Figure 4.10 shows the MSE for different SNRs, different $\theta$ and different decomposition levels. We find that two-level decompositions produce the smallest errors for the lower SNRs, and three-
level decompositions perform best for the higher SNRs (see Fig. 4.10). Four-level and five-level decompositions yield higher errors. A higher $\theta$ often produces a lower MSE.

![Figure 4.10](image)

**Figure 4.10.** Output MSE for different SNRs, with various levels of decomposition and threshold levels. Wiener shrinkage was used, $\theta = 2$ (a) and $\theta = 3$ (b). Wavelet transforms: two-level ($\times$), three-level($\circ$), four-level ($\square$), five-level($\ast$).

### Different low-frequency trends

Four different types of low-frequency trends were tested (see Fig. 4.4b). We observe that only the type of frequency domain shrinkage influences the result significantly (see Fig. 4.11). Tikhonov shrinkage yields a higher MSE than Wiener shrinkage, especially for lower SNRs. This may be because trends are not removed perfectly; Wiener shrinkage has extra knowledge about the signal $f$ and the estimated power spectral density of $h$, which enables it to deal with the residuals of the trend.

### 4.4.3 Conclusions

As shown in Fig. 4.6, the MSE of the reconstructed signal was lower than the input MSE in most of the tested situations. The method is quite robust with respect to changes of parameter settings and changes of signal properties, such as the SNR and the sample frequency.

### 4.5 Event-Related fMRI Experiments

We demonstrate the HRF extraction routine of section 4.3.3 and the HRF model of section 4.2.3 in two event-related fMRI experiments of one subject, measured on different
Extracting the HRF using Fourier-wavelet regularised deconvolution

Figure 4.11. Output MSE for different SNRs and low-pass trends in the data, using Tikhonov shrinkage (a) and Wiener shrinkage (b). The signals contained no trend (×), a linear trend (○), a sinusoidal trend (□), or a quadratic trend (∗).

days. We compute HRFs for the whole brain and in a region of interest, respectively, which are then used in covariance analyses.

4.5.1 Fixed-ISI experiment

In this experiment, the subject had to make a fist on the appearance of a visual stimulus, and immediately relax. Stimuli were presented on a white screen placed inside the scanner: a white disc was shown as the default, a red disc was a cue to make a fist. The experiment consisted of 156 scans, acquired as described in section 4.4. Cues were given every 24 s (8 scans × 3 s), starting at scan 2. Expected areas of increased activity were the motor cortex, the premotor cortex, the supplementary motor area and the cerebellum. The first part of this experiment tested the detectability of an HRF in those areas.

Detecting activation

The scanned brain volumes were denoised with a wavelet-based technique (Wink and Roerdink 2004), using SUREShrink in the wavelet domain (Donoho and Johnstone 1995). Realignment, normalisation, and statistical analysis were done with the SPM program (Friston et al. 1995c). We made a statistical parametric map of all responses synchronous with the stimulus pattern, using a design matrix \( X \) containing a constant signal, modelling the time series mean for each voxel, and a set of 6 Fourier basis functions (3 sines, 3 cosines), modulated by a Hanning window, in the time interval of 8 scans after each stimulus. The variance ratio was computed in each voxel to test the amount of variance explained by the design. The variance ratio is the ratio of the variance explained by the model (in this case, the Fourier basis functions) and the variance of the residual (noise), as com-
computed by the linear model (Josephs and Henson 1999). Significant points were selected using an F-test, and false discovery rate (FDR) control (Genovese et al. 2002) with the FDR parameter \( q=0.05 \) was used to correct for multiple hypothesis testing. Activation maps are shown in Fig. 4.12a as maximum intensity projections (MIP) in the orthogonal directions. The voxel location with the most significant activation is marked with a ‘<’ sign. We found activation in all expected areas, predominantly in the motor cortex.

**Figure 4.12.** Maps of the variance ratio in the transverse and coronal direction, respectively, for the fixed-ISI (a) and the random-ISI (b) experiments, thresholded with FDR control for \( q=0.05 \). The indicated areas are: left motor cortex(1), supplementary motor area (2), premotor areas (3), right cerebellum (4).

### Extracting the HRF

To evaluate the performance of the ForWaRD method, HRFs were extracted by ForWaRD and selective averaging, respectively. Given a long ISI, selective averaging (Buckner et al. 1996) is a simple and robust technique to obtain the HRF. Selective averaging yielded a time series of eight volumes containing the averaged post-stimulus activation at each voxel location. A much stricter FDR-corrected threshold \( (q=0.0001) \) was applied to the map shown in Fig. 4.12a, to limit the number of voxel locations contributing to the HRF (see Fig. 4.13). A whole-volume HRF was extracted from the post-stimulus volumes by averaging the response of each volume, weighted by the map of significant variance ratio values (see Sec. 4.5.1). A region-specific HRF in the \( 7 \times 7 \times 7 \)-voxel neighbourhood of a selected voxel (see the crosshairs in Fig. 4.13) was computed by using only the time signals from that region. Figure 4.14a-b shows the extracted HRFs.

The ForWaRD algorithm used 128 scans of the experiment, starting with scan 2 (first stimulus). The resulting post-stimulus time series was used to create a whole-volume
Extracting the HRF using Fourier-wavelet regularised deconvolution

Figure 4.13. Maximum intensity projections of the variance ratio in the fixed-ISI time series, after FDR-corrected thresholding with $q=0.0001$: transverse view (a), sagittal view (b), coronal view (c). The crosshairs show the selected voxel location.

HRF and a region-specific HRF in the same way as with selective averaging. The HRFs are shown in figure 4.14(c−d). The HRFs extracted by ForWaRD are similar to those extracted by selective averaging, with the difference that the baseline of the ForWaRD-extracted HRF appears to decrease. This may be explained by the fact that the HRF does not return to baseline within the sampled interval, so that in the GLM the response decreases at every next stimulus. A modelled HRF was obtained by fitting HRF_{par} to the extracted HRFs with the Levenberg-Marquardt nonlinear curve-fitting algorithm. We compared the $L_2$-difference between the extracted coefficients and the values of the modelled HRF at the sample points. A standard HRF, in this case HRF_{spm} sampled at the same points as the other signals, was used as a reference. All signals were normalised to have a unit $L_2$-norm. Table 4.1 shows that the fitted HRF_{par} matches the measured signal much better than the standard HRF_{spm}.

Table 4.1. $L_2$ differences of the HRF models and the HRFs extracted from the fMRI data sets.

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<tr>
<th></th>
<th>fixed ISI</th>
<th>random ISI</th>
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<tr>
<td></td>
<td>selective averaging</td>
<td>$ForWaRD$</td>
</tr>
<tr>
<td>$</td>
<td>h_\kappa - \text{HRF}_{\text{par}}</td>
<td>$</td>
</tr>
<tr>
<td>$</td>
<td>h_\kappa - \text{HRF}_{\text{spm}}</td>
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4.5.2 Random-ISI experiment

We repeated the experiment with a randomised interstimulus interval (ISI). The stimulus signal was made by thresholding a vector of random values. The length of the ex-
Experiment was 256 scans, the scanning parameters and image preprocessing steps were equal to those in section 4.4.

Detecting activation

Because of the overlapping responses, the windowed Fourier basis set could not be used to measure the explained variance. Instead, the canonical HRF of the SPM program and its time and dilation derivatives were used as basis functions in the GLM. The variance ratio map was thresholded with FDR control and $q=0.05$, resulting in the activation map shown in Fig. 4.12b. The activation is more localised than in the fixed-ISI experiment, and there is more contrast between the regions of interest and the rest of the brain.
Extracting the HRF

A post-stimulus time series, containing the HRF at each voxel location, was created with ForWaRD, using all 256 scans of the experiment. Selective averaging could not be used here because of the overlapping responses. Thanks to the random ISI, a much longer post-stimulus interval could be sampled (Burock et al. 1998). The post-stimulus volumes produced by the extraction routine were used to create a whole-volume HRF and a region-specific HRF, respectively, in the same way as in the fixed-ISI experiment. The volume thresholded with $q=0.001$ and the selected voxel for the region-specific HRF are shown in Fig. 4.15. Instead of using one function $\text{HRF}_{\text{par}}$ to describe the HRF, two of these functions were used: one to model the initial peak, and one to model the undershoot following the peak. In the fixed-ISI experiment we did not use a function to model the undershoot, because the post-stimulus interval was too short to make a reliable fit. Figure 4.16 shows the extracted HRF coefficients, together with the modelled HRFs.

The $L_2$-differences between the measurements and the fits were computed for both extracted HRFs, in the same way as for the fixed-ISI HRFs. The standard HRF $\text{HRF}_{\text{spm}}$ again shows a greater difference from the measurements than the fitted HRF $\text{HRF}_{\text{par}}$.

### 4.5.3 Using the extracted HRFs in covariance tests

HRFs measured from an fMRI data set cannot be used to test for activation in the same data set: a model must be specified a priori, and inferences cannot be made from models that are determined by the data itself. Therefore, we tested for activation in the random-ISI experiment with the HRF $\text{HRF}_{\text{par}}$ fitted to the points extracted from the fixed-ISI data, and vice versa. The cross-covariance was computed between the responses, predicted by the stimulus times and the modelled HRFs, and the measured time signals. A one-sample $t$-test on the covariance map was used to detect activated areas, using the residual time

**Figure 4.15.** Maximum intensity projections of the variance ratio in the random-ISI time series thresholded with $q=0.0001$: transverse view (a), sagittal view (b), coronal view (c). The crosshairs show the selected voxel location.
Figure 4.16. HRFs extracted from the random-ISI experiment by ForWaRD: whole-volume (a) and region-specific (b). ×: extracted HRF, solid line: two functions HRF_{par} fitted to ×, dashed lines: function HRF_{spm}.

The first covariance analysis was performed with HRF_{spm}. Figure 4.17 shows the covariance maps from both experiments. Differences can be seen between Figs. 4.17a-b, most notably the large active region in the left motor cortex, detected in the fixed-ISI experiment and showing up only faintly in the random-ISI experiment. The motor cortex
and the supplementary motor area show less activation in the random-ISI experiment, whereas the cerebellum and the premotor areas are more pronounced. These maps, together with the graphs of Figs. 4.14 and 4.16 indicate that the HRF measurable in the random-ISI experiment differs significantly from HRF_{spm}.

Figure 4.18. Maximum intensity projections of the cross-covariance found in the fixed-ISI data set, using the HRFs computed from the random-ISI experiment by ForWaRD. (a) using the whole-volume HRF, (b) using the region-specific HRF.

The covariance maps constructed with the extracted HRFs are shown in Figs. 4.18 and 4.19. Figures 4.18a-b show the activation detected in the fixed-ISI dataset with the HRFs extracted with ForWaRD from the random-ISI dataset. The differences between (a) and (b) are much smaller than those between Fig. 4.17a-b, and like in Fig. 4.17a, the detected activation matches our expectation. Figure 4.19 shows the activation detected in the random-ISI dataset with the HRFs from the fixed-ISI dataset. The analysis was done with the HRFs made after selective averaging (a-b) and ForWaRD (c-d). The maps are in very good agreement: for the experiments in which selective averaging is possible, ForWaRD yields results very similar to those produced by selective averaging. The differences for ForWaRD between the fixed-ISI and random-ISI time series are also small (selective averaging is not possible with a random ISI), indicating that ForWaRD works on the random-ISI data set as well. Table 4.2 shows the maximum values for the variance ratio in the covariance analyses. A high variance ratio indicates that much of the variance in the signal is explained by the model, and that the residual noise in the GLM (see Eq. (4.1)) is small. It shows that ForWaRD works as well on the random-ISI dataset as it does on the fixed-ISI data set. Its performance is similar to that of averaging on the fixed-ISI dataset. The modelled region-specific HRFs generally perform better than whole-volume HRFs, and the maps of detected activation indicate that the modelled HRFs do not only detect activation in the region from which they were extracted, but
4.6 Conclusions

We have developed a deconvolution method to extract the HRF from fMRI time series based on ForWaRD. Deconvolution in the frequency domain allows extraction of the HRF even when the responses to subsequent stimuli overlap, and the sensitivity to noise of frequency-domain deconvolution is compensated by Wiener or Tikhonov shrinkage.

Figure 4.19. Maximum intensity projections of the cross-covariance found in the random-ISI data set, using the HRFs computed from the fixed-ISI experiment by selective averaging (a-b) and ForWaRD (c-d). Left: whole-volume HRF, right: region-specific HRF.

that they are general enough also to detect activation in other areas.
Extracting the HRF using Fourier-wavelet regularised deconvolution

Table 4.2. Maximum variance ratio values found in the tests.

<table>
<thead>
<tr>
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<th>ForWaRD volume region</th>
<th>selective averaging volume region</th>
<th>HRF$_{spm}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>fixed-ISI</td>
<td>113 162</td>
<td>– –</td>
<td>117</td>
</tr>
<tr>
<td>random-ISI</td>
<td>103 102</td>
<td>102 104</td>
<td>74</td>
</tr>
</tbody>
</table>

in the frequency domain, followed by wavelet domain Wiener shrinkage. Before applying ForWaRD, low-frequency trends are removed from the time signal with a standard wavelet-based method. Tests of the extraction routine using noise from a real fMRI time series and simulated activation, demonstrate its robustness. Test results show that the method is robust to trends in the data, and the performance does not differ much between the noise levels we tested. The output of our algorithm is a post-stimulus time series, representing the HRF in every voxel.

We have presented a model for the HRF based on damped oscillations that can be used in combination with the extracted coefficients, to predict event-related fMRI responses. An HRF using this model is compared with the standard HRF from the SPM program and shows a better match with extracted responses. A comparison of statistical analyses with (i) the standard HRF$_{spm}$ and (ii) an HRF based on HRF$_{par}$ using the coefficients extracted from another experiment with the same subject, shows the benefits of HRF modelling. With the modelled HRF, detected regions are larger, and the statistical analysis is more powerful than with the standard HRF$_{spm}$. At present, the extraction method is capable of recovering one HRF from one time series. A possible extension of the method is the extraction of multiple HRFs from one or multiple experiments.